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Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.01

Topic: A.03. Stem Cells and Reprogramming

Title: Evaluating neuronal, synaptic, and network function in stem cell models of neural development and disease

Authors: H. B. HAYES, S. A. CHVATAL, D. C. MILLARD, M. CLEMENTS;
Axion BioSystems, Georgia, GA

Abstract: Induced pluripotent stem cell (iPSC) technology has allowed complex human biology to be reproduced *in vitro* at high throughput scales. Further, advances in genetics and proteomics have accelerated neural disease-in-a-dish models, while 3D cell preparations, such as organoids, have enabled models that better recapitulate human development. To optimize, validate, and utilize complex *in vitro* neuronal models, it is critical to characterize the function of neurons, synapses, and networks over relevant time courses. Here, we present data supporting the use of label-free, multi-well microelectrode array (MEA) technology as an efficient approach for reliable, repeated quantification of cellular and network function across development and in disease. First, the Maestro multi-well MEA system (Axion BioSystems) was used to characterize human iPSC-derived cortical organoid function across 10 months *in vitro.* Organoids exhibited increasingly complex spiking activity over time, with network events becoming more frequent. Local field potentials were also compared to electroencephalograms from premature neonates, revealing that the development of complex network oscillations in cortical organoids mimic and predict the network dynamics of early human brain development. In addition, we also validated two human iPSC disease-in-a-dish models. In a model of Dravet syndrome, patient-specific hiPSC-derived neurons were tracked for 36 days *in vitro*. Dravet syndrome cultures exhibited significantly higher mean firing rate, network burst duration, and network burst density compared to wild type controls, reflecting an epileptic phenotype. In a model of Fragile X syndrome, hiPSC-derived neurons exhibited reduced FMR1 mRNA and FMRP expression compared to isogenic controls. Reduced expression corresponded to increased neural activity after DIV21. The disease phenotype was reversed with addition of FMR1 mRNA or co-culture with control neurons, both in a dose-dependent manner. By bringing human biology to a dish, hiPSC-derived neurons deliver biologically-relevant models for studying neural development and disease. The Maestro multi-well MEA platform enables label-free chronic tracking of neural network function ideal for validating neuronal models and developing novel therapeutics.

Disclosures: H.B. Hayes: A. Employment/Salary (full or part-time):; Axion BioSystems. **S.A. Chvatal:** A. Employment/Salary (full or part-time):; Axion BioSystems. **D.C. Millard:** A. Employment/Salary (full or part-time):; Axion BioSystems. **M. Clements:** A. Employment/Salary (full or part-time):; Axion BioSystems.

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.02

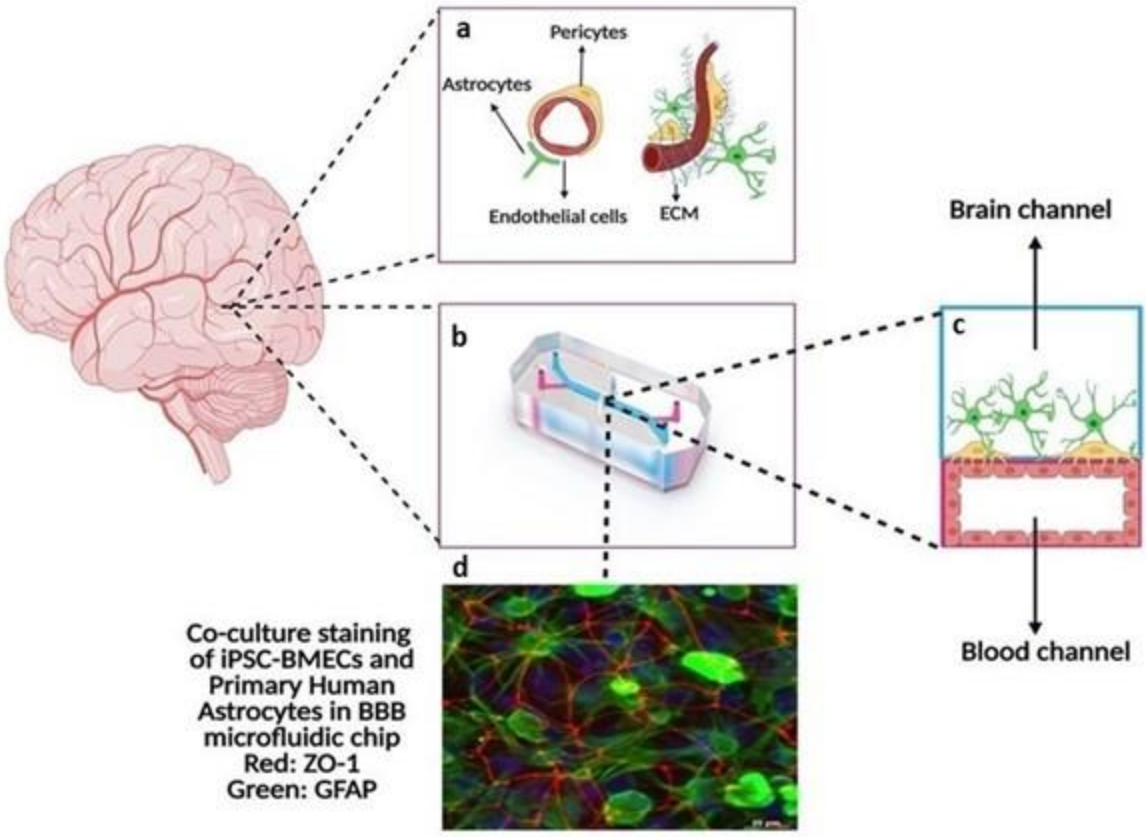
Topic: A.03. Stem Cells and Reprogramming

Support: NIH 2R01DA029121-01A1

Title: A quasi-physiological microfluidic blood-brain barrier model for brain permeability studies

Authors: *A. BHALERAO[1], B. NOORANI[2], L. CUCULLO[3];
[1]Biol. Sci., Oakland Univ., Rochester, MI; [2]Pharmaceut. Sci., Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX; [3]Dept. of Foundational Med. Studies, Oakland Univ. William Beaumont Sch. of Med., Rochester, MI

Abstract: Microfluidic-based organ-on-a-chip technology allowed for developing a new class of in-vitro BBB models that recapitulates many hemodynamic and architectural features of the brain microvasculature not attainable in conventional two-dimensional platforms. Herein we describe and validate a novel microfluidic BBB model that closely mimics the one in situ. Induced pluripotent stem cell (iPSC) derived BMECs were co-cultured with juxtaposed primary human pericytes and astrocytes to enable BBB-specific characteristics such as low paracellular permeability, efflux activity, and osmotic responses. The permeability coefficients of [$^{13}C_{12}$] sucrose and [$^{13}C_6$] mannitol were assessed using a highly sensitive LC-MS/MS procedure. The resulting BBB displayed continuous tight junctions' patterns, very low permeability to mannitol and sucrose, and quasi-physiological responses to hyperosmolar opening and treatment with a p-glycoprotein inhibitor as demonstrated by a decreased BBB integrity and increased permeability of Rhodamine 123, respectively. Astrocytes and pericytes on the abluminal side of the vascular channel provided at large the environmental cues necessary to form very tight barrier and extend its long-term viability for time-course studies. In conclusion, our novel multi-culture microfluidic platform showcased the ability to replicate a quasi-physiological brain microvascular, thus enabling the development of a highly predictive and translationally relevant BBB model.



Disclosures: A. Bhalerao: None. **B. Noorani:** None. **L. Cucullo:** None.

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.03

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R01AG054720
NIH Core Grant P30CA008748
Starr Foundation grant for the Tri-institutional Stem Cell Initiative

Title: Combined chemical treatment accelerates functional maturation of human stem cell-derived neurons

Authors: *E. HERGENREDER[1], Y. ZORINA[2], H. MUNGUBA[3], E. CALDER[2], A. MINOTTI[3], Z. ZHAO[3], A. BAGGIOLINI[2], R. WALSH[2], G. CICERI[2], C. LISTON[3], J. LEVITZ[3], R. GARIPPA[2], S. CHEN[3], L. STUDER[2];

[1]Cornell Univ. / Weill Cornell Medic Neurosci. Program, New York, NY; [2]Mem. Sloan Kettering Cancer Ctr., New York, NY; [3]Weill Cornell Med., New York, NY

Abstract: The maturation of human pluripotent stem cell (hPSC)-derived neurons follows the timing of human brain development, requiring extensive periods of culture before the emergence of adult-like function. This prolonged in vitro maturation presents a major challenge to stem cell-based models and treatments of neurological disease. We designed a high-content imaging assay based on morphological and functional readouts in hPSC-derived cortical neurons to reveal underlying pathways and to identify chemicals capable of accelerating neuronal maturation. Probing a library of 2688 bioactive drugs, we identified multiple compounds that drive neuronal maturation including regulators of chromatin remodeling and calcium signaling. By performing combinatorial assays of screen hits, we designed a cocktail of four small molecule that triggered maturation across all tested phenotypes, including measures of synaptic density, electrophysiology and transcriptomics. Remarkably, this drug cocktail was also effective in promoting the maturation of 3D cortical organoids and spinal motor neurons, and improved aspects of functional maturity in non-neural lineages such as melanocytes and pancreatic beta cells. These results demonstrate that the maturation of hPSC-derived cell types can be promoted by pharmacological intervention and suggests that some of the mechanisms controlling the timing of human maturation are shared across lineages.

Disclosures: E. Hergenreder: None. **Y. Zorina:** None. **H. Munguba:** None. **E. Calder:** None. **A. Minotti:** None. **Z. Zhao:** None. **A. Baggiolini:** None. **R. Walsh:** None. **G. Ciceri:** None. **C. Liston:** None. **J. Levitz:** None. **R. Garippa:** None. **S. Chen:** None. **L. Studer:** None.

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.04

Topic: A.03. Stem Cells and Reprogramming

Title: Neuronal and synaptic maturation in long-term cultures of human iPSC-derived neurons generated by transcription factor-based rapid differentiation

Authors: *W. LIN[1], S. YAMADA[1], H. WATANABE[1], Y. KAWASHIMA[1], Y. SEKINO[2];
[1]Biomed. Business Ctr., Ricoh Company, Ltd., Kawasaki-shi, Japan; [2]Dept. of Chem. Pharmacol., The Univ. of Tokyo, Tokyo, Japan

Abstract: Rapid differentiation methods based on the transient expression of neurogenic transcription factors allow an efficient and scalable generation of neurons from human induced pluripotent stem cells (iPSCs), thus emerging as a promising strategy for regenerative medicine and disease modeling. However, characterizing the degree of cell-type specificity and maturity in these transcription factor-induced neurons remains a challenge.
To examine the maturation process in iPSC-derived neurons, we performed a time-course evaluation of neuronal marker expression and of electrophysiological properties in cultures maintained for 3 months after induction of differentiation. Rapid elongation of neurofilament-positive neurites was observed as

expected from the first week of culture. Measurement of electrical activity with a microelectrode array (MEA) system showed spontaneous firing and generation of synchronous network bursts at 1 month of culture, which suggests that multiple neurons start connecting to each other. Immunocytochemistry showed the concomitant formation of MAP2-positive dendrites and expression of presynaptic vesicle markers, which then increased significantly over time after 2 to 3 months of culture. We further evaluated the subcellular localization of drebrin, an actin-binding protein involved in the morphology and dynamics of excitatory dendritic spines. Drebrin clusters were shown to develop along MAP2-positive dendrites at late culture stages. This indicates for the first time that iPSC-derived neurons generated by the rapid differentiation method can reach dendritic spine maturation required for neuroplasticity and response to excitotoxicity.
Transcriptome analysis by RNA sequencing (RNA-seq) also confirmed the increase of neuronal markers over time. Moreover, the expression patterns of several markers of brain development suggested that our iPSC-derived neurons undergo a transition from an immature neuron profile to a more mature cortical deep layer profile. Our results suggest that iPSC-derived neurons continue maturation after the initial differentiation period, by following hallmarks of development including establishment of neurotransmission and synaptogenesis. Optimizing iPSC-derived neuron cultures for synapse maturation would prove useful for the development of *in vitro* models that are physiologically relevant to higher brain functions and cognitive disorders.

Disclosures: W. Lin: A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **S. Yamada:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **H. Watanabe:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **Y. Kawashima:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **Y. Sekino:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ricoh Company, Ltd..

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.05

Topic: A.03. Stem Cells and Reprogramming

Support: NIH/NINDS SBIR Grant R44NS102088

Title: Chemically defined substrates in a ready to use format that promote differentiation, accelerated maturation and neurite extension of multiple neuronal subtypes for screening applications

Authors: W. RICHARDS, J. ZIMMERMANN, *S. VISURI, C. LEBAKKEN;
Stem Pharm, Inc, Madison, WI

Abstract: Human neural cells manufactured from induced pluripotent stem cells (iPSCs) hold great promise for modeling neurodevelopmental disorders, screening for potential risks from environmental toxins and as cell replacement therapies. However, most protocols require the use of complex, animal derived substrates that need to be prepared prior to cell plating and introduce variability to culture and

assay workflows. We have developed chemically defined substrates employing norbornene-functionalized polyethylene glycol and synthetic peptides that can be applied to cell culture surfaces, dehydrated, packaged, sterilized, and stored ready for re-hydration and use. We employed Design of Experiment (DOE) methodology utilizing Box-Behnken response surface modeling to screen for formulations that promoted viability, cell adhesion, desired morphology, and accelerated maturation of cortical glutamatergic and motor neurons or differentiation to glutamatergic neurons. These formulations were tested for compatibility with other commercially available iPSC-derived neurons including GABAergic neurons and transcriptionally induced excitatory neurons. Transcriptional profiling utilizing bulk RNASeq analysis was performed comparing neural cultures on the substrates to those cultured on standard substrates including charged polymers (poly-lysines) or animal-derived substrates (PLO-Laminin or Geltrex). Cells cultured on Stem Pharm's hydrogel substrates demonstrated an increase in transcription of gene ontology sets expressing extracellular matrix proteins, cell adhesion molecules, neuron projection guidance and cell-substrate adhesion in day seven samples and enhanced cell differentiation, migration, signaling at the cell periphery and vesicles at day fourteen. The pre-plated substrates reduce time for experimental preparation, reduce the substrate complexity, eliminate ethical considerations of animal-derived substrates, and improve assay metrics when applied to screening campaigns.

Disclosures: W. Richards: A. Employment/Salary (full or part-time):; Stem Pharm, Inc. **J. Zimmermann:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc. **S. Visuri:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc. **C. Lebakken:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc.

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.06

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant NS080913
NIH Grant AG064077
Donald E. and Delia B. Baxter Foundation Grant
L.K. Whittier Foundation Grant
Eli and Edythe Broad Foundation Grant
NIH Grant AG053382
NIH Grant AG055797

Title: Rejuvenating neural stem cell function with computational single cell drug discovery

Authors: *L. PENG[1,2,3], M. M. BAY[1,2,3], A. B. SCHROER[7,10], A. IBRAYEVA[1,3,4,5], N. ZHANG[1,3], L. SUMROW[1,3], J. LEVI[1,3,4,5], W. XIANG[1,3,4,5], S. A. VILLEDA[7,8,9,10], M. A. BONAGUIDI[1,2,3,5,6];
[1]Eli and Edythe Broad CIRM Ctr. for Regenerative Med. and Stem Cell Res. at USC, Los Angeles, CA; [2]Neurosci. Grad. Program, [3]Dept. of Stem Cell Biol. and Regenerative Medicine, Keck Sch. of Med.,

[4]Davis Sch. of Gerontology, [5]USC Davis Sch. - Buck Inst. Grad. Program in the Biol. of Aging, [6]Zilkha Neurogenetic Institute, Keck Sch. of Med., USC, Los Angeles, CA; [7]Dept. of Anat., [8]Biomed. Sci. Grad. Program, [9]Dept. of Physical Therapy and Rehabil. Sci., Univ. of California San Francisco, San Francisco, CA; [10]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res. at UCSF, San Francisco, CA

Abstract: Regenerative medicine offers the unrealized potential to reverse brain aging. However, endogenous neural stem cell (NSC) function declines with age of unclear mechanisms. Here, we developed a single cell computational drug screening technology to reinstate NSC activity, neurogenesis, and cognition in older mice through mimicking younger NSC programs. “Revealing Origins and Ontological Targets (ROOT)” first reconstructed single cell transcriptomes in cell-lineage pseudotime and identified transcriptomic signatures (TS) that define age-related NSC activity loss. ROOT then screened 1309 clinically relevant small molecules for their ability to recapitulate the TS gene networks mediating NSC activity. Three of the top 5 prioritized compounds reactivated NSCs from quiescence within middle-aged mice. Among them, Sulindac Sulfone (SS) further proved to sustain NSC proliferation, expand the NSC pool, increase neurogenesis, and improve cognitive function. We thus demonstrate the utility of a new single cell pharmacogenomics platform by revealing unexpected neural stem cell capacity for regenerative medicine.

Disclosures: L. Peng: None. **M.M. Bay:** None. **A.B. Schroer:** None. **A. Ibrayeva:** None. **N. Zhang:** None. **L. Sumrow:** None. **J. Levi:** None. **W. Xiang:** None. **S.A. Villeda:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH (AG053382; AG055797) grants to S.A.V. **M.A. Bonaguidi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH (NS080913; AG064077), Donald E. and Delia B. Baxter Foundation, L.K. Whittier Foundation, Eli and Edythe Broad Foundation grants to M.A.B..

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.07

Topic: A.03. Stem Cells and Reprogramming

Support: Swedish Research Council

Title: Reprogramming Human Adult Fibroblasts into GABAergic Interneurons

Authors: *A. BRUZELIUS, S. KIDNAPILLAI, D. OTTOSSON;
Lund Univ., Lund, Sweden

Abstract: Somatic cells such as human fibroblasts can be converted into mature and functional neurons termed induced neurons (iNs) through the process of over expressing ectopic neuronal conversion factors. Direct reprogramming of human fibroblasts into iNs is emerging as a promising technology to acquire patient- and disease-specific neurons for disease modeling and drug screening applications. Direct

reprogramming approaches has allowed human fetal fibroblast to be converted into a variety of subtypes, including dopaminergic, cholinergic, spinal motor and serotonergic neurons. However, conversion of adult fibroblasts into iNs remains challenging as there appears to be an intrinsic blockade of neuronal fate commitment pathways. We have applied methods for direct reprogramming of adult skin fibroblasts using REST inhibition to promote successful conversion and combined it with GABAergic interneuron fate determinants to successfully generate induced GABAergic interneurons. GABAergic interneurons are highly relevant for cognitive impairments and brain disorders such as Alzheimer's, Parkinson's diseases, schizophrenia and autism. Our results showed that we can obtain induced GABAergic interneurons from adult fibroblasts in 21 days of culture with a high survival of cells using different conversion factor cocktails. Moreover, we could detect subtype specific interneurons; calbindin and calretinin within our cultures of iNs. Despite the difficulty to convert adult fibroblasts into functional neurons in vitro, we could detect immature action potentials along with inward and outward sodium channels using whole-cell patch-clamp technology further indicative of a successful neuronal conversion.

Disclosures: A. Bruzelius: None. **S. Kidnapillai:** None. **D. Ottosson:** None.

Poster

P015. Advances in Neural Stem Cell Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P015.08

Topic: A.03. Stem Cells and Reprogramming

Support: T32 GM118288

Title: Directed differentiation of medium spiny neurons using an inducible transgenic technology 'MADR'

Authors: *P. LINESCH, N. KOBRITZ, A. YANG, H. PARK, D. PACHECO, V. B. MATTIS, J. J. BREUNIG;
Board of Governors Regenerative Med. Inst., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: A technique to direct stem cell differentiation would be a novel therapy for replenishing lost neurons in neurodegenerative diseases, such as Huntington's Disease, and would allow us to study pure populations of specific cell types in vitro. By transiently expressing a mixture of key developmental transcription factors using an inducible transgenic system, preliminary results indicate we can directly differentiate neurons. Using an inducible cocktail of transcription factors (CTIP2 and DLX2) responsible for the differentiation of Medium Spiny Neurons (MSNs), we believe we can control the identity of cells and directly reprogram them into MSNs. A transgenesis method developed by the Breunig Lab called 'MADR', Mosaic Analysis with Dual recombinase-mediated cassette exchange, uses two recombinase (Cre & FlpO) to integrate a donor DNA cassette between lox and flox sites (Kim GB, 2019 *Cell*). The donor cassette we created has two parts; a constitutively active side expressed under the mouse's CAG promoter and a doxycycline (DOX) inducible tet-on element to express genes of interest; currently MSN transcription factors CTIP2 and DLX2, as well as BCLXL, miR-9 & 124, and our reporter SMFP-MYC-bright. We have successfully validated nucleofection *in vitro* and *in vivo* using mTmG mice, primary

mouse neural stem cells (NSCs), and human iPSCs. Primary mouse NSCs displayed a morphological change resembling a neuronal cell type and IHC and genomic analysis are underway. Future directions will be to culture iPSCs into an organoid with a mixed population of inducible plasmids to make a complex mixed organoid culture. Postnatal electroporation allows the MADR system to be transfected into mice at postnatal day 1-2. At this age, the Radial Glia progenitors lining the ventricle are transfected and any daughter cells contain the inserted cassette. The mice are aged for 21 days and then administered food containing doxycycline for various time points spanning 3 days to 6 months. Around day 15 post dox, neuronal looking projections begin to be seen in SMFP-MYC-bright positive cells and between 1 - 2 months, large amounts of reporter positive projections are seen in the striatum. The correct timing of DOX is being examined but preliminary data suggests short term administration results in the differentiation of immature neurons. If MADR can tightly control directed differentiation, it could be used in cell culture models examining the complex relationship between difficult to isolate and culture neuron cell types. Additionally, this technology would be key for transplant studies in neurodegenerative disease to replenish lost cell types.

Disclosures: P. Linesch: None. **N. Kobritz:** None. **A. Yang:** None. **H. Park:** None. **D. Pacheco:** None. **V.B. Mattis:** None. **J.J. Breunig:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.01

Topic: A.07. Developmental Disorders

Support: AMED Grant 20dm0107160h0005
AMED Grant 19dm0107077h0004
KAKENHI Grant JP20K07917

Title: Intranasal oxytocin reduces facial affect misrecognition between disgusted and angry faces in adults with autism spectrum disorders

Authors: *T. OKADA[1,2], Y. UNO[2,3];
[1]Dept. of Developmental Disorders, Natl. Inst. of Mental Health, Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Tokyo, Japan; [2]Dept. of Child and Adolescent Psychiatry, Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan; [3]Dept. of Psychiatry, Yokohama Psycho-Developmental Clin., Yokohama, Japan

Abstract: Objectives Administration of intranasal oxytocin (OXT) was reported to enhance the ability to recognize emotional facial expression in autism spectrum disorders (ASD). However, the whole picture of enhancements in six basic facial affect recognition and their relationship with improvements in social impairments remain unclear. Methods This study is conducted in male adults with ASD who participated in randomized controlled trial (RCT) of intranasal oxytocin (Mol Psychiatry, 2020) at Nagoya University Hospital. 24 male adults with ASD were randomly assigned to OXT and placebo groups. They were administered OXT (24 unit, twice a day) or placebo for seven weeks. In open trial following the RCT, all participants were administered OXT for six weeks. Benton Facial Recognition Test and facial expression

recognition task were examined for all participants at three time points (baseline, after randomized controlled trial, after open trial). This study protocol was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine, and this study was funded by Japan Agency for Medical Research and Development (AMED) and Grants-in-Aid for Scientific Research (KAKENHI). Results OXT does not influence on the identifications of unfamiliar faces. Although the correct response rates for angry and disgusted faces after RCT are higher than those at baseline only in OXT group, it does not reach the significance level. After the open trial, patients recognized more accurately angry faces (p < 0.01) and disgusted faces (p < 0.05) than baseline. In error analysis, the misrecognition of angry for disgusted faces (p < 0.05) and misrecognition of disgusted for angry faces (p < 0.01) reduced after OXT administration. These effects are not significantly correlated with reduction in severity of social impairments. Discussion Although both anger and disgust are negative emotions, they were followed by different aggressive expressions to the others. Misrecognition between disgusted and angry faces was also reported in delinquents (Child Adolesc Psychiatry Ment Health. 2009). Oxytocin reduces misrecognition of negative facial emotions in ASD, and it may be the neuropsychological background for improvements associated with social disturbances. This hypothesis should be examined in larger samples in future.

Disclosures: T. Okada: None. **Y. Uno:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.02

Topic: A.07. Developmental Disorders

Support: Nevada Undergraduate Research Award

Title: Empathy and sociability across the subclinical autism spectrum

Authors: *T. P. WALFORD, S. M. HAIGH;
Univ. of Nevada, Reno, NV

Abstract: Difficulties in social communication is a key characteristic of Autism Spectrum Disorder (ASD). As ASD is a spectrum, the characteristics that define the diagnosis of autism can be seen to a more subtle degree in the general population. This study focuses on a measure of social cognition (friendship quality) and a measure of cognitive style (ability to empathize) to assess their relationship with autism-related symptoms. One hundred participants (76% female, 23% male and 1% non-binary or 3rd gender with an age range of 18-51 and a median of 19) were recruited and completed the Autism Quotient (AQ; to quantify the autism-related symptoms), the Friendship Questionnaire (FQ; a measure of relationships, friendships and interaction), and the Empathy Quotient (EQ; to measure the ability to regulate emotions and interpret emotional cues during social interactions). This study examined the mediation effect of EQ on the relationship between AQ and FQ. The direct relationship between AQ and FQ indicated that a higher AQ predicted worse friendship quality (b=-1.12, SE=0.25, p<.001). Higher AQ also predicted poorer ability to empathize (lower QE score; b=-1.11, SE=0.16, p<.001). When EQ was

accounted for, the effect of AQ on friendship quality was reduced, but still significant (b=0.42, SE=0.15, *p*=.007), suggesting that both autism-related traits and the ability to empathize independently impact friendship quality. These findings indicate that similar deficits in social cognition exist in the general population and are related to subclinical autistic symptoms.

Disclosures: T.P. Walford: None. **S.M. Haigh:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.03

Topic: A.07. Developmental Disorders

Support: NIH K23 ES026239/ES/NIEHS
NIH T34 GM008078/GM/NIGMS

Title: Restrictive and Repetitive Behaviors in children with Autism Spectrum Disorder, and amygdala subnuclei involvement

Authors: *D. SEGUIN, A. HENNESSY, S. CORREA, J. MARTINEZ-TRUJILLO, R. NICOLSON, E. G. DUERDEN;
Western Univ., London, ON, Canada

Abstract: Introduction: Restrictive and repetitive behaviors (RRBs) are a diagnostic criteria for autism spectrum disorder (ASD). These heterogenous behaviors can include motor stereotypies such as hand flapping, and restrictive play. Some forms of RRBs, like stereotypic movements, are thought to be linked to anxiety, and may serve as a self-soothing mechanism. The amygdala is a key structure involved in regulating emotion and controlling inhibitory behaviors. Our study aimed to investigate whether RRBs in children with ASD are associated with amygdala subnuclei development and whether this relationship is modified by anxiety. Methods: A total of 123 children underwent an MRI scan,44 (34M) children with a diagnosis of ASD, and 79 (38M) typically-developing (TD) children. Children were aged 5-10 years old (mean=7.98, SD=1.45 yrs). Parents completed the Child Behavior Checklist (CBCL), the Autism Screening Questionnaire and the Screen for Child Anxiety Related Disorders (SCARED). RRBs were measured using the subscale of the CBCL. We extracted the amygdala subnuclei volumes using FreeSurfer.Statistical Analyses: To examine whether RRBs were associated with amygdala subnuclei volumes and parent-reports of anxiety, a general linear model (GLM) with RRB total score as the dependent variable and amygdala subnuclei volumes, diagnosis (Dx), CBCL-Anxiety/Depression subscale scores, and SCARED-P scores were predictor variables, adjusting for gender, age, scan site, and total cerebral volume (TCV). Results: Children's RRB scores were significantly higher in children with ASD (p<.001). Child's gender (p=.003), age (p<.001), left anterioamygdalaoid area (AAA) volume (p=.006), left central subnuclei volume (p=.008), left medial subnuclei volume (p<.001), right accessory basal (AB) subnucleus volume (p=.008) and right medial nucleus volume (p=.002) were all significantly associated with increased RRBs. Neither anxiety measures were associated with RRBs. An interaction analysis found significant main effects of diagnosis on left AAA volumes (F 1,113)= 6.81, p=.010) and

right AB volumes (F(1,113)=7.40, p=.008). Autistic males had larger volumes, and autistic females had smaller volumes for these nuclei.Conclusion: Left AAA and right AB subnuclei, regions crucial for sensory information related to anxiety and fear processing, were significantly larger in children with higher levels of repetitive behaviors. These amygdaloid subregions may be key influencers of repetitive behaviors in children with ASD.

Disclosures: D. Seguin: None. **A. Hennessy:** None. **S. Correa:** None. **J. Martinez-Trujillo:** None. **R. Nicolson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; La Roche. **E.G. Duerden:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.04

Topic: A.07. Developmental Disorders

Support: Prodep Grant
Profexce Support

Title: Neurodevelopmental disorders that present pediatric patients through the NASA TLX Protocol

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Abstract: Introduction: The economic impact of risk factors and pathologies present in pediatric patients today has been increasing, which is worrying for our health system. Preserving health through proper monitoring of child development on a regular and regular basis will allow early detection of warning signs with respect to alterations in the normal development of the human being. With this in mind, the present research aimed to know the factors inherent to stress and anxiety in children of a Public Hospital in Pachuca, Hidalgo, especially related to Neurodevelopmental Disorders; which will allow identifying primary elements for prevention and mitigation of the increase in health expenses that this population group represents. A non-experimental, observational, non-participant descriptive method was used with a sample of 150 children who were invited to manipulate a haptic device combined with computer software, while their degree of stress was measured with the NASA-TLX Protocol. Among the results we found that 49 were female, 101 males, aged between 4 to 17 years; A peculiar characteristic of the sample is that the patients were receiving rehabilitation, however, at least 70% of the study participants had a mental load that reflected stress in NASA-TLX (6 items) when undergoing rehabilitation therapy. The Spence test (44 items) was also applied to measure anxiety, where it was found that the prevalence of generalized anxiety was 48%. For all the above, we can conclude those pediatric patients, even with

neurodevelopmental disorders are capable of performing tasks with haptic devices; However, the mental burden and anxiety that this brings them, together with their physical therapies in the Public Institution does not exempt them from suffering emotionally, which opens a window of opportunity to support them from disciplines such as Nursing, Psychology, and Neuroscience

Disclosures: J. Arias-Rico: None. **R. Barrera-Gálvez:** None. **E. Ramírez-Moreno:** None. **C. Solano-Pérez:** None. **J. Cuevas-Cancino:** None. **G. Samperio-Pelcastre:** None. **R. Jiménez-Sánchez:** None. **O. Flores-Chávez:** None. **L. Rivera-Ramírez:** None. **P. Silva-Maldonado:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.05

Topic: A.07. Developmental Disorders

Title: Association between autism-related gene CNTNAP2 polymorphism and subthreshold autism spectrum disorder in Japanese children

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Abstract: Subthreshold autism spectrum disorder (ASD) is a subclinical condition that shows less prominent autistic traits than fully diagnosed ASD. As children with subthreshold ASD are recognized as typically developing (TD) but often have difficulties in social adaptation, it is important to develop biomarker(s) to detect subthreshold ASD in TD children. However, no specific marker has been available, so far. Therefore, we studied genetic polymorphisms associated with autistic traits in TD children and as well as in children with ASD. One of them, the rs2710102 in the *CNTNAP2* gene encoding contactin-associated protein 2 showed significant association with ASD (Alarcon *et al.*, 2008) and higher AQ scores (Bai *et al*., 2019). Hence, the present study was focused on single-nucleotide polymorphism (SNP) of rs2710102. The subjects consisted of 77 Japanese children with ASD (49 boys, 18 girls, aged 38-98 months) and 57 TD children (34 boys, 23 girls, aged 38-98 months); informed consent/assent was obtained from each subject and parents. This study was approved by the Kanazawa University Hospital ethical committee. The ASDs diagnosis was given according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (American Psychiatric Association, 2000) using the Diagnostic Interview for Social and Communication Disorders (Wing et al., 2002) or the Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000). To assess the participants' intelligence and social reciprocity, we used the Japanese version of the Kaufman Assessment Battery for Children (K-ABC) and the Social Responsiveness Scale (SRS), respectively. In parallel,
genomic DNA was extracted from the buccal mucosa and subjected to genotyping by real-time PCR. Linear regression models were applied to estimate K-ABC and SRS-T scores based on the participants' condition (i.e., TD vs ASD), genotype, and interaction between condition and genotype; *p*-values less than 0.05 were considered statistically significant. As a result, we detected a significant difference

between genotypes and conditions [χ^2 (2) =6.56, p =0.038]. There was no significant difference in age and sex between conditions. When a co-dominant model was assumed, TD children with A-carriers (AA + AG) showed higher SRS total T-scores [t (55) = 2.11, p =0.039] and lower simultaneous processing scale scores [t (55) = -2.19, p =0.032] than GG homozygotes. These results suggest that the A-allele of rs2710102 could be useful in detecting subthreshold ASD.

Disclosures: Y. Shiota: None. **T. Hirosawa:** None. **M. Kikuchi:** None. **S. Yokoyama:** None.

Poster

P040. Autism: Behavioral Analysis I

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Program #/Poster #: P040.06

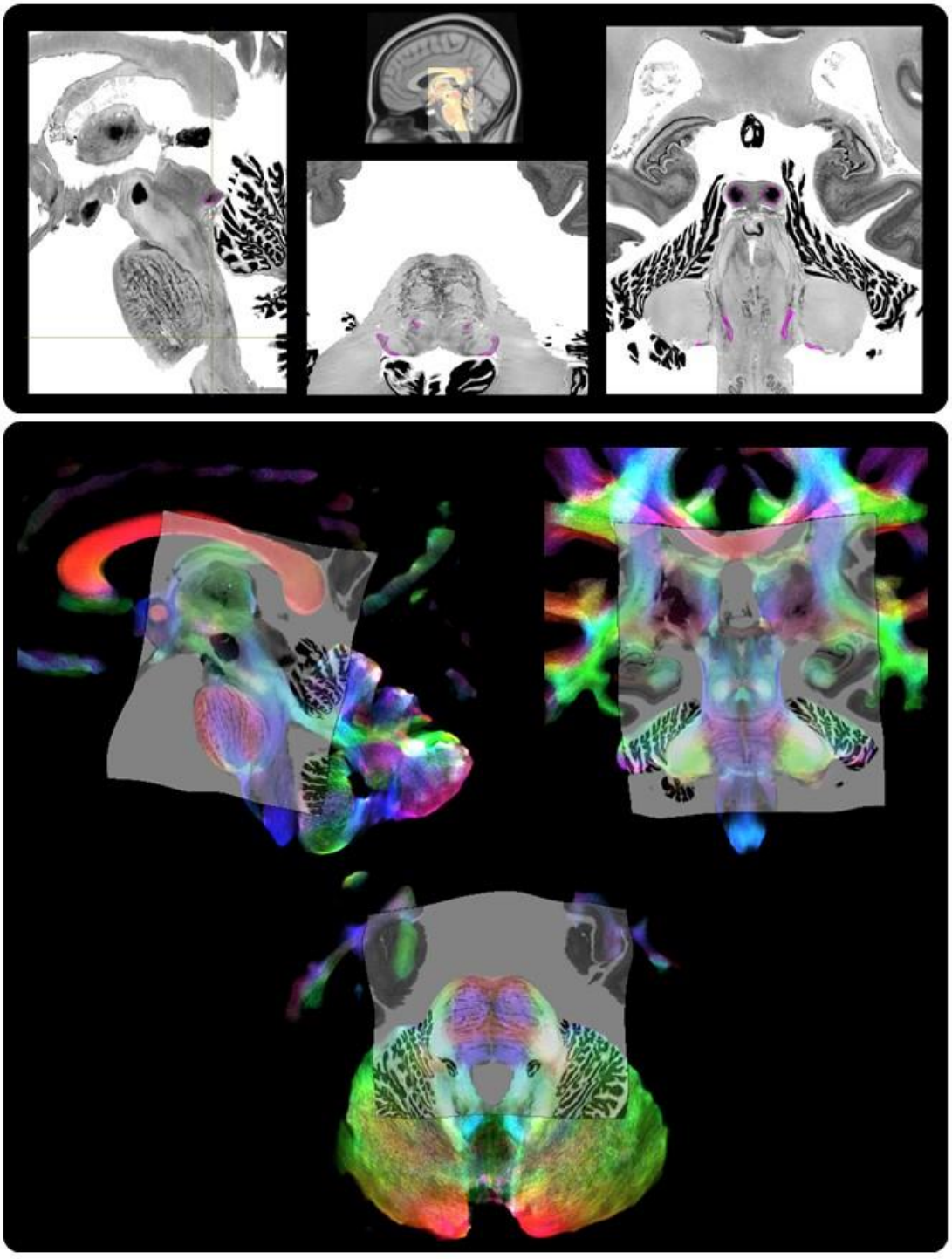
Topic: A.07. Developmental Disorders

Support: NIH R01 HD094715-01
The Hartwell Foundation
NIH P30 HD003352
NIH U54 HD090256

Title: Image registration-based high resolution diffusion MRI in the human brainstem in autistic and non-autistic children

Authors: J. GUERRERO-GONZALEZ, N. ADLURU, G. KIRK, S. KECSKEMETI, O. J. SURGENT, D. DEAN, III, A. L. ALEXANDER, ***B. TRAVERS**;
Univ. of Wisconsin-Madison, Madison, WI

Abstract: Diffusion weighted magnetic resonance imaging (dMRI) of the brainstem is technologically challenging, especially in young children with autism. This hinders access to high resolution images, which are desirable for improving the ability to study brainstem structures. Furthermore, increasing the resolution at the acquisition level may be limited by low signal-to-noise ratios from small voxels as well as other hardware constraints. Head motion in young children may additionally affect image quality. To address these challenges, we implement a method for reliably increasing spatial resolution in dMRI that hinges on accurate geometric distortion correction and high fidelity image registration between dMRI and motion-corrected anatomical MPnRAGE images (Kecskemeti et al., 2016; Kecskemeti & Alexander, 2020). Data used in this work consists of dMRI data (1.8 mm voxels, corrected using FSL's Topup) and T1-weighted MPnRAGE anatomical data (1 mm voxels) acquired from 154 autistic and non-autistic children (ages 6-11 years-old). Within each subject, dMRI and MPnRAGE data were spatially aligned in the MPnRAGE space permitting a further reliable increase in resolution of the dMRI scan. Then, estimation of tensors and fiber orientation distributions were carried out in the up-sampled space. Figure 1 shows the advantages of this processing, including sharper details in the brainstem, which may prove useful for improving accuracy in locating white and gray matter structures. Indeed, with this approach we achieved exquisite spatial alignment between the dMRI track density images and Sitek et al.'s (2019) histology-based delineations of brainstem auditory nuclei.



Disclosures: J. Guerrero-Gonzalez: None. **N. Adluru:** None. **G. Kirk:** None. **S. Kecskemeti:** None. **O.J. Surgent:** None. **D. Dean:** None. **A.L. Alexander:** None. **B. Travers:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.07

Topic: A.07. Developmental Disorders

Support: MH118388
MH114976
MH123154
MH118451
MH109685
MH109685-04S1

Title: Defining Neurophysiological Subgroups in Autism Spectrum Disorder using Resting-State Connectivity

Authors: *A. M. BUCH[1,2], L. GROSENICK[2], P. VERTES[3], J. SEIDLITZ[4,5], S. KIM[2], C. LISTON[2]; [1]Cornell Univ. / Weill Cornell Medic Neurosci. Program, New York, NY; [2]Psychiatry and Brain and Mind Res. Inst., Cornell Univ. / Weill Cornell Med. Col., New York, NY; [3]Psychiatry, Univ. of Cambridge, Cambridge, United Kingdom; [4]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [5]Child and Adolescent Psychiatry and Behavioral Sci., Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Autism Spectrum Disorder (ASD) describes a diverse group of neurodevelopmental disorders encompassing a wide range of clinical impairments. The two core symptoms that define ASD are social communication impairments and restricted and repetitive behaviors, and there is a wide range of cognitive and language abilities. How distinct neurobiological substrates give rise to differing clinical symptoms in subsets of ASD patients is unknown. Using a large, publicly available neuroimaging dataset comprising resting state functional magnetic resonance imaging (rsfMRI) scans from N=299 subjects with ASD and N=907 neurotypical controls, we identified three latent dimensions of functional brain network connectivity that predict individual differences in ASD symptoms and behaviors. We show that patients with ASD can be grouped into distinct neurophysiological subgroups based on patterns of dysfunctional connectivity and clinical behaviors. In this cohort, functional connectivity features were extracted from rsfMRI data, regularized canonical correlation analysis was used to identify associations between connectivity features and behavioral data, and ASD subjects were clustered along these dimensions. Cross-validation analyses showed high stability in the brain-behavior dimensions, with replicable clusters in held-out data. Next, we integrated neuroimaging data with gene expression data from the Allen Human Brain Atlas, and found that within each subgroup, ASD-related functional connectivity was explained by regional differences in the expression of distinct gene sets that were enriched for ASD-associated genes (SFARI database) and different molecular associations. In sum, our results identify discrete ASD subgroups associated with specific ASD behaviors and neurophysiological signatures, and these different forms of ASD implicate distinct genetic mechanisms. The results of this study suggest a promising new approach for understanding the neurobiological substrates of ASD.

Disclosures: A.M. Buch: None. **L. Grosenick:** None. **P. Vertes:** None. **J. Seidlitz:** None. **S. Kim:** None. **C. Liston:** None.

Poster

P040. Autism: Behavioral Analysis I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P040.08

Topic: A.07. Developmental Disorders

Support: Hartwell Foundation
Stanford Bio-X
Stanford PHIND

Title: Joint Analysis of Shared Familial Psychiatric and Genetic Characteristics for Synthetic Phenotypes: Application to Autism Spectrum Disorder

Authors: K. PASKOV[1], ***N. T. STOCKHAM**[2], D. WALL[3];
[1]Biomed. Informatics, [2]Neurosciences IDP, [3]Pediatrics, Stanford Univ., Stanford, CA

Abstract: The genetic architecture of complex psychiatric disorders has remained elusive despite the rise of national-scale genomic and phenotypic databases and tens of thousands of cases and controls. In the field of Autism Spectrum Disorder (ASD) recent work by Warrier,V et al. (2019) demonstrate the genetic dissociation of social and non-social ASD-associated traits in larger populations, implying that the social and non-social traits in ASD may actually reflect distinct genetic etiologies. Parsing the genetic architecture of complex diseases will likely require analysis of more specific phenotypes than simply case/control status. However, it is extremely difficult apriori to define a psychiatric phenotypic measure that captures a relevant genetic effect. Moreover confirming that a proposed trait does reflect an underlying genetic effect typically requires twin studies that may be cost-prohibitive or simply infeasible. To address this difficultly we have developed a computational method that leverages nuclear family-based Identity-by-Descent (IBD) statistics to create synthetic phenotypes that are consistent measures of genetic variation. This method can be applied using full or half siblings, and furthermore this IBD approach avoids confounding by environment and population substructure, thereby recovering a key advantage of twin studies. We demonstrate this method on the Autism Genetic Resource Exchange (AGRE), the Simons Simplex Collection (SSC), and the Simons SPARK cohorts for ASD. We recapitulate the twin-analysis heritability estimates of the subdomains of the Autism Diagnostic Interview Revised (ADIR) and the Social Communication Questionnaire (SCQ) in each cohort. Instead of attempting to find a genetic basis for an already defined psychiatric phenotype, this work uses genetic and familial information directly to define synthetic psychiatric phenotypes. This approach is cost-effective, only requiring inexpensive genotyping arrays as available from consumer vendors and small families. Furthermore, by avoiding the confounding factors of population substructure and environment this IBD method permits the analysis of large heterogeneous populations. In this work we emphasize simultaneous analysis of genetic IBD and phenotype as a complementary approach to the current paradigm of searching for causal genetic variants for a given disorder; we focus instead on the study of causal mechanisms that explain shared familial psychiatric phenotypes through shared genetic architecture.

Disclosures: K. Paskov: None. **N.T. Stockham:** None. **D. Wall:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.01

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSERC RGPIN-2019-04925

Title: SLC17A9 is likely a resident ER/Golgi protein rather than a vesicular protein based on colocalization analyses and phylogenetic analysis of protein trafficking motifs.

Authors: *G. JENSEN[1], *G. JENSEN[2], A. DOS SANTOS[2], E. ABBASI[2], J. YANG[2], L. GASTALDELLO[2], S. RAYNER[2], D. POBURKO[2];
[2]Biomed. Physiol. and Kinesiology, [1]Simon Fraser Univ., Burnaby, BC, Canada

Abstract: BACKGROUND: Purinergic signaling is essential for neurogenesis, neuroglial communication, and neuropathic pain perception. The vesicular nucleotide transporter (SLC17A9/VNUT) is an important player in ATP release, as it is needed to load vesicles with ATP. While vesicular glutamate, acetylcholine and norepinephrine transporters are found on small synaptic vesicles, VNUT does not typically colocalize with these markers in mammalian models. It is unclear if it localizes to synaptic vesicles or another membrane bound organelle. There is little imaging data to show VNUT localizing to such vesicles. In central and peripheral nerves of rats and mice, VNUT does not colocalize with VGLUT or VMAT2. In glial cells and epithelial cells, VNUT is reported to be found in lysosomes rather than small vesicles. METHODS: We compared the primary sequence of VNUT between chordates ranging from cartilaginous fish to snakes using regex search tools in R to assess whether VNUT contains C-terminal dileucine and tyrosine motifs that are essential for synaptic vesicle localization of SLC17A5-8 and SLC18A2-3. We also conducted blob-based, epifluorescence colocalization analyses of VNUT with markers of synaptic vesicles (Syt1, Syt2, Syt5, SV2a, Synapsin), active zones (ELKS1), lysosomes (LAMP1), ER and Golgi in Neuro2A neuroblastoma cells, along with A7r5, HeLa and HEK293 cells using both antibodies and fluorescent protein conjugated marker proteins. RESULTS: Across species, VNUT has high variability in the length and primary sequence of the N-terminus and S6-7 cytosolic loop. The C-terminus is shorter than other vesicular transporters and is highly conserved between phylogenetic Classes. Dileucine and tyrosine-based motifs are absent in sharks and mammals but appear in sauropods. We found a C-terminal KDEL-like sequence (HEDL) that is unique to mammalian VNUT. We assessed colocalization as the fraction of regions of interest (ROIs) for a reference marker (e.g., VNUT) with a nearest neighbor marker whose center was within the ROIs border. VNUT colocalization with vesicle markers and lysosomal markers ranged from ~10-30%, only slightly above colocalization of randomized ROIs. In contrast, EGFP-VNUT is highly colocalized with mTagBFP2-ER-5 and mDsRed-Golgi-7 expression constructs (>70%). CONCLUSION: Mammalian VNUT seems to lack canonical, vesicle-localization motifs, while endogenous and exogenous VNUT localize mainly to the ER and Golgi. This localization suggests that vesicular release of ATP may rely on vesicles acquiring ATP at the Golgi or axonal Golgi outposts rather than being loaded by a pump on the vesicle membrane.

Disclosures: G. Jensen: None. **A. Dos Santos:** None. **E. Abbasi:** None. **J. Yang:** None. **L. Gastaldello:** None. **S. Rayner:** None. **D. Poburko:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.02

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: In silico studies of spontaneous purinergic neurotransmission on urinary bladder smooth muscle with special reference to overactive bladder

Authors: *C. MAHAPATRA[1,2], R. MANCHANDA[3];
[1]Indian Inst. of Technol. Bombay, Mumbai, India; [2]Cardiovasc. Res. Inst., Univ. of California San Francisco, San Francisco, CA; [3]Indian Inst. of Technol. Bombay, Mumbai, India

Abstract: The overactive bladder (OAB) syndrome, which is characterized by a sudden urge to urinate, has substantial negative effects on physical, social, and emotional functioning. A plethora of clinical and experimental studies have supported the association of OAB with elevated frequency of spontaneous action potentials (sAP) in urinary bladder smooth muscle (UBSM) cells. The spontaneous purinergic neurotransmission (SPN) evokes spontaneous excitatory junction potential (sEJP) to initiate sAPs in UBSM cells. Information on how these sEJPs modulate the shape and time course of sAPs is sparse because of underlying complexities in the experimental setup. An in-silico investigation of the UBSM cell is established to advance our understanding of the electrophysiological basis of sAP modulation because of SPN. The UBSM cell membrane is described as an equivalent electrical circuit comprising a membrane capacitance connected in parallel with several variable conductances representing nine ion channels. This model has incorporated voltage-gated Ca^{2+} (T - type and L- type) channels, three voltage-gated potassium (Kdrs, Kdrf and Ka) channels, and two calcium-dependent potassium (BK and SK) channels. The ion channels are biophysically detailed and validated with experimental data. Multiple UBSM cells are connected via gap junctions to investigate the propagation of sEJP from one cell to another cell. The purinergic synaptic conductance profile is comprising a sum of two exponentials and defined by synaptic conductance, maximum synaptic conductance, and time constant for both rising and decay phases. The resting membrane potential (RMP) is set at ─50mV by balancing the depolarizing currents and repolarizing currents through various ion channels. The AP is characterized by rising (depolarizing) phase, falling (repolarizing) phase, and presence of an after-hyperpolarization (AHP) or after depolarization (ADP) phase. The AP with lower synaptic conductance (0.0001 μs) shows ─10mV of AHP and a slow rise in the depolarization phase. However, the AP with higher synaptic conductance (0.0002 μs) shows 5mV of ADP and a fast rise in the depolarization phase. It is observed that L-type Ca^{2+} channel is essential for AP generation in an isolated cell. However, the activation of both L-type and T-type Ca^{2+} channels is essential for AP generation in cells with propagated sEJP. As the maximum synaptic conductance is directly proportional to the amount of purinergic neurotransmission, an important implication of our simulation result is that the shape and time course of sAPs are purely neurogenic. Therefore, a moderate dose of antipurinergic drugs will be beneficial to treat OAB.

Disclosures: C. Mahapatra: None. **R. Manchanda:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.03

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSFC grant 81821092
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Beijing Municipal Science & Technology Commission Z181100001318002
Beijing Municipal Science & Technology Commission Z181100001518004
National Key R&D Program of China 2020YFE0204000
National Key R&D Program of China 2019YFA0801603

Title: An ultrasensitive GRAB sensor for detecting extracellular ATP in vitro and in vivo

Authors: *Z. WU[1,2], K. HE[1,2], Y. CHEN[3], H. LI[4], S. PAN[1,2,5], B. LI[1,2], T. LIU[4], H. WANG[1,2], J. DU[4], M. JING[3], Y. LI[1,3,2,5];
[1]State Key Lab. of Membrane Biology, Peking Univ. Sch. of Life Sci., Sch. of Life Sciences, Peking Univ., Beijing City, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [3]Chinese Inst. for Brain Res., Beijing, China; [4]Inst. of Neuroscience, State Key Lab. of Neurosci., Ctr. for Excellence in Brain Sci. and Intelligence Technology, Shanghai Res. Ctr. for Brain Sci. and Brain-Inspired Intelligence, Chinese Acad. of Sci., Shanghai, China; [5]Peking-Tsinghua Ctr. for Life Sci., Acad. for Advanced Interdisciplinary Studies, Peking Univ., Beijing, China

Abstract: The purinergic transmitter ATP (adenosine 5'-triphosphate) plays an essential role in both the central and peripheral nervous systems, and the ability to directly measure extracellular ATP in real time will increase our understanding of its physiological functions. We developed an ultrasensitive GPCR Activation–Based ATP sensor called $GRAB_{ATP1.0}$, with a robust fluorescence response to extracellular ATP when expressed in several cell types. This sensor has sub-second kinetics, ATP affinity in the range of tens of nanomolar, and can be used to localize ATP release with subcellular resolution. Using this sensor, we monitored ATP release under a variety of in vitro and in vivo conditions, including primary hippocampal neurons, a zebrafish model of injury-induced ATP release, and LPS-induced ATP-release events in individual astrocytes in the mouse cortex measured using in vivo two-photon imaging. Thus, the $GRAB_{ATP1.0}$ sensor is a sensitive, versatile tool for monitoring ATP release and dynamics under both physiological and pathophysiological conditions.

Disclosures: Z. Wu: None. **K. He:** None. **Y. Chen:** None. **H. Li:** None. **S. Pan:** None. **B. Li:** None. **T. Liu:** None. **H. Wang:** None. **J. Du:** None. **M. Jing:** None. **Y. Li:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.04

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSERC RGPIN-2019-04925

Title: Novel VNUT-pHluorins and the GRAB-ATP sensor reveals that VNUT can support ATP release despite being localized to the ER/Golgi in N2a and A7r5 cells.

Authors: L. GASTALDELLO[1], J. YANG[1], *D. POBURKO[1,2];
[1]Biomed. Physiol. and Kinesiology, [2]Ctr. for Cell Biology, Develop. and Dis., Simon Fraser Univ., Burnaby, BC, Canada

Abstract: BACKGROUND: Purinergic signaling by ATP plays important roles in neurogenesis, neuroglial communication, neuropathic pain perception, and diverse roles outside of the nervous system. ATP can be released by vesicular mechanisms and pannexin channels, and the vesicular nucleotide transporter (VNUT/SLC17A9) is widely accepted to mediate the loading of secreted vesicles with ATP. The fusion of pHluorins, pH-sensitive GFPs, into lumen facing domains of transporters for neurotransmitters like glutamate and catecholamines provided valuable tools to study the regulation of vesicle release and recycling. We aimed to create a VNUT-pHluorin to better understand the regulation of vesicular ATP release. METHODS: We used the CCTOP server and comparison with SLC17A5 (sialin) and SLC17A6-8 (VGLUT1-3), to predict VNUT's 12 transmembrane domains and insert superecliptic pHluorin into the s1-2, s7-8 and s11-12 loops of rat VNUT (NM_001108613.1) and s3-4 loop of a mouse-codon optimized human VNUT (NM022082). We also fused the s1-2 loop of VGLUT-pHluorin into VNUT's s1-2 loop, and we made a red VMAT2-pHuji. To visualize ATP release we used the Li Lab's GRAB-ATP. Constructs were expressed in mouse Neuro-2a (N2a) and rat smooth muscle A7r5 cells. RESULTS: We assessed surface localization and the pH of pHluorin-containing organelles by changing external pH or puffing NH4Cl or sodium butyrate onto cells. The s3-4, s7-8 and s11-12 pHluorins localized to a neutral (pH 7.0-7.5), diffuse organelle, likely the endoplasmic reticulum (ER). The s1-2 and VNUT::VGLUTs1-2 pHluorins localized to ER and a perinuclear locus with a pH ~6.5 that colocalized with a RFP-labelled Golgi marker. Small acidic puncta were seen in A7r5 cells, but not in N2a cells. Depolarization (105 mM KCl) and hypotonic stress (0.5x imaging buffer), but not ionophores (A23187, ionomycin), stimulated ATP release as seen with GRAB-ATP, but failed to cause VNUT-pHluorin externalization. A second, but not initial, release of ATP was blocked with the VNUT inhibitor clodronate (5 µM, 5 hr). By comparison, VMAT2-pHuji largely localized to small, mobile acidic (pH 5.5-6.0) vesicles that were externalized on some cells, but were not released upon stimulation of the cells. CONCLUSION: VNUT's s1-2 loop is the optimal position for a lumen-facing pHluorin. VNUT seems to be an ER/Golgi resident protein that poorly traffics to acidic vesicles in N2a and A7r5 cells. Clodronate's inhibition of a second bout of ATP release suggests that VNUT-dependent loading of vesicles occurs at the Golgi and or Golgi outposts, rather than at the site of release and recycling, which would be a paradigm shift in our understanding of vesicular ATP release.

Disclosures: L. Gastaldello: None. **J. Yang:** None. **D. Poburko:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.05

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Florida State University Start-up Funding

Title: Differential modulation of acetylcholine signaling on anterior and posterior paraventricular thalamic neurons

Authors: *Q. YE, X. ZHANG;
Psychology, Florida State Univ., Tallahassee, FL

Abstract: Paraventricular nucleus of thalamus (PVT) connects brain structures such as the brainstem, zona incerta, and the hypothalamus to the nucleus accumbens and the amygdala for the regulation of the motivated behaviors including feeding and drug addiction. Both glutamatergic and GABAergic neurotransmissions have been recently studied for the modulation of PVT neurons and the control of food intake. However, it remains unknown whether other neurotransmitters also regulate feeding by modulating the activity of PVT neurons. Although the midbrain-originated cholinergic axons have been found in PVT, little is known about the function and modulation of cholinergic signaling in PVT. In this study, we used slice patch-clamp recordings to functionally characterize the effects of acetylcholine (ACh) on PVT neurons. We found that 60% of anterior PVT (aPVT) neurons were excited by ACh, 23% were inhibited, and the rest (17%) were nonresponsive. The ACh-induced excitation was mimicked by the nicotinic acetylcholine receptor (nAChR) agonist nicotine and blocked by the nAChR antagonist mecamylamine in 67% of ACh-excited neurons. However, the selective alpha7 nAChR antagonist methyllycaconitine (MLA) produced little effect on ACh activation of aPVT neurons. In contrast, ACh inhibited 70% of posterior PVT (pPVT) neurons and the inhibitory effect was blocked by the muscarinic acetylcholine receptor (mAChR) antagonist atropine, indicating mAChRs contribute to ACh inhibition of pPVT neurons. The remaining pPVT neurons were excited (8%) by ACh or had no response. Together, these preliminary data suggest that ACh excites aPVT neurons by activating nAChRs but inhibits pPVT neurons via binding to mAChRs. In future studies, we will study how PVT is functionally innervated by midbrain ACh projections and whether the differential modulation of ACh on aPVT and pPVT regulates food intake using optogenetics and virus-based neural circuit mapping.

Disclosures: Q. Ye: None. **X. Zhang:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.06

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Striatal fiber photometry reflects primarily non-somatic activity

Authors: *A. LEGARIA[1], B. YANG[3], B. AHANONU[4], J. A. LICHOLAI[5], J. G. PARKER[6], A. V. KRAVITZ[2];
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Abstract: Calcium recording via fiber photometry is commonly used as a proxy for recording population neuronal activity in vivo, yet the biological source of the photometry signal remains unclear. Here we used simultaneous in vivo extracellular electrophysiology and fiber photometry in the striatum, along with endoscopic 1-photon and 2-photon calcium imaging in mice, to investigate the electrophysiological correlates of fiber photometry recordings. We found that fiber photometry transients correlate only moderately (r2 ~ 0.3) with spiking activity. Furthermore, we found that in both 1-photon and 2-photon calcium imaging, fiber photometry has a very strong correlation with changes in non-somatic calcium, but only moderate correlations with changes in somatic calcium.

Disclosures: A. Legaria: None. **B. Yang:** None. **B. Ahanonu:** None. **J.A. Licholai:** None. **J.G. Parker:** None. **A.V. Kravitz:** None.

Poster

P083. Small-Molecule Neurotransmitters

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P083.07

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Chair in Neuroscience UAM-Fundación Tatiana Pérez de Guzmán el Bueno (C.C and I.P.-S.)
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Title: Noradrenaline innervation and alpha receptors in the primate mediodorsal and pulvinar thalamic nuclei

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Abstract: The mediodorsal (MD) and pulvinar nuclei are the two main primate Higher Order nuclei. In the macaque brain, they are within the most densely innervated by NA and display high alpha adrenoceptor concentrations. The purpose of this study is to compare the patterns of NA innervation and adrenoceptors in the macaque and human MD and pulvinar nuclei. NA axons in the human thalamus were revealed by immunostaining against the noradrenaline transporter and mapped with the software Neurolucida®. The alpha adrenoceptors were analyzed by Quantitative autoradiography using the following ligands: [3H]-Prazosin to reveal alpha-1 receptors, [3H]-RX-821002 to reveal whole alpha-2 adrenoceptor population, and [3H]-UK-14,304 to reveal high-affinity state alpha-2 adrenoceptor. The distributions of axons and receptors were compared to previously published data from macaques. The human MD had a moderate NA innervation, with the highest densities in the medial and ventral regions. Within the human pulvinar complex, the oral pulvinar nucleus (Pul O) had the highest NA innervation; the medial pulvinar (Pul M) showed moderate densities of NA axons, and the lateral and inferior pulvinar (Pul L, Pul I) displayed low NA axon densities. Regarding alpha-1 adrenoceptors, the highest densities were present in the dorsal and medial regions of MD, and in the medial regions of Pul M. alpha-2 receptor concentrations were highest in Pul I. Pul O showed high alpha-2 receptor revealed by [3H]-RX-821002 but rather low revealed by [3H]-UK-14,304 suggesting that this nucleus has a low proportion of high-affinity alpha-2 receptors. Overall, the distributions of NA axons and alpha adrenoceptors in the human MD and pulvinar nuclei are similar to those in macaques, but some differences are present: alpha-1 receptor concentrations are higher in macaques than in humans, and the high-affinity alpha-2 receptor concentrations in the Pul O are higher in macaques.

Disclosures: I. Pérez-Santos: None. **N. Palomero-Gallagher:** None. **K. Zilles:** None. **C. Cavada:** None.

Poster

P083. Small-Molecule Neurotransmitters

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Program #/Poster #: P083.08

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH MH094527
NIH/NINDS NS116914
NIH F32 MH120966-01

Title: Serotonergic IL-1R1 modulates serotonin transporter activity and impacts neuronal activity after LPS in a sex-dependent manner

Authors: *P. GAJEWSKI-KURDZIEL[1], A. TILLMAN[1], N. L. BAGANZ[2], M. J. ROBSON[3], N. QUAN[2], R. D. BLAKELY[2];
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Abstract: Dysfunction of serotonin (5-HT) producing and/or responsive circuits is believed to support the expression of behaviors observed in neuropsychiatric disorders including depression, autism, and schizophrenia. The presence of elevated inflammatory cytokines in subjects with mood disorders and the significant comorbidity of neuropsychiatric disorders with chronic inflammatory conditions suggests a commonality in the manifestation of these conditions. However, exact relationships remain ill-defined, leaving a gap in the development of mechanism-based treatments. Inflammatory cytokines impact multiple aspects of neural signaling, but neuronal expression of cytokine receptors has not been extensively characterized. We and others have shown that 5-HT neurons of the raphe express high levels of the receptor for IL-1β (IL-1R1). Interestingly, mRNA studies suggest a non-uniform expression of IL-1R1 throughout distinct raphe subregions, suggesting discrete 5-HT circuits contribute to the behavioral output of CNS IL-1β. We have shown in mouse brain synaptosomes that activation of the peripheral innate immune system as well as direct exposure to IL-1β rapidly increases the activity of the presynaptic 5-HT transporter (SERT), a key protein for the control of extracellular serotonin availability and signaling. Here we report the use of multiple approaches to validate the actions of serotonergic IL-1R1 on SERT function and search for evidence of circuit-specific sensitivity to serotonergic IL-1R1 activation. Using a transgenic approach to knockout serotonergic IL-1R1, we show that the ability of peripheral LPS treatment to stimulate SERT in midbrain synaptosomes is lost. Consistent with these findings, high-speed chronoamperometry in hippocampal CA3 reveals that local IL-1β speeds up 5-HT clearance. Additionally, serotonergic IL-1R1 activation is in part responsible for the ability of peripheral immune activation to modulate neuronal activity of distinct regions innervated by 5-HT neurons. In these studies, we find distinct sex-dependent differences in the role of serotonergic IL-1R1 in LPS induced cFos production in areas including septum and lateral habenula. We are currently using retrograde tracing to confirm the projection of IL-1R1 expressing 5HT neurons to these sites and hypothesize that the changes in activation observed represent circuit level contributions of serotonergic IL-1R1 to the ability of peripheral immune activation to drive behavior. Altered signaling by these circuits may support neuropsychiatric disorders which may be testable through human brain imaging approaches and remediable by immunosuppressive treatments.

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Poster

P083. Small-Molecule Neurotransmitters

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Program #/Poster #: P083.09

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH grant MH103222

Title: The Protobiotic Lactobacillus reuteri Preferentially Synthesizes Kynurenic Acid from Kynurenine

Authors: *F. M. NOTARANGELO, A. E. FOO, K. V. SATHYASAIKUMAR, R. SCHWARCZ; Psychiatry, Maryland Psychiatric Res. Ctr., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The gut-brain axis is increasingly understood to play a major role in a variety of neuropsychiatric disorders. Of special interest, studies in germ-free and antibiotic-treated rodents have revealed that intestinal bacteria can regulate cognitive functions in the host. Separate studies showed that metabolites of the kynurenine pathway (KP) of tryptophan degradation, and specifically the neuroactive KP metabolite kynurenic acid (KYNA), may link gut dysbiosis with cognitive impairments (Dehhaghi et al., 2019). *Lactobacillus (L.) reuteri*, a common and well-studied probiotic bacterium which is present in many mammals including humans, may play a special role in this context (e.g. Marin et al., 2017; Verbeek et al., 2021). We showed in a pilot study that newly produced KYNA can be readily recovered in the extracellular compartment after *L. reuteri*, suspended in Hank's Balanced Salt Solution, was incubated at 37°C with KYNA's immediate bioprecursor L-kynurenine. Interestingly, however, exposure to L-tryptophan did not generate KYNA. *De novo* synthesis of KYNA increased in a linear fashion with bacterial concentration (up to 10^8 CFU/ml), L-kynurenine concentration (up to 1 mM) and time (up to 3 hours) (Foo et al., 2019). Using the same experimental conditions (mostly 10^8 CFU/ml, 100 µM kynurenine, 3 hour incubation), we now examined the characteristics of L-kynurenine metabolism in greater detail. In line with studies in mammalian tissues, L-kynurenine readily entered the cultured cells, newly formed KYNA was promptly and essentially quantitatively released into the extracellular milieu, and KYNA neosynthesis was effectively blocked by either of two selective inhibitors of mammalian kynurenine aminotransferase II (PF-048559989 and BFF-122). However, in marked contrast to processes that are well-established in mammals, kynurenine uptake was *not* affected by tryptophan, leucine or other substrates of the large neutral amino acid transporter LAT-1 (all at 5 mM). Moreover, kynurenine was only minimally converted to 3-hydroxykynurenine and not at all to anthranilic acid, i.e. along the two other branches of the mammalian KP, and KYNA neosynthesis was *not* reduced by co-incubation with millimolar concentrations of presumed competitive enzyme substrates (α-aminoadipate and glutamine). Taken together, these results demonstrate substantive differences between bacterial and mammalian KP metabolism. Extrapolation to bacterial species other than *L. reuteri*, and especially possible implications for the effects of bacterial L-kynurenine metabolism on physiology and pathology in the host brain, are currently under investigation in our laboratory.

Disclosures: F.M. Notarangelo: None. **A.E. Foo:** None. **K.V. Sathyasaikumar:** None. **R. Schwarcz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KyNexis, VistaGen.

Poster

P110. LTP: Mechanisms and Properties

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P110.01

Topic: B.07. Synaptic Plasticity

Support: R01 - 5R56MH095980
NSF NN1 - 1707356
NSF NN2 - 2014862

Title: Quantifying the information capacity of synapses in hippocampal area CA1 and DG in rat

Authors: *M. SAMAVAT[1], T. M. BARTOL, Jr.[1], C. BROMER[1], D. D. HUBBARD[2], D. C. HANKA[2], M. KUWAJIMA[2], J. M. MENDENHALL[2], P. H. PARKER[2], W. C. ABRAHAM[3], K. M. HARRIS[2], T. J. SEJNOWSKI[1];
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Abstract: The substantial variability of synapse sizes motivated us to measure the precision and calculate the information capacity of spine head volumes (SHVs) that are known to have high correlation with synaptic strength. Three-dimensional reconstructions from serial section electron microscopy (3DEM) of dendrites in rat hippocampal area CA1 and dentate gyrus (DG) were analyzed. Motivated by our earlier study (Bartol et al, eLife 2015) we expanded and enhanced our protocol to overcome a limitation in the earlier study. The eLife work assumed that spines sharing the same dendrites and same axons (SDSA) would be most similar in activation histories, and thus synaptic strength. The CV between SDSA SHVs was computed to give the separation of peaks with an overlap of 31% between consecutive Gaussians spanning the range of SHVs for the SDSA pairs. Here we used information theory plus non overlapping clustering to determine the number of discrete clusters formed, based on all of the SHVs without overlap. The median CV of the SDSA pairs was used to determine the borders of each bin. The new analysis of all 288 SHVs in the prior CA1 cube revealed 24 distinguishable clusters of synaptic strength and entropy of 4.1 bits per synapse. New results show that the DG synapses are less precise than the CA1 synapses with a value of 5 and 6 distinguishable clusters and entropy of 2 and 2.05 bits for 30 min and 2 hours control synapses, respectively. Production of LTP increased the precision and boosted the number of distinguishable clusters of SHV to 10 at 30 min and 8 at 2 hours. In addition, the entropy of SHV increased relative to controls by 1 bit at 30 min and 0.7 bit at 2 hours post induction of LTP. Using the new protocol revealed that the KL divergence distance [H(P,Q)-H(P)] between the distribution of SHV clusters (P) and uniform distribution of states (Q) for the 2 hours LTP was less than half of the control condition. These findings imply that learning moves distributions of SHVs toward a more uniform distribution with maximum information.

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Poster

P110. LTP: Mechanisms and Properties

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P110.02

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01NS095123

Title: Effects of direct current stimulation on synaptic plasticity in a single neuron

Authors: *F. FARAHANI[1], G. KRONBERG[2], H. V. OVIEDO[1], L. C. PARRA[1];
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Abstract: Background: Transcranial direct current stimulation (DCS) has lasting effects that may be explained by a boost in synaptic long-term potentiation (LTP). We hypothesized that this boost is the result of a modulation of somatic spiking in the postsynaptic neuron. Previous studies with population activity provided only indirect evidence for this hypothesis. To test this directly, we record somatic spiking in a postsynaptic neuron during LTP induction with concurrent DCS. **Methods**: We performed whole-cell patch-clamp recordings at the soma of individual CA1 pyramidal neuron. LTP was induced with theta-burst stimulation (TBS) applied concurrently with DCS. To test the causal role of somatic polarization, we manipulated somatic polarization via somatic current injections. We also used a computational multi-compartment model of a CA1 pyramidal neuron that captures the effect of electric fields on membrane polarization and activity-dependent synaptic plasticity. **Results**: TBS-induced LTP was enhanced when paired with anodal DCS as well as depolarizing current injections. In both cases, somatic spiking in the postsynaptic neuron during the TBS was increased, suggesting that evoked somatic activity is the primary factor affecting LTP modulation. However, the boost of LTP with DCS was less than expected given the increase in spiking activity alone. In some cells, we also observed DCS-induced spiking, suggesting DCS also modulates LTP via induced network activity. The computational model reproduces these results and suggests that they are driven by both direct changes in postsynaptic spiking and indirect changes due to network activity. **Conclusion:** DCS enhances synaptic plasticity by increasing postsynaptic somatic spiking, however, we also find that an increase in network activity may limit this enhancement.

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Poster

P110. LTP: Mechanisms and Properties

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Program #/Poster #: P110.03

Topic: B.07. Synaptic Plasticity

Support: ERC Grant ADOS 339541
ERC Grant Dyn-Syn-Mem 787340
FRM Grant AMPA-MO-CO DEQ20180339189
CIHR Grant 158090
IdEx Grant

Title: Experimental model for high-resolution imaging and manipulation of endogenous AMPA receptor surface mobility during synaptic plasticity and behavioural adaptation

Authors: *A. M. GETZ[1], M. DUCROS[2], C. BREILLAT[1], A. LAMPIN-SAINT-AMAUX[1], S. DABURON[1], U. FRANÇOIS[1], H. ZIEGER[1], A. NOWACKA[1], M. FERNÁNDEZ-MONREAL[2], F. LANORE[1], M. SAINLOS[1], E. HOSY[1], Y. HUMEAU[1], D. CHOQUET[1,2];
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Abstract: Regulation of surface synaptic receptor content by reversible diffusing-trapping tunes synaptic function, in particular during experience-dependent plasticity and behavioural adaptation. However,

experimental approaches to track and modify receptor movements in integrated experimental systems are limited. Exploiting AMPA-type glutamate receptors (AMPAR) as a model system, we used CRISPR-Cas9 genome editing to generate a knock-in mouse line expressing the 15 amino acid biotin acceptor peptide tag (AP) on the extracellular N-terminus of GluA2 (AP-GluA2). Labelling specificity of AP-GluA2 containing AMPAR is achieved by the directed expression of biotin ligase (BirA), which selectively biotinylates the AP tag. Target-specific introduction of BirA allows the use of monovalent or tetravalent avidin variants (monomeric StreptAvidin (mSA) or NeutrAvidin (NA)) to respectively monitor or manipulate the surface mobility of endogenous AMPAR containing biotinylated AP-GluA2. Due to their small size, mSA (~3 nm) and NA (~6 nm) efficiently target membrane proteins in confined synaptic domains and organized brain tissue. This AP tag modification does not perturb GluA2 protein expression or localization, AMPAR channel function, synaptic physiology, or animal behaviour. We built a Lattice Light Sheet microscope and added a custom photostimulation module, where we performed FRAP imaging in organotypic hippocampal slices to measure the mobility dynamics of endogenous AMPAR. Using fluorophore-conjugated mSA, we found that AMPAR in CA1 stratum radiatum are highly mobile at extrasynaptic sites and more confined at synaptic ones. NA immobilized AMPAR and arrested surface mobility in both domains. Crosslinking of surface AMPAR by NA precluded the expression of LTP at CA3-CA1 synapses in acute slices, and in vivo delivery of NA into the CA1 region by implanted cannula blocked the formation of contextual fear memory. This knock-in mouse model represents a new genetic labelling strategy that enables target-specific measurement and control of the mobility dynamics of endogenous cell surface proteins in integrated experimental systems. For studying AMPAR dynamics, this system opens new possibilities to explore as-yet unanswered questions regarding the molecular links between synaptic plasticity and behavioural learning. With the CRISPR-Cas9 revolution in targeted genome engineering, this methodology can be adapted for the study of a large variety of synaptic proteins, with broad implications for advancing our understanding of brain organization and function.

Disclosures: A.M. Getz: None. **M. Ducros:** None. **C. Breillat:** None. **A. Lampin-Saint-Amaux:** None. **S. Daburon:** None. **U. François:** None. **H. Zieger:** None. **A. Nowacka:** None. **M. Fernández-Monreal:** None. **F. Lanore:** None. **M. Sainlos:** None. **E. Hosy:** None. **Y. Humeau:** None. **D. Choquet:** None.

Poster

P110. LTP: Mechanisms and Properties

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P110.04

Topic: B.07. Synaptic Plasticity

Support: CIHR

Title: Glun3a-containing nmda receptors limit long-term potentiation in the adult ventral hippocampus

Authors: *E. HURLEY, B. MUKERJEE, J. ADUNDO, F. NAFAR, L. FANG, M. PARSONS;
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Abstract: The dorsal and ventral hippocampus (DH and VH) are dramatically different structures. The DH is involved in cognition and undergoes robust synaptic plasticity, while the VH functions in emotional processing and exhibits poor plasticity. N-methyl-D-aspartate receptors (NMDARs) assemble as functionally diverse heterotetramers with essential roles in synaptic plasticity. Incorporation of the GluN3A subunit into NMDARs delays synapse maturity, opposes synaptic plasticity and alters conventional NMDAR properties. GluN3A-containing NMDARs have reduced sensitivity to magnesium (Mg^{2+}) and reduced calcium (Ca^{2+}) permeability. The GluN3A subunit was initially thought to be important in development, as expression is nearly eliminated in the adult brain. In agreement with recent reports, we show that GluN3A remains elevated, particularly in extrasynaptic locations, in the adult VH and not the DH. Despite GluN3A persistence, VH spines matched the maturity level observed for the DH. As presynaptic and postsynaptic GluN3A-NMDARs can facilitate glutamate release and blunt Ca^{2+} permeability, respectively, we performed real-time glutamate and calcium imaging experiments to further understand the consequences of GluN3A persistence in the adult VH. Compared to the DH, the VH accumulated more glutamate during afferent stimulation yet exhibited less NMDAR-mediated Ca^{2+} influx. We hypothesized that prolonged GluN3A expression acts as a brake on VH synaptic plasticity. Indeed, in wild type (WT) mice, long-term potentiation (LTP) was significantly lower in the VH compared to the DH. In contrast, GluN3A knockout (KO) mice exhibited strong VH LTP that exceeded the magnitude of LTP in the DH. Whole-cell patching of CA1 pyramidal neurons revealed an increase in glycine-induced currents in the WT VH. In addition, the Mg^{2+} sensitivity was significantly reduced in the WT VH. Together these results conclude that the VH has a higher number of GluN3A-containing NMDARs that assemble as functional GluN1/GluN3A excitatory glycine receptors and GluN1/GluN2/GluN3A containing glutamate receptors with reduced Mg-sensitivity. In sum, our data show that GluN3A persistence limits VH plasticity in adulthood, perhaps to serve a protective role to prevent overexcitation of anxiety and fear circuitry.

Disclosures: E. Hurley: None. **B. Mukerjee:** None. **J. Adundo:** None. **F. Nafar:** None. **L. Fang:** None. **M. Parsons:** None.

Poster

P110. LTP: Mechanisms and Properties

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Program #/Poster #: P110.05

Topic: B.07. Synaptic Plasticity

Support: Wellcome Trust/DBT India Alliance, grant number IA/I/12/1/500529

Title: Multiple pathways of store-driven calcium signaling shape the long-term dynamics of CA1 excitatory synapses

Authors: *S. NADKARNI[1], V. JALTARE[1,3], G. MAHAJAN[2];
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Abstract: A transient increase in the calcium concentration in dendritic spines drives activity-dependent long-term synaptic plasticity, which is believed to be a substrate for enduring information storage. While

calcium entry through NMDA receptors is a primary source for this calcium, additional pathways of calcium, associated with the endoplasmic reticulum (ER), are also likely involved in this process. Interestingly, the expression of both IP3 and ryanodine receptors (RyRs) is observed in the ER of predominantly large dendritic spines. The distinct biophysical properties of these receptors (calcium signaling through IP3 receptors can be slow and long-lasting, while RyRs respond in short and quick bursts of calcium) raises fundamental questions on the range of attributes bestowed to the spine by various sources and sinks of calcium. To address this gap in understanding, we developed a computational model of calcium signaling in an ER-bearing dendritic spine. We investigated the consequence of a wide range of physiological activity patterns on the induction of plasticity. Our model accurately captures the interplay among various components regulating calcium exchange between the cytosol, the ER, and the exterior. We show that 1) the differences in the kinetic profiles of the IP3 and RyR channels produce distinct effects on the rate-dependent plasticity profile, and 2) the store-operated calcium entry (SOCE) is involved during induction of both LTD and LTP when local depletion of the ER is taken into account. We further extend our model to include a biophysical description of receptor-trafficking-based structural plasticity to examine the scaling of calcium signaling with changing spine volume in the presence of the ER store. Altogether, results from the model provide a context for experimental findings and predict a considerable physiological impact of the ER store on the dynamic range of synaptic plasticity. When synapses of variable sizes were simulated, our results show that the presence of both IP3 and RyR receptors ER ensures effective and efficient use and re-use of synapses for storing information in the patterns of synaptic connection strengths.

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Poster

P110. LTP: Mechanisms and Properties

Location: Virtual Only

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Program #/Poster #: P110.06

Topic: B.07. Synaptic Plasticity

Support: Samsung science and technology foundation / SSTF-BA1602-11

Title: The role of beta-actin mRNA localization at single dendritic spines during structural long-term potentiation

Authors: *J. SHIM[1], H. AHN[1], B. LEE[1], H. MOON[2], H. CHOI[1], H. PARK[1];
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Abstract: mRNA localization and local translation in dendrites and axons are required for spatiotemporally efficient gene expression. A synaptic stimulus can induce localization of mRNA and local protein synthesis. Such stimulus-induced synaptic plasticity underlying learning and memory is represented in the form of long-term potentiation by spine volume changes. To investigate the physiological role of beta-actin mRNA localization in dendritic spines, we employed two-photon glutamate uncaging and glycine induced chemical LTP to stimulate dendrite spines. Hippocampal neurons cultured from the MCP × MBS knock-in mice in which all endogenous beta-actin mRNAs are

fluorescently labeled were used for live-cell imaging of beta-actin mRNA. Our results suggest that localization of beta-actin mRNA has a strong correlation with structural LTP process. This study sheds a light on the implication of beta-actin mRNA localization and local translation for LTP in neurons and their role in long-term memory formation.

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Poster

P110. LTP: Mechanisms and Properties

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Program #/Poster #: P110.07

Topic: B.07. Synaptic Plasticity

Support: SFB944

Title: Lack of tau in hippocampal CA1 neurons - what is altered?

Authors: N. D. MONTEIRO ABREU, N. I. TRUSHINA, M. HRYNCHAK, M. RIEROLA-CARRERA, K. TULVA, *R. BRANDT, L. BAKOTA;
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Abstract: Alzheimer's disease is a progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks. One of the key molecules that has been linked to the disease is the microtubule-associated protein tau since it is a principal component of the neurofibrillary tangles, which are present in neurons of the diseased brain. However, it is unknown how a protein that is primarily located in the axon shaft is involved in a disease that is believed to have a synaptic origin. In this regard, the function and morphology of CA1 neurons from tau knock out (tauKO - B6.129X1-Mapt^{tm1Hnd}/J) male mice were studied. Analysis of potential functional alterations in synaptic transmission was performed by microelectrode array (MEA) system. Induction of LTP by high-frequency stimulation (HFS) leads to a higher potentiation of the population spikes and fEPSP in 12-months-old tauKO mice. Interestingly, 3-months-old tauKO mice lose the ability of a potentiated response in the *stratum radiatum* over time, but not at the site of the generation of the action potential. To understand the potential reason for these differences, both the length and distance of axonal initial segments (AIS) were analyzed, revealing that tauKO mice generally have shorter AIS and in particular, AIS in the hippocampi of the 3-months-old mice are located further away from the soma than in control mice. The signal propagation down the dendritic branch appears unchanged in 12-months-old mice, because no difference was found in the length of dendrites or branching number between the two genotypes. However, tauKO mice at that age are possessing a higher fraction of mushroom spines on their dendrites. On a molecular level, mass spectrometry data showed that in 12-months-old tauKO mice the amount of $GABA_A$ receptor subunit is decreased. The data indicate that tau has a complex effect on synapse function, which is dependent on the developmental stage of the animals. This is of particular importance because current therapeutic strategies aim to reduce tau level in the brain of diseased patients.

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Poster

P110. LTP: Mechanisms and Properties

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Program #/Poster #: P110.08

Topic: B.07. Synaptic Plasticity

Support: NIH NS112706

Title: Mitochondria-dependent metabolic re-programming drives long term potentiation and synaptic maturation.

Authors: A. SHTEYMAN[1], H. ROLYAN[1], N. MNATSAKANYAN[1], J. WU[1], P. LICZNERSKI[2], R. ZUKIN[3], V. K. GRIBKOFF[4], *E. JONAS[1];
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Abstract: Long-term potentiation (LTP) and depression (LTD) are mechanisms of inherent synaptic plasticity of neurons and support the storage and recovery of memories in the mammalian brain. The ability to potentiate a synapse long-term is a model for long term memory formation. Our previous work has shown that the anti-apoptotic protein Bcl-xL not only prevents apoptosis, but also potentiates long-term synaptic responses. Here, we present that Bcl-xL is required for changes in ATP synthase stoichiometry that in turn induce dramatic changes in ATP levels in hippocampal neurons during LTP stimulation and progression. Using fluorescence imaging with a FRET based ATP construct (ATeam) in live hippocampal neurons, we find that LTP induction causes a sharp decrease in ATP levels followed by a persistent long-term increase in ATP production, suggesting that intense synaptic stimulation causes neuronal ATP synthase to become metabolically more efficient. In agreement with this, the later increase in ATP levels is associated with decreases in oxygen consumption by single neurons, with maturation of dendritic spines and with insertion of AMPA receptors into the plasma membrane. The LTP-associated increase in ATP levels and maturation of dendritic spines is blocked by application of Bcl-xL specific inhibitors and by inhibition of mitochondrial ATP synthase activity. Bcl-xL and ATP synthase inhibition also prevent LTP-induced increase in surface glutamate receptor insertion. During LTP, components of the ATP synthase are synthesized. This causes a change in stoichiometry of the ATP synthase, decreasing the ratio of free membrane-bound c-subunit to assembled ATP synthase. The increase in ATP production efficiency results in localized ATP production required for CAMKII and AMPA-serine 845 phosphorylation. The latter phosphorylation events are prevented by Bcl-xL inhibition and by ATP synthase inhibition. In hippocampal slice recordings, inhibition of Bcl-xL impairs early stage LTP and prevents late stage LTP. Our findings suggest that long-term changes in mitochondrial efficiency brought on by activity-dependent Bcl-xL translocation to mitochondria are required for LTP and shed light upon the role of mitochondrial metabolic plasticity in acute induction and long-term maintenance of learning and memory formation. If such mitochondria-dependent metabolic changes fail to occur, synaptic dysfunction and neurodegeneration may ensue.

Disclosures: A. Shteyman: None. **H. Rolyan:** None. **N. Mnatsakanyan:** None. **J. Wu:** None. **P. Licznerski:** None. **R. Zukin:** None. **V.K. Gribkoff:** None. **E. Jonas:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.01

Topic: B.08. Intrinsic Membrane Properties

Title: $Ca_v1.3$ calcium channels are simple linear amplifiers of firing activity in DA SN neurons

Authors: *J. SHIN[1], L. KOVACHEVA[1], D. THOMAS[2], S. STOJANOVIC[1], C. A. PALADINI[3], G. GEISSLINGER[2], J. STRIESSNIG[4], J. ROEPER[1];
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Abstract: Studying the role of Cav1.3 channels in dopamine neurons of the substantia nigra pars compacta (DA SN) and its potential relevance in the context of neuroprotection in Parkinson disease has been complicated due to the lack of selective pharmacological targeting. We combined on-cell, whole-cell and perforated patch-clamp recordings of labelled and identified DA SN neurons in acute slice preparations of 8 - 12 weeks old C57BL6/N wildtype and Cav1.2 $DHP^{-/-}$ knockin mice. In the latter, only Cav1.3 channels are sensitive to dihydropyridines (DHP) like isradipine, while the DHP binding site of Cav1.2 has been rendered non-functional by mutagenesis. We demonstrate that in vitro autonomous pacing is amplified by Cav1.3 channels with a linear gain of about 30% of the intrinsic baseline frequency. The Cav1.3 gain was unaffected by somatodendritic D2 autoreceptors or the presence of DHP-sensitive Cav1.2 channels in wildtype mice, suggesting a universal role of Cav1.3 channels as a rate-dependent linear amplifier in DA SN neurons. To characterize Cav1.3 channel function across the entire dynamic firing range of DA SN neurons observed in vivo (ca. 1-50 Hz), we utilized the dynamic-clamp technique for evoking these frequencies via in silico NMDAR conductances. By using 300 nM isradipine, we demonstrated that Cav1.3 channels linearly amplified firing frequencies across the entire range selectively in lateral DA SN neurons. We also evaluated clinically relevant (3 - 10 nM) concentrations of isradipine in vitro in a similar fashion. These low nanomolar concentrations partially reduced lateral DA SN firing across the dynamic range by about 25%, consistent with incomplete Cav1.3 channel inhibition. We then tested whether in vivo firing of lateral DA SN neurons was selectively reduced by 25% upon systemic application of isradipine (3 mg kg-1) as predicted by our in vitro experiments. Our in vivo recordings confirmed these predictions for lateral DA SN neurons and also demonstrated that medial DA SN neurons were not affected in vivo by clinically relevant concentrations of israpipine. Our study demonstrated that Cav1.3 channels function as linear amplifiers of autonomous pacemaking and selectively boost firing frequency in vivo across the entire dynamic firing range of lateral DA SN neurons. We also show that targeting the highly vulnerable DA neurons in the lateral SN with DHPs in the clinical concentration range is feasible and might be applicable in Parkinson Disease.

Disclosures: J. Shin: None. **L. Kovacheva:** None. **D. Thomas:** None. **S. Stojanovic:** None. **C.A. Paladini:** None. **G. Geisslinger:** None. **J. Striessnig:** None. **J. Roeper:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.02

Topic: B.08. Intrinsic Membrane Properties

Support: R37AG008796

Title: R and T-type Ca2+ channels underlie persistent firing in LEC III pyramidal neurons

Authors: *C. LIN, M. M. OH, J. F. DISTERHOFT;
Physiol., Northwestern Univ., Chicago, IL

Abstract: Persistent firing in LEC III has been shown to underlie associative learning and memory (Fuster, 1972, Lin et al, 2020). However, the mechanisms that underlie this phenomenon are yet to be determined. There have been many candidates, including Ca2+-activated nonselective cation (CAN) channels (Fraser and MacVicar, 1996; Tahvildari et al, 2008), Ether-a-Go-Go Related Gene (ERG) channels (Cui and Stowbirdge, 2018), transient receptor potential canonical (TRPC) channels (Arboit et al, 2020), voltage-gated Ca2+ channels (Fraser and MacVicar, 1996, Tahvildari et al, 2008), and persistent Na+ currents (Zylberberg and Stowbridge, 2017).
Although the channels that underlie persistent firing are still unknown, Ca2+ seems to be an important component of the mechanism (Tahvildari et al, 2008, Lin et al, 2020). We have determined that the R/T-Types, but not L-type voltage-gated Ca2+ channel contribute to persistent firing in LEC III pyramidal neurons. Application of Ni2+ (a blocker of R/T-type channels) eliminates the afterdepolarization (ADP) and plateau potential (PP) that underlies persistent firing and prevents firing. Application of nimodipine (blocker of L-type Cav1.2 channels) and isradipine (blocker of L-type Cav1.3 channels), however, had no effect on the ADP or persistent firing.
Future experiments will continue to determine the specific contributions of R vs. T-type channels and the overall role that these channels play in eliciting persistent firing.

Disclosures: C. Lin: None. **M.M. Oh:** None. **J.F. Disterhoft:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.03

Topic: B.08. Intrinsic Membrane Properties

Support: DBT/Wellcome Trust India Alliance [Senior Fellowship No. IA/S/16/2/502727]
Revati and Satya Nadham Atluri Chair Professorship
the Department of Biotechnology through the DBT-IISc partnership program
Ministry of Education, Govt. of India

Title: Dominant role of calcium and calcium-dependent potassium channels in regulating complex spike bursting in a heterogeneous population of CA3 pyramidal neuron models

Authors: *R. ROY[1], R. NARAYANAN[2];
[1]Indian Inst. of Sci., Bengaluru, India; [2]Indian Inst. of Sci., Bangalore, India

Abstract: Complex spike bursting (CSB) is a characteristic neuronal signature exhibited by hippocampal CA3 pyramidal neurons. Although complex burst patterns have been implicated in place cell formation and in inducing synaptic plasticity, assessment of the heterogeneities in the ionic mechanisms underlying CSB generation in CA3 pyramidal neurons remains unexplored. In this study, we employed an unbiased stochastic search algorithm (involving 11 ion channels and 14 parameters) to generate a heterogenous population of morphologically realistic CA3 pyramidal neurons models that accounted for their ion-channel kinetics, gating properties, and associated heterogeneities. We validated 12,000 stochastically generated models against 11 signature electrophysiological intrinsic measurements, and found 236 valid models. These valid models were endowed with broad distributions of underlying parameters showing weak pair-wise correlations. We found two functional subclasses of valid models, intrinsically bursting (IB; n=67) and regular spiking (RS; n=169), which exhibited two distinct clusters in the parametric space with both linear (PCA) and non-linear (t-SNE) dimension reduction analyses. As the clustering was predominantly along the first principal component, which aligned with the parametric axes for calcium and calcium-activated conductances, we tested if those parameters were different between the two subpopulations. We found the N-type calcium (CaN) conductance to be significantly higher and the small-conductance calcium-activated potassium (SK) conductance to be significantly lower for IB neurons compared to RS neurons. We then triggered CSB in all 236 models by subjecting them to 5 different kinds of inputs, and observed considerable heterogeneity in their propensity for exhibiting CSB. Quantitatively, these models manifested heterogeneities in the 3 characteristic signatures of CSBs: (i) amplitude difference between the first and the last action potential within the CSB; (ii) sub-threshold ramp voltage; and (iii) CSB rate with 4 consecutive pulse-current inputs. Finally, we employed virtual knockout analyses involving 7 voltage- and/or calcium-dependent channels as well as NMDA receptors, and showed that synergistic interactions among several ion channels regulated CSB. Of these different ion channels and receptors, we found dominant roles for NMDA receptors as well as CaN and SK channels in regulating CSBs across models. Together, our analyses unveil the expression of ion-channel degeneracy in CA3 pyramidal neurons and emphasize the dominance of calcium and calcium activated potassium channels in the emergence of CSB.

Disclosures: R. Roy: None. **R. Narayanan:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.04

Topic: B.08. Intrinsic Membrane Properties

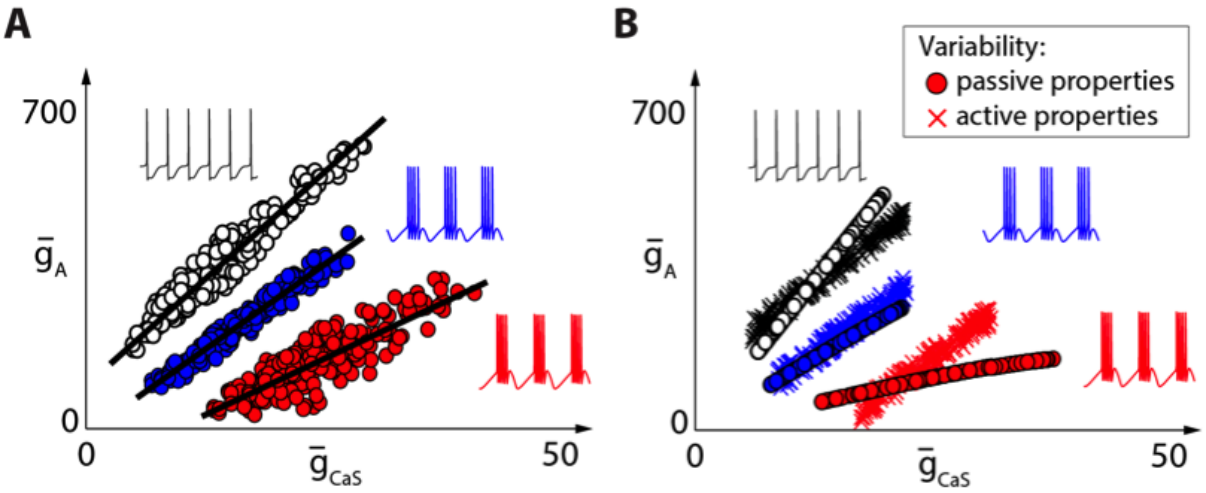
Title: Neuromodulation-dependent correlation levels in neuron ion channel expression result from a competition between passive and active membrane properties.

Authors: A. FYON, *G. DRION;
Univ. of Liège, Liege, Belgium

Abstract: Neurons and circuits are subject to significant changes in their firing activity and responsiveness to external inputs via neuromodulation (Marder, 2012). Many nervous system functions depend on reliable neuromodulation, yet the physiological properties of neurons that are targeted by neuromodulators are often highly variable (Grashow et al., 2009 ; Marder et al., 2014). In this work, we use conductance-based neuron models to investigate the mechanisms by which neuromodulation can be reliable in variable neurons by tuning correlations in ion channel expression. We show that the correlations required for reliable neuromodulation depends on the type of variability in neuron intrinsic properties. Variability in neuron passive properties such as input resistance results in correlations whose slope is affected by neuromodulation state. Variability in neuron active properties such as voltage-gated channel densities results in correlations of constant slope that are translated by neuromodulation state. As a result, the global correlation level in neurons that are variable in both passive and active properties will appear strongly correlated when correlations due to both variability types are aligned, i.e. when they are of similar slope, and appear to decorrelate as neuromodulation state varies due to a misalignment of correlation slopes.

References

Grashow R, Brookings T, Marder E (2009) Reliable neuromodulation from circuits with variable underlying structure. Proc Natl Acad Sci U S A. 106:11742-6.
Marder E (2012) Neuromodulation of neuronal circuits: back to the future. Neuron. 76:1-11.
Marder E, O'Leary T, Shruti S (2014) Neuromodulation of circuits with variable parameters: single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. Annu Rev Neurosci. 37:329-46.



Disclosures: A. Fyon: None. **G. Drion:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.05

Topic: B.08. Intrinsic Membrane Properties

Title: Ion channel dynamics contribute to altered excitability in a genetic model of Angelman Syndrome

Authors: *A. PRATT[1], C. MALLOY[2], D. A. HOFFMAN[3];
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Abstract: Angelman Syndrome (AS) is a rare neurodevelopmental disorder that causes delayed development and a predisposition to seizures, among other neurological phenotypes. Loss-of-function mutations in the maternal allele of Ube3a, the gene that encodes for E3A ubiquitin ligase, is known to be the cause of this condition. Our group sought to investigate how Ube3a impairment leads to an increased prevalence of seizures and behavioral phenotypes associated with this condition. To model AS, heterozygous knockout (KO) of Ube3a was employed and its effect on pyramidal cell excitability in the CA1 of the mouse hippocampus was examined. Firing property recordings revealed dampened basal excitability at hyperpolarized membrane potentials in the KO group. Reduced excitability was primarily due to increased inter-spike interval duration at the beginning of current steps under the hyperpolarized condition. Interestingly, no difference was observed in excitability between groups at resting membrane potential. Differences in ion channel dynamics in the hyperpolarized state suggest that membrane potential contributes to differences in ion channel availability between groups.

Disclosures: A. Pratt: None. **C. Malloy:** None. **D.A. Hoffman:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.06

Topic: B.08. Intrinsic Membrane Properties

Support: NIH/NIMHD- Grant Number: S21MD001830
NIH/NIAAA- Grant Number: 1R01AA027808-01A1

Title: Characterization of BK Channels isoforms stably transfected cell lines differing in miR-9 3'UTR recognition sites

Authors: *E. CARTAGENA[1], K. CORDERO[2], H. G. MARRERO-HERNANDEZ[3], Y. ROMERO[3], J. O. GARCIA[4], C. VELAZQUEZ-MARRERO[5];
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Carolina, Carolina, PR; [5]Inst. of Neurobio., Univ. of Puerto Rico Med. Sci. Campus/ Inst. of Neurobio., San Juan, PR

Abstract: Eliezer Cartagena-López, Katherine Cordero Padilla, Héctor G. Marrero Hernández, Yolimar Romero Estremera and Cristina Velázquez-MarreroAbstract:Research has identified the large conductance voltage- and calcium-activated channel (BK) as va key regulator of neuronal excitability genetically associated to behavioral alcohol tolerance in invertebrates. Similarly in mammals, decreasing BK channel alcohol sensitivity by knocking out its 4 subunit leads to increased alcohol voluntary consumption in mice. Sensitivity to ethanol at the molecular level is characterized by acute potentiation of channel activity. However, different isoforms of the BK channel show variations in alcohol sensitivity and are differentially distributed on the plasma membrane surface in response to prolonged exposure, also known as persistent alcohol tolerance (PMT). miRNA targeting of alcohol-sensitive isoforms coupled with active internalization of BK channels in response to ethanol are believed to be key in establishing homeostatic adaptations that produce persistent changes within the striatum. These mechanisms may operate independently, with the same end point of increasing the representation of alcohol insensitive BK channels or interact to orchestrate and optimize these persistent adaptive changes at the translational and trafficking level of regulation. In our current study we have designed and expressed cDNA constructs containing sequences for two important BK channel isoforms and created stably transfected cell lines expressing both; STREX and ZERO. These isoforms differ in their sequence by a 53 amino acid cassette in the C-terminus region present in STREX and absent in ZERO. This uniquely confers STREX with an insensitivity to acute alcohol exposure. The cDNAs where further designed to include a GFP-tag for in-vivo studies and contain differing 3'UTR regions to explore the role of miR-9 expression on protein translation for both isoforms. Our results indicate significant effects correlating miR-9 exposure to BK channel internalization in the absence of translational regulation supporting the link between miR-9 and Wnt/beta-catenin signaling in the internalization of BK channels during molecular alcohol tolerance.

Disclosures: E. Cartagena: None. **K. Cordero:** None. **H.G. Marrero-Hernandez:** None. **Y. Romero:** None. **J.O. Garcia:** None. **C. Velazquez-Marrero:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.07

Topic: B.08. Intrinsic Membrane Properties

Support: NINDS Intermural Research Program NS003134

Title: The sodium leak channel Nalcn contributes to pacemaking activity of dopaminergic neurons

Authors: *D. E. COBB-LEWIS[1], Z. M. KHALIQ[2];
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Abstract: Dopaminergic neurons fire spontaneous action potentials in a rhythmic, pacemaker fashion, setting tonic dopamine levels in the basal ganglia. Alterations to tonic dopamine levels are associated with

Parkinson's disease, depression, and schizophrenia. Past work has suggested that a sodium leak conductance may be the largest contributor to pacemaking in dopaminergic neurons, but the molecular correlate of this conductance remains a matter of debate. Here we investigated the contribution of the sodium leak channel, NALCN, to spontaneous pacemaker activity of dopaminergic neurons. Using calcium imaging to monitor action potential firing, we found that the vast majority of control dopaminergic neurons fire spontaneously (85.95%) at low rates (1.71 Hz, n=242) both in the ventral tegmental area (VTA) and substantia nigra (SNc). Similarly, using electrophysiology we found 91.59% of dopaminergic neurons in the SNc fire spontaneously (2.85 Hz, n=107). By contrast, dopaminergic neurons in the VTA lacking expression of NALCN were largely quiet (80.73%, n=192) in calcium imaging experiments. We conducted additional electrophysiology experiments to determine the effect of acute manipulation of NALCN on spontaneous firing. Consistent with previous work in hippocampus showing that NALCN is potentiated in low external calcium, we found that pacemaking was increased (+178.8%) in low calcium but not in the presence of Gd3+, a non-specific blocker of NALCN. Additionally, we found that Co2+, another non-specific blocker of NALCN, significantly reduced pacemaking (-51%) while Gd3+ had no effect. Because pacemaking is known to involve multiple conductances, including L-type calcium (LCa) and hyperpolarization-activated (IH), we tested the unique contribution of NALCN to spontaneous firing by blocking these conductances. While pacemaking was not significantly affected by LCa and IH antagonists, the addition of Gd3+ significantly reduced firing (-79.3%). Thus, we have identified NALCN as a novel ionic contributor to the robust pacemaking process of dopaminergic neurons.

Disclosures: D.E. Cobb-Lewis: None. **Z.M. Khaliq:** None.

Poster

P127. Excitability Control: Ion Channel

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P127.08

Topic: B.08. Intrinsic Membrane Properties

Support: NIH grant 5R01NS102871 (MPI: Hochman, Prinz)

Title: Ensemble computational models of mouse thoracic sympathetic postganglionic neurons simultaneously tuned across neurophysiological modalities

Authors: K. PUSULURI[1], Y. LI[2], S. HOCHMAN[2], *A. A. PRINZ[1];
[1]Dept. of Biol., [2]Dept. of Physiol., Emory Univ., Atlanta, GA

Abstract: Thoracic sympathetic postganglionic neurons (tSPNs) regulate downstream effector targets including vasomotor and thermoregulatory systems by receiving, integrating, and transforming synaptic inputs from preganglionic neurons in the spinal cord [1]. The mechanisms underlying tSPN excitability changes, such as may occur after spinal cord injury (SCI), can be studied by understanding the biophysical properties of tSPNs, their integrative capacity, and recruitment principles.
A conductance-based computational model of mouse tSPNs was previously described in [1]. The current study presents ensembles of tSPN models tuned to individual neurons to effectively describe experimental

recordings simultaneously across different electrophysiological modalities, including voltage-clamp (VC) step and ramp, as well as current clamp (CC) protocols. The maximal conductances, decay time constants, and other kinetic properties of relevant ion channels based on previously studied mRNA profiles in tSPNs are determined. The dynamics of transient currents via Na^+ and A-type K^+ channels are modeled using VC step protocol data, further separated by the application of the Na^+-channel blocker tetrodotoxin. Various long-lasting currents (delayed rectifier K^+, M-type K^+, Ca^{2+}-dependent K^+ etc.) are separated based on their characteristic dynamics seen under VC ramp protocol, and their aggregate under VC step protocol. Using data from CC recordings, all channel properties are also simultaneously tuned to match the passive and firing properties of the cells in response to current injections. We included a model of electrode resistance and capacitance [2] to separate experimental artifacts from ion channel dynamics and to describe the voltage-dependent delays observed in the onset of Na^+ currents under VC step protocol. Future work will employ these ensemble tSPN models to study systematic differences between genetically identified subpopulations and the mechanisms of putative homeostatic plasticity engaged to maintain excitability after lost central drive as seen after high level SCIs.
References:
1) McKinnon M, et al. Dramatically Amplified Thoracic Sympathetic Postganglionic Excitability and Integrative Capacity Revealed with Whole-Cell Patch-Clamp Recordings. Eneuro. 2019 Mar;6(2).
2) Günay C, Prinz A. An offline correction method for uncompensated series resistance and capacitance artifacts from whole-cell patch clamp recordings of small cells. BMC Neurosci 2011, 12(Suppl 1):P259

Disclosures: K. Pusuluri: None. **Y. Li:** None. **S. Hochman:** None. **A.A. Prinz:** None.

Poster

P136. Oscillations and Synchrony: LFP Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P136.01

Topic: B.09. Network interactions

Support: KIST Intramural Grant (2E30962)
NRF of Korea (2017R1A2B3012659)

Title: Distinct roles of beta and gamma bursts in the mouse basolateral amygdala-medial prefrontal cortex circuitry in the presence of a predatory robot

Authors: *J. KIM[1,3], H.-B. HAN[2,4], S. CHO[1], J. CHOI[5,6];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol., Seoul City, Korea, Republic of; [3]Kyung Hee Univ., Seoul, Korea, Republic of; [4]Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [5]Korea Inst. of Sci. and Tech. (KIST), Seoul, Korea, Republic of; [6]Univ. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Oscillatory activities in the basolateral amygdala (BLA) are known to regulate emotion-related behaviors with the medial prefrontal cortex (mPFC). Several studies on the rodent BLA have reported that transient oscillations at the high beta (~25 Hz, beta bursts) and low gamma (~40 Hz, gamma bursts)

frequency range emerge during the emotion- or reward-related situations. However, whether the beta and gamma bursts have similar or different neuronal contexts is unclear. To characterize the functional roles of the beta and gamma bursts in the BLA-mPFC circuit, we examined their relevance to mouse behaviors by introducing a predatory robot in the open field arena. To classify the behavioral states, we used the dynamic parameters of the position data to classify the response of the mice towards or their interactions with the robot (e.g., attack, escape, freeze, avoid, etc.). We observed that the BLA-mPFC circuit predominantly displays both beta and gamma bursts in a significant level compared to the baseline. However, the moments during which these bursts occurred showed discrepancy: while most of the beta bursts were associated with the executive behaviors, the gamma bursts didn't show such behavior-specificity. Rather, the gamma bursts occurred in an elevated manner during the situations of enhanced threat. Our observations so far concede with the recent findings and suggest the updated view of high beta and low gamma oscillations. Even the resonance frequencies are at proximate, the generative mechanisms of beta and gamma oscillations are different. The beta and gamma bursts in the mPFC and BLA may reflect distinct functional role in emotional and non-emotional cognitive processes.

Disclosures: J. Kim: None. **H. Han:** None. **S. Cho:** None. **J. Choi:** None.

Poster

P136. Oscillations and Synchrony: LFP Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P136.02

Topic: B.09. Network interactions

Support: Packard Fellowship for Science and Engineering
Lane Family
Friends and Alumni of Georgia Tech
NIH-NINDS R01 NS109226

Title: Noninvasive rhythmic sensory stimulation modulates widespread brain networks: a mechanistic study in neurosurgery patients with intracranial depth electrodes.

Authors: *L. T. BLANPAIN[1], E. CHEN[2], J. PARK[3], M. Y. WALELIGN[4], R. E. GROSS[3], J. T. WILLIE[6], A. C. SINGER[5];
[1]Neurosci. Grad. Program, MD-PhD program, [2]Emory Univ., Atlanta, GA; [3]Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [5]Wallace H. Coulter Dept. of Biomed. Engin., [4]Georgia Inst. of Technol., Atlanta, GA; [6]Neurosurg., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Our limited means to non-invasively modulate deep brain circuits constrain the development of new therapeutic strategies for many neurological disorders such as Alzheimer's disease (AD). Previously, we showed that periodic sensory stimulation, or sensory flicker, modulates neural activity in rodent higher cognitive regions, suggesting this approach could be a powerful non-invasive tool to modulate such circuits. However, we do not know whether this method could be used to modulate these circuits in humans, the extent of its effects across brain regions, nor the mechanism by which this stimulation affects non-sensory circuits. We studied the effects of visual and auditory flicker in humans at both the local field

potential (LFP) and single neuron level, across a comprehensive set of brain regions. To do so, we recruited treatment-resistant epileptic patients undergoing presurgical intracranial seizure monitoring with stereotactic EEG, who were not suspected to be sensitive to photic-induced seizures. Subjects were exposed to visual-only, auditory-only, and audiovisual stimulation at a range of frequencies between 5.5Hz to 80Hz, as well as to single pulses of stimulation. We show that sensory flicker increases LFP oscillations at the frequency of the flickering stimulus in higher cognitive regions such as the hippocampus and prefrontal cortex, and our data suggests that it may also modulate the activity of single neurons in such regions. We confirmed that these findings cannot be explained by electrical artifacts or volume conduction from sensory areas. Moreover, we investigated the mechanisms by which sensory flicker propagates from sensory to higher cognitive brain regions. Specifically, we tested whether sensory flicker responses result from a linear or non-linear combination of single sensory pulse responses or result from amplification of specific frequencies due to resonant properties of local or long-range circuits. Our data points to the latter as a possible mechanism by which sensory flicker modulates deep brain circuits. This is the first extensive study examining the neurophysiological response to sensory flicker at such a high spatial and temporal resolution in humans. Our results suggest that this stimulation effectively modulates circuits involved in disease, including deep circuits that are hard to target non-invasively. Finally, our data sheds light on the potential mechanism by which sensory flicker modulates such non-sensory circuits.

Disclosures: L.T. Blanpain: None. **E. Chen:** None. **J. Park:** None. **M.Y. Walelign:** None. **R.E. Gross:** None. **J.T. Willie:** None. **A.C. Singer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics.

Poster

P136. Oscillations and Synchrony: LFP Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P136.03

Topic: B.09. Network interactions

Title: Inter-areal coherence differences are explained by differences in gamma frequency

Authors: *J. R. DOWDALL[1,2], M. SCHNEIDER[2], M. VINCK[2];
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Abstract: Inter-areal coherence in the gamma band (30-90 Hz) has been postulated to mediate the feedforward flow of information between anatomically connected brain areas (Fries 2005, Bastos, et. al. 2015). Several studies have observed an increase in inter-areal coherence with attention, which co-occurs with a shift in the gamma peak frequency (Bosman, et. al 2012, Ferro, et. al. 2021). These frequency shifts may be a mechanism by which the attended stimulus gains preferential processing at downstream targets, yet the underlying mechanism remains unclear. To this end, we studied the role of frequency shifts and their effect on inter-areal coherence by theoretical analysis and numerical simulations using damped harmonic oscillators. We contrasted two general mechanisms through which frequency shifts can cause changes in the magnitude of coherence, namely resonance (Izhikevich, et. al. 2003) and source mixing (Buzsáki & Schomburg, 2015, Schneider, et. al. 2020). These two mechanisms make distinct and

opposite predictions on the relationship between the magnitude of inter-areal coherence and frequency shifts. Our findings have strong implications toward understanding the mechanism of coherence, the degree to which coherence reflects inter-areal communication, and the utility of coherence for quantifying the flow of the information between anatomically connected brain areas.

Disclosures: J.R. Dowdall: None. **M. Schneider:** None. **M. Vinck:** None.

Poster

P136. Oscillations and Synchrony: LFP Studies I

Location: Virtual Only

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Program #/Poster #: P136.04

Topic: B.09. Network interactions

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Title: Metastability of Down states in the cerebral cortex: dynamics and modulation

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Abstract: Under unconscious brain states, the cortical dynamics is dominated by a rhythm know as "slow oscillations" (SO) characterized by the alternation between periods of activity, or Up states, and periods of silence, or Down states. In this context, the Down states play a critical role for the cerebral cortex function, being responsible of resetting the system and breaking causal interactions between cortical areas. These cortical quiescent periods account for the drop of cortical complexity reported under unconscious brain states (e.g. Rosanova et al, *Nature communications* (2018) 9: 1), and as such they are key components for the understanding and characterization of the dynamics and mechanistic differences between conscious and unconscious brain states. The mechanisms underlying SOs are still under debate, so here we focused on the less-studied silent period, the Down state, and analysed the instantaneous phase and synchronization (Kuramoto order parameter) of the local field potential and multiunit activity in multielectrode recordings obtained from *in vivo* and *in vitro* cortical networks, and from a multimodular network of spiking neurons *in silico* (Capone et al. (2019) *Cereb. Cortex* 29:319). Through this multiscale exploration we identified a metastable dynamic within the Down states characterized by two phases: 1) a sustained period of high synchronization right after the Up-to-Down transition, where the collective phase behavior shows an exponential trend and high synchronization, eventually followed by 2) a second period characterized by poor network synchronization, in which the collective phase randomly fluctuates between $-\pi$ and $+\pi$. For this reason, we decided to name these stages "deterministic" and "stochastic" respectively. A large parameter space was investigated through different experimental manipulations (anesthesia levels, electric fields, alterations of excitation/inhibition, etc) in order to validate this framework, that integrates a broad range of slow oscillatory frequencies. The identification of the

metastable periods of the Down states and the possibility of inferring local and global features of network dynamics through the analytical approach used here, illustrates the value of the combined recording and analysis of LFPs and spikes, which offer insights that cannot be obtained at present by examining spikes alone (Mazzoni et al (2013) *Princ. Neural Coding* 411-430). Accordingly, we propose here a more detailed description of the Up and Down state cycle dynamics that bridges cortical properties emerging at the mesoscale with their underlying mechanisms at the microscale.

Disclosures: A. Camassa: None. **A. Galluzzi:** None. **M. Mattia:** None. **M. Sanchez-Vives:** None.

Poster

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Title: Co-occurrence of hippocampal theta- and ripple-frequency rhythms in foraging rats

Authors: *P. SEENIVASAN[1], R. BASAK[2], R. NARAYANAN[1];
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Abstract: Brain rhythms have been postulated to play central roles in animal cognition. The occurrence of theta- and ripple-frequency hippocampal rhythms is known to be significantly dissociated with respect to both physiology and behavior. While θ-frequency (4-12 Hz) oscillations are assigned to encoding processes during exploratory behavior and rapid eye movement (REM) sleep, ripple-frequency (120-250 Hz) oscillations are linked to consolidation phenomena during non-REM sleep and wakeful rest. However, as the two oscillations are differentially expressed across hippocampal *strata*, reports of exclusivity need validation through simultaneous recordings across *strata*. Additionally, intracellular counterparts of sharp waves (dendritic plateau potentials), that occur in close association with ripples, have been observed simultaneously during θ oscillations. Motivated by these observations, we assessed their potential co-occurrence by recording hippocampal extracellular potentials from rats (n=3) that foraged in an open arena using 32-channel silicon polytrodes spanning different *strata*. We identified individual *strata* based on histology, laminar profiles of extracellular signals during sharp wave ripples (SPW-Rs), and characteristic cross-*strata* θ-phase reversal. Theta epochs and ripple events were exclusively identified from the distal *stratum radiatum/stratum lacunosum moleculare* and *stratum pyramidale* respectively, to account for their differential expression profiles. A simultaneous detection of the two rhythms from their respective *strata* was defined as a co-occurrence, termed as *θ ripple* events. Across rats, we found 10-20% of total ripples to be *θ ripples*, with the frequency of occurrence of ripples within θ epochs (median across sessions: 0.2-0.4 Hz) higher than their occurrence outside (0.1-0.2 Hz). Further, we found the magnitude of θ power during and in the vicinity of *θ ripples* to match that within

identified θ epochs. We also assessed the behavioral state of the rat during ripple events, and found a distribution of ripple kinds - e-θ, i-θ, e-nonθ, and i-nonθ, with distinctions based on physiology (θ *vs.* non-θ epochs) and behavior (exploratory *vs.* immobile), emphasizing the need to consider ripples other than the dominant i-nonθ ripples. Finally, we found that *θ ripple*s expressed a strong phase preference (range $[\pi/2,\pi]$) with respect to the θ oscillation. Together, our analyses provide direct quantitative evidence urging the need to revisit the dichotomy between the two rhythms, by demonstrating their co-occurrence during different behavioral states.

Disclosures: P. Seenivasan: None. **R. Basak:** None. **R. Narayanan:** None.

Poster

P136. Oscillations and Synchrony: LFP Studies I

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FP7 600925

Title: The timescale and magnitude of aperiodic activity decreases with cortical depth in humans, macaques and mice

Authors: *M. HALGREN[1], R. KANG[1], B. VOYTEK[2], I. ULBERT[3], D. FABÓ[4], L. EROSS[3], L. WITTNER[5], J. MADSEN[6], W. K. DOYLE[7], O. DEVINSKY[7], E. HALGREN[8], M. T. HARNETT[1], S. S. CASH[9];
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Abstract: Cortical dynamics obey a 1/f power law, exhibiting an exponential decay of spectral power with increasing frequency. The slope and offset of this 1/f decay reflect the timescale and magnitude of aperiodic neural activity, respectively. These properties are tightly linked to cellular and circuit mechanisms (e.g. excitation:inhibition balance, firing rates) as well as cognitive processes (perception, memory, state). However, the physiology underlying the 1/f power law in cortical dynamics is not well understood. Here, we compared laminar recordings from human, macaque and mouse cortex to evaluate how 1/f aperiodic dynamics vary across cortical layers and species. We report that 1/f slope is steepest in superficial layers and flattest in deep layers in each species. Additionally, the magnitude of this 1/f decay

is greatest in superficial cortex and decreases with depth. Both of these findings can be accounted for by a simple model in which transmembrane currents have longer time constants and greater densities in superficial cortical layers. Together, our results provide novel mechanistic insight into aperiodic dynamics in cortex and suggest that the timescale and magnitude of aperiodic cortical currents decrease with cortical depth.

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Poster

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Topic: B.09. Network interactions

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MIT Picower Institute Innovation Fund

Title: Traveling waves in the prefrontal cortex during working memory

Authors: *S. BHATTACHARYA, S. L. BRINCAT, M. LUNDQVIST, E. K. MILLER;
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Abstract: Neural oscillations are evident across cortex but their spatial structure is not well explored. Are oscillations stationary or do they form “traveling waves”, i.e., spatially organized patterns whose peaks and troughs move sequentially across cortex? Here, we show that oscillations in the prefrontal cortex (PFC) organized as traveling waves in the theta (4-8Hz), alpha (8-12Hz) and beta (12-30Hz) bands. Some traveling waves were planar while many rotated around an anatomical point. The waves were modulated during performance of a working memory task. During baseline conditions, waves flowed bidirectionally along a specific axis of orientation. Waves in different frequency bands could travel in different directions. During task performance, there was an increase in waves in one direction over the other, especially in the beta band.

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Poster

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Topic: B.09. Network interactions

Support: NIH 5 R03AG061645-02

Title: Opposite effects of ketamine on the generation of hippocampal sharp wave ripples: A comparison of brain slices and the whole brain.

Authors: *J. GU[1,3], S. VICINI[2], J.-Y. WU[1];
[1]Neurosci., [2]Dept Parmacology & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [3]Col. of William and Mary, Williamsburg, VA

Abstract: Ketamine is a promising, fast-acting antidepressant that act as a non-competitive NMDA antagonist. Its action on other transmitter systems (e.g., AMPA receptors, monoaminergic, cholinergic and opioid systems) have been widely noted but remain elusive.
To investigate the non-NMDA effects of ketamine, we tested ketamine on the occurrence of hippocampal sharp wave-ripples (SWRs) in mouse hippocampal slices and whole animals. SWRs are a spontaneous neuronal activity essential for memory consolidation, generated locally in the hippocampus. The generation of SWR is known to be insensitive to NMDA receptors but highly sensitive to other neurotransmitter receptor systems including AMPA, GABA, acetylcholine, dopamine, serotonin, norepinephrine, and opioids in the CA3 local circuits.
We found ketamine has opposite effects on SWRs when comparing slices and the whole brain *in vivo*. In mouse hippocampal slice, ketamine reduced the SWRs occurrence rate without affecting their amplitude. In contrast, when applied to whole animal (ip injection), ketamine increases the occurrence rate and ripple amplitude.
The *in vivo* and *in vitro* effects began to occur at a similar sub-anesthetic dose of 25-50 mg/kg and became more obvious at higher doses (100 mg/kg, 40 μM). In brain slices, high doses (200 mg/l, 80 μM) sharply reduce the occurrence rate of SWRs, yet some of the remaining SWRs continued to exhibit a high amplitude.
The *in vitro* effect is unlikely to related to the NMDA antagonism, because the effect of ketamine persisted after a complete blockage of NMDA receptors with 150 μM of AP5. We also found that manipulating AMPA, GABAa, acetylcholine, dopamine, or serotonin receptors can all change the SWR occurrence rate and amplitude, but none of them exhibited a reduction in occurrence without affecting amplitude. The effects of ketamine on SWR generation circuits will be further explored.
Our results suggest that the changes of SWR induced by ketamine *in vivo* is a combination of direct (local) and indirect effects. The indirect effects may be derived from metabolic products of ketamine and/or neurotransmitters released from other brain structures.

Disclosures: J. Gu: None. **S. Vicini:** None. **J. Wu:** None.

Poster

P136. Oscillations and Synchrony: LFP Studies I

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Topic: B.09. Network interactions

Support: NRF of Korea (2017R1A2B3012659)
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Title: Competing patterns of oscillatory activity in the basolateral amygdala-medial prefrontal cortex circuitry during freeze-or-flight response

Authors: *H.-B. HAN[1,2], Y. JEONG[3], J. CHOI[1];
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Abstract: Confronting a predatory threat, our brain quickly evaluates relevant behavioral strategies among different types of defensive behaviors, for example, freeze-or-flight. Converging evidence suggests that bidirectional connections in mPFC-BLA circuits play key roles for defensive behaviors, however, the underlying mechanism remains largely unknown. Here, we propose the distinct rhythmic states in mPFC-BLA and their interactions support flexible switching in freeze-or-flight decision process, the rhythms of which may bridge functionally relevant neural ensembles through coherence and resonance as well. Using LFP recordings in mice, we observed the emergence of various rhythmic states in mPFC-BLA. By identifying the different types of defensive behavior manifested in a naturalistic predator-avoidance task, we found freeze-related rhythmic state (mPFC→BLA 5 Hz) and flight-related rhythmic states (BLA→mPFC 10 Hz & mPFC→BLA 30 Hz) in mPFC-BLA. The rhythmic states were not only distinctive but also mutually-exclusive; the two behavior-specific states in mPFC-BLA barely coexist, as if the behavioral states of freeze/flight do not coexist. Two flight-related rhythms also showed a functional segregation, whereas the 30 Hz represents the top-down aspect of flight behavior (e.g., refuge-oriented moving), the 10 Hz simply correlated to the speed of movement during flight. The frequency channels of rhythms match well with the characteristics of previously-reported functional networks that mPFC-BLA deploys (e.g., 5 Hz with basal ganglia, 10 Hz with hippocampus), suggesting a bridging role of mPFC-BLA during different defensive behaviors. Taken together, our results provide empirical data of mPFC-BLA exhibiting various frequency channels during defensive behaviors, and further suggest the role of oscillatory switching for flexible functional transition in the single brain circuits of mPFC-BLA.

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Poster

P138. Network Interactions: Awake and Behaving

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Topic: B.09. Network interactions

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Title: Encoding behavioral information by dynamic reorganization of a prefrontal microcircuit

Authors: *N. FROST[1], K. DONAHUE[2], V. S. SOHAL[3];
[1]Univ. of Utah, Salt Lake City, UT; [2]Univ. of California, San Francisco, San Francisco, CA; [3]Dept. of Psychiatry, U. California, San Francisco, San Francisco, CA

Abstract: Changes in multineuron activity within the brain underlie our ability to accurately represent information pertinent to cognitive tasks. The prefrontal cortex in mice plays important roles in regulating both anxiety and social interactions. While activity is modulated during both types of behaviors, the nature by which information is encoded is unclear. We reasoned that modulation of the temporal patterning of neuronal groups into behavior-specific patterns might both contribute to specific computational processes and increase the reliability by which information might be transmitted between neurons during behavior. We utilized implanted microendoscopes to record calcium activity of prefrontal neurons as mice engaged in social and anxiety-provoking behaviors to generate multi-dimensional datasets. This allowed us to identify neurons or groups of neurons which specifically encoded features pertinent to anxiety-provoking or social behaviors. We then trained a neural network receiving input from randomly assigned subsets of real neurons from each dataset to identify specific ensembles of neurons whose activity was modulated during each behavior. We show that the activity of identified ensembles convey information that is specific for each behavior with little overlap between ensembles and different behaviors. Demonstrating that the temporal patterning of neuronal activity is critical, shuffling datasets randomly reduces the performance of our classifier to chance, whereas shuffling data in a manner that preserves correlations maintains above-chance accuracy. We reason that in neurodegenerative or neurodevelopmental disorders this temporal patterning may be altered both due to changes input or changes in the function of the local microcircuit.

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Poster

P138. Network Interactions: Awake and Behaving

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Title: Evoked Potentials for Programming Dentate Nucleus Deep Brain Stimulation in Stroke Rehabilitation

Authors: *J. K. HERMANN[1], A. BORSETH[1], F. PUCCI[2,3], C. TOTH[1], O. HOGUE[4], H. H. CHAN[1], A. G. MACHADO[2,3], K. B. BAKER[1];
[1]Dept. of Neurosciences, [2]Ctr. for Neurolog. Restoration, [3]Dept. of Neurosurg., [4]Dept. of Quantitative Hlth. Sci., Cleveland Clin., Cleveland, OH

Abstract: Elevating excitability in cortical tissues surrounding ischemic stroke lesions is hypothesized to enhance the efficacy of motor rehabilitation through promotion of plasticity mechanisms and functional reorganization. Our group has demonstrated that chronic activation of the dentatothalamocortical pathway (DTC), via deep brain stimulation (DBS) of the cerebellar dentate nucleus (DN), enhances excitability

across widespread cortical regions. Moreover, we have shown that continuous DN DBS enhances chronic post-stroke motor rehabilitation in several rodent models of cerebral ischemia and a phase-I clinical trial in patients with post-stroke hemiparesis is currently underway. With the intent of identifying methods to predict efficacious DN DBS stimulation parameters via changes in cortical excitability, we investigated the effects of DN DBS on somatosensory evoked potentials (SSEPs) in a rodent model. SSEPs were generated in eight awake Long-Evans rats by stimulating the sciatic nerve with an implanted nerve cuff and recording cortical responses from EEG screws implanted above contralateral S1 hindlimb cortex. DBS was delivered to the rodent homologue of the DN ipsilateral to the stimulated sciatic nerve via an implanted concentric electrode. Each trial contained 5 minutes of SSEPs (DBS OFF), 5 minutes of rest, 2 minutes of DBS, and 5 minutes of SSEP concurrent with DBS (DBS ON). Peak-to-peak SSEP measurements were compared between the OFF and ON DBS conditions. Among recurring peaks in the SSEP waveforms, only the mid- and later-latency features exhibited significant elevations in peak-to-peak amplitude ratios of DBS ON to DBS OFF. When DBS was delivered at 30 Hz, peaks occurring near 16 and 21 ms after stimulation exhibited a 4.4% increase in peak-to-peak amplitude relative to DBS OFF ($p = 0.044$, Wilcoxon Signed Rank/Mixed Effects Model). When DBS was delivered at 100 Hz, peaks occurring near 16 and 21 ms after stimulation exhibited a 32.5% increase ($p = 0.018$) and peaks occurring near 21 and 36 ms after stimulation exhibited a 4.2% increase in peak-to-peak amplitude relative to DBS OFF ($p=0.003$). Elevations in SSEP peak-to-peak amplitude during DN DBS suggest that activation of the DTC pathway enhances excitability in structures generating the cortical SSEP response. Although significant, the changes in cortical excitability detected by SSEPs were modest and do not appear to be sufficiently robust to reliably predict efficacious DN DBS settings for stroke rehabilitation. Regardless, our findings expand upon the range of anatomical regions affected by DN DBS therapies.

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Poster

P138. Network Interactions: Awake and Behaving

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Title: Somatostatin interneurons control critical dynamics

Authors: *T. RIBEIRO[1], M. VICTOR[1], E. GEIST[1], A. VAKILI[1], D. CHIALVO[2], D. PLENZ[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Escuela de Ciencia y Tecnologia, Univ. Nacional de San Martin, San Martin, Argentina

Abstract: The critical brain dynamics hypothesis has gained a lot of attention since the seminal work of Beggs & Plenz, characterizing the so-called neuronal avalanches in 2003. Since then, criticality has been observed in a number of brain regions and spatial scales, ranging from hundreds of microns to the whole brain. Most importantly, criticality has been shown to optimize information processing, with deviations from it linked to disease states. Yet, the mechanisms employed by the brain to maintain this dynamical state are still poorly understood. One hypothesis is that the balance in excitatory-inhibitory (E-I) plays a key role. Here we study the relationship between critical dynamics and E-I balance in the visual cortex of awake mice subject to visual stimuli. We employed two-photon imaging of head-fixed mice positioned on a running wheel to infer spiking activity in neurons. Retinotopic mapping was performed to discriminate areas of the visual cortex. Viral-injection into cortical layer 2/3 resulted in robust expression of the genetically encoded calcium indicator (GECI) GCaMP7s. In order to measure effects of changes in the E-I balance, we also injected transgenic mice (PVCre, SST-Cre and VIP-Cre) with the Cre-dependent opsin ChrimsonR allowing us to optically drive those interneurons. A chronic cranial window was centered over the primary visual cortex (V1) and mice were subjected to passive viewing of drifting bars at different angles (1 s each, randomly chosen) at maximum contrast interspaced by 3 s of gray screen. During the experiment, for randomly selected trials, optogenetic drive of the opsin-expressing cells was achieved by either wide-field stimulation with a LED or individual-cell stimulation through a spatial-light modulator (SLM). At any point, mice could self-initiate locomotion. Pupil diameter was assessed continuously to measure the animal's state of arousal. More than ~150 neurons were recorded consistently in a ~450 x 450 μm area at a frame rate of ~45 Hz. We analyzed neuronal avalanche statistics in those populations with and without optogenetic drive. Avalanche dynamics as well as tuning properties changed during stimulation of SST interneurons. Furthermore, using a spatial correlation analysis recently introduced by Palmieri and Jensen, we observed deviations from the correlation structure predicted for criticality only during stimulation of SST interneurons, in line with the results obtained using avalanche statistics. We therefore conclude that the visual cortex maintains critical state dynamics and a particular E-I balance during visual processing through control of SST activity.

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Poster

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Topic: B.09. Network interactions

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Title: Longitudinal quantification of neural activation in awake animals evoked by low-current intracortical microstimulation

Authors: *R. LYCKE, R. KIM, C. XIE, L. LUAN;
Neuroengineering Initiative, Rice Univ., Houston, TX

Abstract: The goal of brain-machine interfaces is to record neural activity and evoke meaningful sensations in the brain. Over the years researchers have developed tools and techniques to record and stimulate the brain with increasing spatial and temporal resolution, but stimulated sensations are often perceivably different than natural stimuli, due to classical electrical neural stimulation techniques exciting large populations of neurons rather than select neurons. Observing neural activity in response to natural stimuli, the neural activity can be quantified as ensembles of neurons activating in precise time for sensations, not synchronized bulk activations of a region. To better understand the nature of intracortical microstimulation and develop stimulation to precisely activate neural populations, our lab developed a procedure to electrically stimulate neurons paired with 2P imaging and neural recording in awake animals, quantifying the neural activation in response to stimulations of varying amplitudes and waveforms. Implanting flexible low profile Neural Electronic Thread (NET) electrodes in thy1-GCaMP6s mice, fluorescing neuronal calcium, paired stimulation and 2P imaging experiments were conducted. During experiments volumes of neural tissue was imaged, 1300 um x 1300 um x 500 um, quantifying neurons adjacent and distant from the stimulating electrode. It was observed with increasing stimulation current larger populations of neurons activated both adjacent to the stimulating electrode and at distal regions, with robust activation observed at low currents, less than 5 uA. Utilizing novel differential neural population analysis techniques, neural activation was measured in awake spontaneously behaving animals across multiple months. Investigating the activation response from neighboring electrode sites showed distinct differences in neural populations activated at varying currents. With these analysis techniques, individual neuron activation consistency was chronically quantified and longitudinal changes in the activated profiles across months were measured providing insights into the network stability of stimulated neural populations. These findings and tools to quantify the activated neural populations both define the stimulation capabilities of implanted electrodes and allow for precisely quantifying activated neuron ensembles responding to stimuli. Combing the ability to stimulate targeted populations of neurons with accurate quantifications of the neural ensembles during various external stimuli brings the field of neural engineering one step closer to artificially evoked naturalistic sensation.

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Poster

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Title: Acute ketamine disrupts state-dependent variation in network activity and functional connectivity in the mouse neocortex.

Authors: *R. L. OREN, C. J. BARNES, J. A. CARDIN, M. J. HIGLEY;
Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: Ketamine has emerged as a powerful experimental and therapeutic tool in understanding the links between brain activity and neuropsychiatric disorders. For example, schizophrenia is associated with profound disruptions of cognition and perception that can be mimicked by a single sub-anesthetic dose of ketamine. Schizophrenia patients also exhibit altered functional connectivity across the brain, including among primary sensory and higher-order cortical areas, that may also occur after ketamine administration. At lower doses, systemic ketamine has also been successful at relieving depression in human patients, a finding that is further supported by behavioral studies in rodents. However, the cellular and network mechanisms underlying these effects remain poorly understood. To more fully examine how administration of acute ketamine influences dynamic activity within the neocortex, we took advantage of a newly developed set of techniques for wide-field 'mesoscopic' calcium imaging in awake behaving mice able to freely move on a wheel. We imaged activity across the neocortex in mice expressing the calcium indicator GCaMP6s in either excitatory pyramidal neurons (PNs) or inhibitory parvalbumin-expressing interneurons (PV-INs). Mice received either a psychotomimetic dose of ketamine (30 mg/kg) or saline during alternating imaging sessions. We found that ketamine exerted a state-dependent effect on PNs, producing little effect during quiescence while blunting their activity during locomotion. This result was region-specific, with a few medial areas including the retrosplenial and primary motor cortices showing an increase in locomotion-induced activity after ketamine. In contrast, ketamine reduced activity in PV-INs for most areas regardless of behavioral state. Lastly, ketamine disrupted the long-range functional connectivity between cortical regions, a finding that was greater for PV-IN versus PN signals. In conclusion, our results demonstrate that acute, sub-anesthetic doses of ketamine drive significant alterations in the state-dependent patterned activity of large-scale cortical networks.

Disclosures: R.L. Oren: None. **C.J. Barnes:** None. **J.A. Cardin:** None. **M.J. Higley:** None.

Poster

P138. Network Interactions: Awake and Behaving

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P138.06

Topic: B.09. Network interactions

Support: NIH R35NS097287

Title: State-dependent heterogeneity of cortical cholinergic and noradrenergic activity

Authors: L. N. COLLINS, J. FRANCIS, B. EMANUEL, D. A. MCCORMICK;
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Abstract: Fluctuations in brain state, which are reflected in both behavioral state and widespread cortical activity, are likely supported by broadly projecting neuromodulatory systems. However, the extent to which specific neuromodulators operate synchronously across the brain or in a more regionally specific manner is unclear. It is possible that certain neuromodulatory systems function to provide either a global arousal signal or a more regionally, task-specific signal depending on brain or behavioral state. In this study, we examine spontaneous activity of cholinergic and noradrenergic axons in awake mice to determine the interaction between arousal state and neuromodulatory activity across the cortex. To monitor neuromodulatory activity across the cortex with cellular resolution, we use mesoscale two-photon calcium imaging, allowing for simultaneous monitoring of cortical axons separated by up to 5 mm. We confirm that activity within both basal forebrain-derived cholinergic cells and locus coeruleus-derived noradrenergic cells tracks arousal and behavioral state, providing evidence for a global arousal component for both systems. However, we find a striking decrease in global cholinergic signaling during locomotion but not whisking bouts and an increase in global noradrenergic signaling at the onset of whisking. This result suggests that during certain behavioral states these neuromodulatory systems switch from a global mode to a more regionally specific mode of neuromodulation. In addition, we characterize the activity of cholinergic interneurons in the cortex and find that approximately one third of this population of cells has arousal-linked activity. Together, our results provide evidence that cholinergic and noradrenergic neuromodulatory systems do indeed operate dynamically within the cortex, and that behavioral state is highly predictive of global synchrony in spontaneously active mice.

Disclosures: L.N. Collins: None. **J. Francis:** None. **B. Emanuel:** None. **D.A. McCormick:** None.

Poster

P138. Network Interactions: Awake and Behaving

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Program #/Poster #: P138.07

Topic: B.09. Network interactions

Support: ANR grant JCJC
USIAS fellowship
Neuropole de Strasbourg

Title: Decoding the hippocampal oscillatory complexity to predict behaviour

Authors: *R. GOUTAGNY[1], V. DOUCHAMPS[2], D. BATTAGLIA[3];
[1]CNRS UMR7364, Strasbourg, France; [2]Psychology, Univ. of Strasbourg, Strasbourg, France; [3]INS, Univ. Aix-Marseille, Marseille, France

Abstract: Theta and gamma oscillations are believed to organise hippocampal activity. The current dominant view holds that two gamma frequency sub-bands occur at different theta phases in CA1, are produced by different generators and sub-serve different cognitive operations. Recent evidence suggested however that most individual theta cycles actually contain very diverse and complex gamma contents. We

thus aimed at exploring further this theta-gamma coupling diversity by using a new topological approach based on the detection of several individual gamma bouts per theta cycle. We applied this method to the LFPs recorded in all CA1 layers of mice performing a spatial reference memory task (n=5). These signals were filtered without a priori in a large gamma band (30-200 Hz) using an ensemble empiric mode decomposition. This revealed that gamma bursts could be found for nearly every combination of frequency, amplitude and theta-phase in all layers. Only when restricting the analysis to the theta cycles with very strong gamma bouts could we observe average patterns similar to those proposed in the dominant view and that, despite few of these cycles actually matching these averages. This suggests that the two gamma sub-band generators model might be inadequate. We propose, based on a simple computational model of two neuronal populations (excitatory and inhibitory), that each generator can produce the whole gamma spectrum but might be biased toward some frequencies by modulating the inhibitory-to-excitatory coupling. Importantly, the underlying complexity of theta-gamma coupling considered at the theta cycle timescale seems nonetheless to carry behavioural information: running speed and coarse position within the maze could be predicted by a machine learning algorithm from these seemingly stochastic properties of isolated theta cycles. In conclusion, we propose the existence of an interdependence between behaviour and the rich, complex and largely overlooked diversity of hippocampal theta-gamma oscillations that goes beyond a model with few discrete, mostly mutually-exclusive gamma types.

Disclosures: R. goutagny: None. **V. Douchamps:** None. **D. Battaglia:** None.

Poster

P138. Network Interactions: Awake and Behaving

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Program #/Poster #: P138.08

Topic: B.09. Network interactions

Support: DIRP, NIMH, USA, ZIAMH002797 to D.P.
BRAIN initiative grant U19 NS107464-01 to D.P. and D.R.C.

Title: Universal scaling in the synchronization of cortical cell assemblies

Authors: *E. CAPEK[1], T. L. RIBEIRO[1], P. KELLS[1], K. SRINIVASAN[1], S. R. MILLER[1], E. GEIST[1], M. VICTOR[1], A. VAKILI[1], D. CHIALVO[2], D. PLENZ[1];
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Abstract: Neuronal synchronization is fundamental to many theories on cortex function. Cortical neurons, by preferentially integrating nearby, recurrent activity with distant inputs, establish local and propagated synchrony in the form of oscillations, waves, and neuronal avalanches. These forms of synchrony benefit information processing by flexibly identifying neuronal subgroups; however, they also present with unique limitations. Oscillations emphasize phase-locked firing among neurons, yet the number of different patterns that can be phase-coded per cycle seems to be few. Waves represent compact spatial propagation, which limits their simultaneous occurrence within one region. Neuronal avalanches,

in contrast, constitute highly diverse, scale-invariant patterns of synchrony that carry attractively high information capacity. Yet, it is currently not clear whether, at the cellular level, avalanches exhibit precise unfolding of synchronization. The hallmark of neuronal avalanches has been their scale-invariant spatiotemporal statistics quantified by power laws in size and duration. When interpreted within the framework of self-organized criticality, power laws suggest a critical state of cortex that supports diverse and stable, potentially system-wide propagated synchronization. On the other hand, numerous alternative models that differ from synchronization have been proposed for the generation of power laws. In order to discriminate among generative avalanche models, a single scaling exponent χ can be calculated, which captures the relationships between the mean size of avalanches, as well as the corresponding collapse in avalanche shape for different avalanche durations. Here, we revisited the estimation of χ for neuronal avalanches using 2-photon imaging of pyramidal neurons in the cortex of awake transgenic mice. We show that the synchronization and propagation of pyramidal neuron groups exhibits the hallmark of neuronal avalanches during ongoing activity in prefrontal cortex as well as during visually evoked responses in primary visual cortex. Using temporal coarse graining, we demonstrate that $\chi = 2$ and establish a universal avalanche profile in the form of an inverted parabola. These scaling relationships are in line with recent results for LFP-based avalanches in nonhuman primates. Our findings demonstrate universal scaling of synchronized neuronal avalanches to guide the formation of cortical cell assemblies.

Disclosures: E. Capek: None. **T.L. Ribeiro:** None. **P. Kells:** None. **K. Srinivasan:** None. **S.R. Miller:** None. **E. Geist:** None. **M. Victor:** None. **A. Vakili:** None. **D. Chialvo:** None. **D. Plenz:** None.

Poster

P138. Network Interactions: Awake and Behaving

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Program #/Poster #: P138.09

Topic: F.01. Neuroethology

Support: NSF1912352
NIH R15NS116742

Title: Scale-free behavioral dynamics directly linked with scale-free cortical dynamics

Authors: S. A. JONES, J. H. BARFIELD, ***W. L. SHEW**;
Univ. of Arkansas, Fayetteville, AR

Abstract: Naturally occurring body movements and collective neural activity both exhibit complex dynamics, often with scale-free, fractal spatiotemporal structure. Scale-free dynamics of both brain and behavior are each associated with functional benefits to the organism. In cerebral cortex, the criticality hypothesis is often suggested to explain scale-free dynamics, but previous studies have not directly linked scale-free neural activity fluctuations with corresponding behavioral dynamics. This disconnect between the criticality hypothesis and behavior has long been a criticism of the hypothesis. Here we show that scale-free dynamics of mouse behavior and certain subsets of cortical neurons are one-to-one related. Indeed, we considered many distinct subsets of neurons and found that those with the broadest range of power-law scaling were most correlated with behavior. Surprisingly, the scale-free dynamics of these

subsets of neurons were obscured when considering the entire recorded population of neurons together. This was due to other subsets of neurons that were strongly anticorrelated with the scale-free subsets. The fluctuations of these anticorrelated subsets effectively canceled each other out, resulting in combined dynamics without scale-free fluctuations. This type of competitive critical dynamics is not explained by previous theory of critical neural systems, to our knowledge (but see adjacent poster by us for a new theory). Our results establish neural underpinnings of scale-free behavior and clear behavioral relevance of scale-free neural activity, which was previously thought to represent background noise in cerebral cortex.

Disclosures: S.A. Jones: None. **J.H. Barfield:** None. **W.L. Shew:** None.

Poster

P138. Network Interactions: Awake and Behaving

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Program #/Poster #: P138.10

Topic: F.01. Neuroethology

Support: NSF1912352
NIH R15NS116742

Title: Winnerless competition among cortical neurons: a new theory of scale-free cortical dynamics

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[1]Univ. of Arkansas, Fayetteville, AR; [2]Univ. of Arkansas Fayetteville, Fayetteville, AR

Abstract: Naturally occurring body movements and collective neural activity both exhibit complex dynamics, often with scale-free, fractal spatiotemporal structure. Scale-free dynamics of both brain and behavior are each associated with functional benefits to the organism. In the cerebral cortex, scale-free dynamics have often been explained by the criticality hypothesis, which supposes that cortical neural networks operate at the tipping point of a phase transition, between regimes of synchronous and asynchronous activity. However, previous models and theory of the criticality hypothesis do not explain some prominent recent experimental observations of scale-free neural activity (see nearby poster by us). These experiments showed that scale-free neural activity in visual cortex often occurs among certain subsets of neurons, while the population, as a whole, does not appear to have scale-free activity. This observation was attributed to strongly anticorrelated subsets of neurons whose fluctuations effectively cancel each other out, obscuring critical dynamics at the population level. Here we describe a model that can explain these observations and suggests a new type of critical dynamics not considered previously, to our knowledge. Our model is similar to winner-take-all models, previously used to study decision making. The model generates scale-free dynamics among anticorrelated subsets of neurons when it is tuned to operate at the tipping point between regimes of locked-in winner-take-all dynamics and stochastic winnerless switching. Our model offers a fresh view of the criticality hypothesis and suggests that criticality could play a role in decision making.

Disclosures: J.H. Barfield: None. **S.A. Jones:** None. **W.L. Shew:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.01

Topic: B.10. Epilepsy

Support: Accelerate Mitacs Postdoc Fellowship

Title: Adrenergic signalling contributes to cardiorespiratory death after status epilepticus in an anesthetised rat model

Authors: *A. SABETGHADAM[1], H. EL BEHEIRY[2], A. EBRAHIMAMINI[3], A. PEIMANI[3], P. CARLEN[3,1];
[1]Fundamental Neurobio., Krembil Res. Inst., Toronto, ON, Canada; [2]Dept. of Anesthesia and Pain Med., [3]Biomed. Engin., Univ. of Toronto, Toronto, ON, Canada

Abstract: Background: Status epilepticus (SE) is a common neurological emergency with high mortality rate of 20% in generalized convulsive patients. We hypothesized that the peripheral cardiorespiratory complications due to activation of peripheral adrenoreceptors following seizure spread to brainstem mainly contributes to death in SE. **Methods:** We used adult male Wistar rats anesthetized with isoflurane (1.5-1.7%, mixed with 100% O2), tracheally intubated and connected to an artificial ventilator. Each animal was implanted with a cannulated bipolar stainless-steel electrode into the right hippocampal CA3 region to infuse kainic acid (KA) with simultaneous local field potential (LFP) recording. Medium-impedance glass electrodes were also implanted to record the LFPs of the left parietal cortex (PC) and the right brainstem rostroventrolateral medulla (RVLM) localized by a glutamate-related localization method. Electrocardiogram (ECG), cardiac and respiratory rates, respiratory and plasma gases (mmHg), pH, electrolyte, and glucose (mmol/l) were measured along with core temperature (°C) and cannulated arterial blood pressure (mmHg). In a separate set of experiment, animals (n=5) were pretreated with a non-selective alpha-adrenergic receptor blocker, phentolamine (10mg/kg, i.v.), 5 min before local KA infusion. **Results:** The results showed a gradual increase of blood pressure with increased rates of ventilation in the animal immediately following infusion with KA, which gradually decreased until the apnea occurred, usually within 10-15 min after KA infusion, which was always followed by asystole 5-7 min later. However, in phentolamine pretreated animals, phentolamine dose-dependently prolonged the window before animal become apneic. Also, in KA treated animals in which artificial ventilation was not successful, phentolamine could alleviate the attempted breathing period leading to animal survival. Blood pH, glucose and NE levels significantly increased after KA infusion with no significant change in the electrolyte concentrations. There was no change in the amplitude of the ECG; however there was arrythmia at the time of KA infusion which was associated with transient apnea at that time. **Conclusion:** Increased survival time and alleviated apnea was demonstrated in KA animals pretreated with a non-selective adrenergic receptor blocker, phentolamine, which is a drug of choice for the treatment of neurogenic pulmonary edema. This raises the possibility of pulmonary edema caused by adrenergic activation due to a catecholamine storm induced by brainstem RVLM activation. This process could be a potential cause of death in SE patients.

Disclosures: A. Sabetghadam: None. **H. El Beheiry:** None. **A. EbrahimAmini:** None. **A. Peimani:** None. **P. Carlen:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.02

Topic: B.10. Epilepsy

Support: NIH Grant NS095842

Title: Selective serotonin reuptake inhibitors and 5-HT_2 receptor agonists cause distinct, sleep-state dependent changes in postictal breathing in amygdala kindled mice

Authors: *K. G. JOYAL, A. N. PETRUCCI, M. V. LITTLEPAGE-SAUNDERS, N. A. BOODHOO, G. F. BUCHANAN;
Univ. of Iowa, Iowa City, IA

Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. While the exact etiology of SUDEP is unclear, it is believed seizure-related respiratory failure is a major factor. SUDEP often occurs at night, possibly during sleep. Serotonin (5-HT) is implicated in SUDEP. 5-HT modulates breathing, sleep-wake, and seizure threshold and severity. We hypothesized that enhancing 5-HT tone prior seizure onset would increase postictal breathing frequency (f_R), tidal volume (V_T), minute ventilation (V_E) and breathing regularity and decrease periictal apnea. Since sleep state is implicated in SUDEP, seizures were induced during both wake and NREM sleep. 5-HT_2 receptors were targeted due to their implication in respiratory regulation and SUDEP. 16 adult (8-12 wks) male and female C57BL/6J mice were instrumented for EEG/EMG recording and implanted with a bipolar stimulating/recording electrode into the basolateral amygdala [AP: -1.3 mm; ML: -2.8 mm; DV: -4.7 mm]. After recovery, afterdischarge threshold determination, and kindling (80-380 mA; 1 s train of 1 msec biphasic square waves; 60 Hz; 2x/day), seizures were induced during wake and NREM sleep following treatment with vehicle; 5-HT_2 agonists, TCB-2 (10 mg/kg) and MK-212 (10 mg/kg); and selective 5-HT reuptake inhibitors (SSRI) citalopram (20 mg/kg) and fluoxetine (10 mg/kg), alone, or 15 min after 5-HT_2 receptor antagonists ketanserin (3 mg/kg) or RS-102221 (10 mg/kg). All drugs were given intraperitoneally 30-60 min prior to seizures. Citalopram and the 5-HT_{2C} agonist MK-212 had sleep state-dependent effects on f_R, V_T, and V_E during different postictal timepoints. Citalopram and fluoxetine eliminated ictal and postictal apneas, regardless of sleep state. MK-212 increased ictal apneas compared to vehicle when seizures were induced during NREM. Citalopram decreased breathing variability immediately after seizures compared to vehicle, but only with those induced during wake. This effect persisted when 5-HT_2 receptor antagonists were administered prior to citalopram. MK-212 decreased variability compared to vehicle in the later postictal period, regardless of sleep state. The 5-HT_{2A} agonist, TCB-2, had negligible effects on breathing compared to vehicle. Our results indicate that increasing available 5-HT and activating 5-HT_2 receptors cause distinct, sleep state-dependent changes in breathing following seizures induced in amygdala kindled mice. This suggests that the efficacy of 5-HT-enhancing

treatments on postictal breathing is sleep state dependent and that multiple serotonergic mechanisms govern recovery of eupnea in the postictal period.

Disclosures: K.G. Joyal: None. **A.N. Petrucci:** None. **M.V. Littlepage-Saunders:** None. **N.A. Boodhoo:** None. **G.F. Buchanan:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.03

Topic: B.10. Epilepsy

Title: Extracellular field clamp can suppress generation of epileptiform activity

Authors: *M. SUBRAMANIAN, C.-C. CHIANG, D. DURAND;
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Abstract: *Objective*: Epileptiform activity including spikes and seizures can propagate using electric fields independently of synaptic transmission. Recent studies also show that neural recruitment in epilepsy occurs in part due to electric field (ephaptic) coupling. Therefore, controlling the local electric field could suppress or cancel the generation of abnormally synchronized events. We tested the hypothesis that clamping the local extracellular electric fields can prevent the generation of epileptic spikes and seizures. *Methods*: Spontaneous epileptic spikes and seizures were induced using 4-aminopyridine in an *in vitro* experimental setup using longitudinal hippocampal slices from 4 mice. Two extracellular recording electrodes were used: R1 was placed in the cell layer at the edge of the temporal region of the hippocampal slice to detect the generation of the epileptic activity; R2 was placed in the septal region to observe the propagation of the activity along the longitudinal direction. Two stimulating electrodes S1-2 were placed outside the slice in the transverse direction at the edge of the Temporal region in line with R1. An extracellular voltage clamp system was connected to R1 and S1-2 and designed to maintain the voltage at R1 equal to zero by applying the appropriate feedback current between S1 and S2. *Results:* 4-AP induced spikes and seizures in the temporal region (R1) (focus) which were observed to propagate to the septal region (R2). The electric field produced by the applied current with the feedback circuit "on", cancelled the local extracellular electric field involved in the generation of the epileptic events as evidenced by the clamp achieving 100% suppression of both epileptic spikes and seizure events as observed by R1. No spikes or seizures were observed into the septal region with clamp was "on" at R2 showing complete suppression of epileptiform activity in this slice. Both the spikes and seizure events recovered as soon as the clamp was turned off. *Significance:* The results show that an extracellular clamp applied to a seizure "focus" can completely suppress the generation that epileptiform activity and prevent its propagation away from the focus. Although the spatial extent of the control is currently limited to the region around the recording site, this method could be effective to control seizure generation in a small known focus.

Disclosures: M. Subramanian: None. **C. Chiang:** None. **D. Durand:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Support: This work was supported by JSPS (Japan Society for the Promotion of Science) Grant-in-Aid for Young Scientists (19K16305) & Grant-in-Aid for Scientific Research (B) (21H02585)

Title: Hibernation-like state presents a new approach to understanding and treating temporal lobe epilepsy

Authors: *T. M. MOKHOTHU[1], A. HIRANO[2], T. SAKURAI[2], K. Z. TANAKA[1];
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Abstract: Temporal Lobe Epilepsy (TLE) is a debilitating neurological disease with no cure. Treatments reportedly work in only two-thirds of the patients, and although much research is being done to develop more treatment lines, there is also a growing research interest focused on preventative measures to stop the disease before it becomes fully-fledged chronic epilepsy. To have effective targeted prevention strategies, we should first understand the changes in each stage of the disease progression and pinpoint the therapeutic windows. One such stage of the disease with immense potential for targeted therapy is the Latent phase, a silent/ seizure-free period between the initial insult and the first spontaneous seizure. The consensus is that this period comprises neuronal plasticity changes, aberrant gene expression, and changes in the resting-state functional connectivity between regions and hemispheres. The current study probes the question of whether the presence of a latent period is a determiner of chronic epilepsy or not. We, therefore, ask, if these processes should be stopped, could chronic epilepsy be prevented? We will pause latent period processes in the brain by inducing hibernation in mice following the pilocarpine induction of epilepsy. Using a transgenic mouse line, Qrfp-*iCre, which* expresses icre in Qrfp-expressing neurons in the hypothalamus, we can excite these neurons in a DREADD mediated paradigm, thus initiating a rapid reduction of overall metabolism, which effectively stops all action potentials and neuronal changes. We induce this hibernation-like state immediately after status epilepticus induction to artificially stop molecular, and plasticity changes typically occurring within the latent period and compare the seizure outcome through statistical analyses of spontaneous seizure onset, frequency, and severity in hibernated mice versus typical pilocarpine-induced mice with no hibernation. This experiment will allow us to evaluate whether a state of hibernation that halts the metabolic activities, which we believe governs the development of acute seizures into chronic seizures, is enough to impact the spontaneous recurrent seizures. This work will increase our understanding of the latent period and forge new research paths to further understand the mechanisms underlying epileptogenesis and expand on the timelines of intervention before chronicity.

Disclosures: T.M. Mokhothu: None. **A. Hirano:** None. **T. Sakurai:** None. **K.Z. Tanaka:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Topic: B.10. Epilepsy

Support: ANR LoGIK (ANR-17-CE16-0022-01)

Title: Rescue of intrinsic excitability of Lgi1-deficient CA3 neurons by recovery of Kv1.1 potassium channel.

Authors: *J. EXTREMET[1], J. RAMIREZ-FRANCO[1], L. MOLINIERES[1], N. BOUMEDINE[1], O. EL FAR[1], D. DEBANNE[2], M. RUSSIER[1];
[1]UNIS UMR 1072, Marseille, France; [2]UNIS - Umr_s 1072 - INSERM AMU, Marseille, France

Abstract: Leucine-rich Glioma Inactivated 1 (Lgi1) is a secreted glycoprotein in the central nervous system. It is targeted by auto-antibodies associated with Limbic Encephalitis (LE) and its deletion induces Autosomal Dominant Lateral Temporal Lobe Epilepsy. Accordingly, lethal epileptiform activity is observed in Lgi1 knock-out mice model (Boillot et al., 2014). It has been shown that Lgi1 deficiency leads to a decrease in axonal Kv1.1 channel density, a voltage-gated potassium channel subunit carrying I_D current that dampens intrinsic excitability and glutamate release (Seagar et al., 2017). In order to test whether Lgi1 controls intrinsic excitability through the expression of Kv1 channel-mediated I_D current, Lgi1 expression was rescued in Lgi1 KO neurons by single cell electroporation of Lgi1-encoding gene. Three days after the electroporation, the rescue of a wild-type electrophysiological phenotype was investigated. We evaluated changes in intrinsic excitability (IE) by patch-clamp recording of CA3 pyramidal neurons in current clamp. The Kv1.1-mediated I_D current were measured in voltage clamp and immunoreactivity of Kv1.1 potassium channel were quantified by immunohistochemistry to test the role of this channel in modulating the intrinsic excitability. We observed a reduction in IE and a higher sensitivity to dendrotoxin-K (DTx-K, a selective Kv1.1 subunit blocker) in KO neurons electroporated with Lgi1-encoding gene (KO/Lgi1 neurons). Restored IE was correlated to the rescue of the Kv1.1-mediated I_D current and Kv1.1 channel immunostaining at the Axon Initial Segment of KO/Lgi1 neurons. As Lgi1 is released extracellularly, we assessed its paracrine effect on IE and Kv1.1 immunostaining. We showed a partial rescue of IE in neurons adjacent to the KO/Lgi1 neurons with a change in Kv1.1 channel expression. We conclude that reintroducing the Lgi1 gene is sufficient to rescue IE in Lgi1-deficient neurons by restoring the expression of the Kv1.1 channel and that it affects IE of adjacent neurons through a paracrine effect.

Disclosures: J. Extremet: None. **J. Ramirez-Franco:** None. **L. Molinieres:** None. **N. Boumedine:** None. **O. El Far:** None. **D. Debanne:** None. **M. Russier:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Program #/Poster #: P153.06

Topic: B.10. Epilepsy

Title: Gs967 reduces seizure activity in the zebrafish pentylenetetrazol model

Authors: *P. MILDER, J. MARRS, T. CUMMINS;
Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Epilepsy is a disease caused by the recurrent state of seizures, occurring due to an imbalance between neuronal inhibition and excitation (Scharfman, 2007). Thirty percent of patients with epilepsy do not respond to current anti-epileptic drug (AED) treatments, creating critical need to test current and novel AEDs to improve treatments for refractory patients. The pentylenetetrazol (PTZ) epilepsy model has been employed to test AEDs in both mammal and zebrafish models. We tested the novel AED compound GS967, which has been used in mice models and shown to be specifically effective for SCN8A epilepsy (Baker et al, 2014) and SCN2A epilepsy (Baker et al, 2018) within mice models. Due to GS967 positive efficacy in two different genetic epileptic models, we tested whether this novel compound is useful in the PTZ chemoconvulsant model and may treat generalized epilepsy. We tested two hypotheses: (1) the efficacy of GS967 depends on whether it is administered to zebrafish acutely with PTZ or pretreated with GS967 before PTZ exposure; and (2) the efficacy of GS967 can be demonstrated using various assays, including behavior, electroencephalogram (EEG), and calcium imaging (GCaMP). Pretreatment versus acute application of GS967 showed that GS967 pretreatment had a preventative effect against seizure induction and reduced seizures in acute treatments. We found that there was not a significant difference between the pretreatment groups and acute treatment groups' ability to reduce PTZ induced seizure activity in the behavioral experiments. We next tested acute treatment of the GS967 in the EEG and GCaMP assays using the observation window between 15 min post exposure and 30 min post exposure to see if the results matched the results correlated with the behavioral assays. Consistent and reproducible results in EEG, and GCaMP assays correlated with the behavioral experiments, strengthening and validating the findings using the GS967 AED reported here. This model system is being developed for its potential translational ability as an effective and efficient method to screen future novel AEDs, which could be useful for developing precision medicine and to guide clinicians in treatment choices for patients with refractory epilepsy.

Disclosures: P. Milder: None. **J. Marrs:** None. **T. Cummins:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.07

Topic: B.10. Epilepsy

Title: Mechanisms of neurological protection and death related with transcranial magnetic stimulation using kindled rats.

Authors: *W. MORENO ROMAN[1], P. RODRIGUEZ[2], L. F. HERNANDEZ, Jr.[2], M. RUBIO-OSORNIO[2], C. RUBIO[2];
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Abstract: Epilepsy is an extensively studied neurological disorder, research has been made from animal models to human experimentation, as a result there are several medications and some surgical treatments aim to control this disorder, despite this 30% of patients are hard to control. Transcranial magnetic stimulation (TMS) has been used as an anti-epileptic treatment and neuro-protective barrier, even though this is used as a treatment there is no cellular, molecular or physiological evidence to sustain this. The way we are evaluating cell death is with BCL-2, BAX, citocrom-c and caspase 3 and 8, all of this markers will tell us the pathway of cells death or protection. We are using 25 male Wistar rats, equally divided in five groups, the experimental and sham groups will get an electrode implant by a stereotaxic surgery at the amygdala, the implant will be use for the electrical stimuli using the Kindling model in the experimental group, once the subjects present the conduct associated to Racine 5 they will be randomly included to the TMS or kindling group, TMS group was stimulated before the electrical stimulus, each rat had its own time for the TMS which depended on the time of the last seizure, every EEG was analyzed in both groups, measuring amygdala and cortex response, after ten sessions in Racine 5 the rat will be decapitated immediately after the seizure, the brain will be extracted, dividing it in half, the right hemisphere will be fixated with paraffin for immunohistochemistry, the other half will be dissected for the bulbus olfactorius, motor cerebral cortex, hippocampus, amygdala and cerebellum. So far we have analyzed the EEG and the recordings for both experimental groups, the recording were also examined by a third party to compere the results, showing a difference between groups in a conduct stand of view, the time of seizures decreased as well in the TMS group. Based on the information above our preliminary results shows that there is a behavioral difference during the seizure, with the TMS group having less manifestations, and lower seizure time, with this results only we can say that TMS has an effect in epilepsy, the mechanisms in which the effect is made is still unclear. On the one hand, it can be from the neuro protection created, thus, limiting the recruitment of fibers and structures produced by the recruitment provoked by epilepsy. On the other hand, cell death can also be the cause of this behavioral changes, having fewer neurons to work within the structures affected will also reduce the time.

Disclosures: W. Moreno Roman: None. **P. Rodriguez:** None. **L.F. Hernandez:** None. **M. Rubio-Osornio:** None. **C. Rubio:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.08

Topic: B.10. Epilepsy

Support: CNPq
CAPES
FAPEG

Title: Aceturate Diminazene Improves Cardiac parametrs and Remodeling in The Pilocarpine Model of Epilepsy

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Abstract: Sudden unexpected death in epilepsy (SUDEP) is a main cause of death in people with epilepsy, one of the factors underlying SUDEP is cardiovascular disorders. Thus, we aimed to analyze the effects of the diminazene aceturate (Dize), a potential activator of angiotensin-converting enzyme 2 (ACE2), on the cardiovascular function of rats with epilepsy. For epilepsy induction, we used the pilocarpine model in male Wistar rats. Four groups were formed: (1) CTL (non-epileptic rats treated with 1 ml/kg/day, 0.9% saline, s.c.); (2) EPI (epileptic rats treated with 1 ml/kg/day, 0.9% saline solution, s.c.); (3) DIZE (epileptic rats treated with diminazene aceturate 5 mg/ml/kg/day, s.c.); and (4) DIZE + A-779 (epileptic rats treated with diminazene aceturate 5 mg/ml/kg/day and the antagonist of Mas receptor - A779 120 µg/ml/kg/day, s.c.). Rats were video monitoring (24h/day) to confirm the first spontaneous seizures and only rats with spontaneous seizures of the chronic stage of epilepsy model. Treatment started 1 day after epileptic induction and lasted 60 days. Then cardiovascular function was measured *in vivo*: resting heart rate (HR) in conscious animals, blood pressure (BP), and left ventricular (LV) pressure in anesthetized animals. Also, morphological analyzes of the left ventricle were performed. The treatments do not alter the seizure frequency. Rats of the EPI (384.8 ± 6.4 bpm) group had a significantly higher resting HR than the animals from CTL (343.5 ± 9.3 bpm) and DIZE (345.9 ± 9.8 bpm) groups. In addition, combined treatment with diminazene and A-779 (DIZE+A779: 357.8 ± 14.4 bpm) attenuated the effects of Dize on HR. No significant changes were observed in both systolic and diastolic BP and either in the mean arterial pressure. LV systolic pressure was significantly higher only in rats of the EPI (140.4 ± 14.0 mmHg) group when compared to the CTL (115.3 ± 9.1 mmHg) and DIZE (120.6 ± 7.2 mmHg) and DIZE+A779 (122.6 ± 10.5 mmHg) groups. Cardiomyocyte hypertrophy and higher collagen deposition were observed in the hearts of the EPI (13.37 ± 0.10 µm and 15.54 ± 0.65 %, respectively) group when compared to CTL (13.00 ± 0.09 µm and 10.19 ± 0.67%) and DIZE (12.57 ± 0.07 µm and 10.44 ± 0.67%) groups. On the other hand, DIZE+A779 restored hypertrophy (14.96 ± 0.11 µm) and collagen deposition (18.52 ± 1.71 %) at even higher levels than those found in the EPI group. Taken together, we concluded that treatment with Dize restores cardiac function and remodeling induced by epilepsy, probably activating ACE2.

Disclosures: P.P.P. Braga: None. **K. Gome:** None. **B. Pacheco:** None. **P. Ghazale:** None. **C. Quintino:** None. **E. Mendes:** None. **M. Biancardi:** None. **F. Alcantara:** None. **A.P. Pansani:** None. **C.H. Castro:** None. **D. Colugnati:** None.

Poster

P153. Therapeutic Approaches in Epilepsy

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Program #/Poster #: P153.09

Topic: B.10. Epilepsy

Support: MCST Grant REP-2020-006

Title: Differential role of phyto-, synthetic- and endocannabinoids in Absence Epilepsy

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Abstract: The use of medical/recreational marijuana and its legal market size are on the rise worldwide. Medical Marijuana has potential benefits for different diseases, but the lack of biomedical research and its popularity based on anecdotal evidence poses a risk to society.For instance, medical use of cannabis and derived cannabinoids show promising results in severe paediatric epilepsies. However, cannabinoids acting on the endogenous cannabinoid system can aggravate different types of seizures.Here we have clarified how the cannabinoids affect absence seizure, the most common childhood epilepsy. The failure of first and second monotherapy with anti-absence drugs in 25% of children with absence seizures and the high rate of comorbidity, including attention-deficit-hyperactivity-disorders and learning/memory impairment (which persist in seizure-free children), demand novel therapeutic approaches and the cannabinoid system may be a promising target.Using cutting-edge in vivo and in vitro electrophysiological techniques, we have investigated the effect of drugs that increase the concentration of endogenous cannabinoids in absence seizures GAERS model by blocking key catabolic enzymes. Moreover, we have characterized the effect of exogenous cannabinoids in this absence seizure model. Our preliminary data indicate a complex role of exogenous versus endocannabinoids in controlling absence seizures.Since endocannabinoid modulators with an excellent safety record in humans are already available, our data may identify new targets that in the medium-term lead to a novel treatment for absence and their comorbidity.

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Poster

P153. Therapeutic Approaches in Epilepsy

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P153.10

Topic: A.03. Stem Cells and Reprogramming

Title: Electrophysiological Properties of Human Stem Cell-derived Neurons in Long-term Cell Culture: a Model for Antiseizure Drug Discovery?

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Abstract: The identification and isolation of human stem cells from embryonic, adult and induced pluripotent stem cells (iPSCs) has revolutionized the availability of human neurons for disease modeling and drug discovery [1]. Studies in our lab address the neuropharmacological properties of receptors and ion channels expressed in neurons derived from human stem cell lines [2]. In the current study, we

utilized phase-contrast microscopy, immunocytochemistry and a multi-electrode array (MEA) system to determine the formation of neural networks in TERA2.cl.SP12 stem cell-derived neurons maintained in cell culture for up to 1 year.
The proportion of human stem cells differentiating to a neural phenotype, as indicated by β-III tubulin and MAP2 immunocytochemistry, increased over the first 3 months from approximately 5% at day 10 to ≥35% at day 80 *in vitro*. Using the MEA to record from populations of stem cell-derived neurons, we observed spontaneous spike-like activity from week 2 *in vitro* and burst firing from single cells at week 14. The spontaneously occurring spikes were inhibited by the ion channel modulators, tetrodotoxin (10nM), retigabine (1-10μM) and nifedipine (10μM), consistent with the generation of action potentials in these cells. The development of synchronous action potential firing across multiple neurons only developed by week 9 indicating the formation of neural networks. Utilizing multiple receptor antagonists and allosteric receptor modulators our pharmacological experiments showed that neurotransmission in the maturing neural networks was mediated *via* glutamate and $GABA_A$ receptors, the major excitatory and inhibitory systems in the mammalian brain, respectively.
To investigate the potential of our model for epilepsy studies, epileptiform activity was induced by 4-aminopyridine (100μM), a well-established convulsant agent in *vivo* and *vitro*. Pharmacological experiments showed the antiepileptic drugs topiramate, ethosuximide and carbamazepine significantly reduced seizure-like activity, supporting the potential of this model for drug discovery. To further test this hypothesis, we investigated the effects of the NSAID mefenamic acid on neural activity, because it also modulates $GABA_A$ receptors suggesting it might act as an anticonvulsant [3]. Mefenamic acid (100μM) reduced spike rate, number of neuronal and network bursts and epileptiform activity induced by 4-aminopyridine (100μM), suggesting an antiseizure role for this old drug. In conclusion, our data support the value of human stem cells and their neural derivatives in drug discovery.

Disclosures: H. Salmanzadeh: None. **R.F. Halliwell:** None.

Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P189.01

Topic: C.01. Brain Wellness and Aging

Support: 1 K99 NS117799-01A1
R01NS 103212
Brains Together for a cure foundation

Title: Evaluating effects of reversing distinct facets of immunosuppression in experimental GBM

Authors: *K. AYASOUFI[1], *Z. TRITZ[1], C. PFALLER[3], *L. GULBICKI[1], C. E. FAIN[2], R. KHADKA[1], F. JIN[1], M. J. HANSEN[1], A. J. JOHNSON[1];
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Abstract: Glioblastoma is associated with severe and multifaceted immunosuppression affecting all immune organs. Immunosuppression in GBM is a critical barrier to the success of immunotherapies and patient survival. We demonstrated that immunosuppression in the GL261-model of experimental GBM presents with significant thymic and spleen atrophy, MHCII downregulation, presence of potent immunosuppressive factors in serum, and sequestration of T-cells in the bone marrow. Parabiosis studies determined that soluble factors with molecular weights larger than 100 kDa mediate immunosuppression by inhibiting T-cell proliferation, thymic involution, and loss of peripheral T-cells. In contrast, bone marrow T-cell sequestration was not mediated through soluble factors. While the immunosuppression in GBM is severe, a causative link between each facet of immunosuppression and overall survival is lacking. We used an immunotherapeutic strategy to block T-cell sequestration into the bone marrow and evaluated the extent survival was impacted in experimental GBM. We evaluated the extent a novel and off-the-shelf combination immunotherapy that uses extended 1/2-life IL-2 and anti-PD-1 reverses bone marrow T-cell sequestration. Sham treatment or anti-PD1 monotherapy did not alter T-cell sequestration in the bone marrow and animals had no enhanced survival. Extended 1/2-life IL-2 monotherapy and combination strategy both prevented T-cell sequestration into the bone marrow. However, only combined therapy, which also prevented MHC class II downregulation, improved survival. In addition, we determined that when splenocytes were exposed to serum isolated from glioma-bearing mice, MHCII levels were down regulated. Current studies in our lab are underway to determine the identity of the immunosuppressive factors in serum. In short, bone marrow T-cell sequestration alone does not correspond with overall survival in experimental glioma. Importantly, a concerted effort to reverse MHC class II downregulation and define inhibitory circulating factors may have the highest impact in immunotherapeutic efficacy and improving patient survival.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P189.02

Topic: C.01. Brain Wellness and Aging

Support: RF1 AG043640
R01 AG062515

Title: Rhesus Monkey Model of Hypertension: 2-Kidney 1-Clip Induction of Renovascular Hypertension

Authors: *K. M. NIST[1], N. ARINZE[4], M. MEDALLA[2], D. L. ROSENE[5], R. D. WAINFORD[3], T. L. MOORE[6];
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Abstract: AIM: The prevalence of hypertension (HT) increases with age and is the leading risk factor for cerebrovascular disease and cognitive decline. Both HT and aging are associated with increased neuroinflammation. While studies in rodent models of HT have shown evidence of HT related increases in neuroinflammation, the combined effect of HT and aging on neuroinflammation remains unclear with no data for the primate brain. To address this gap in knowledge, we developed a model of renovascular HT in the aging rhesus monkey to explore the concomitant effects on the brain in an animal similar to human brain.
METHODS: In this pilot study, three middle aged rhesus monkeys (2 females- AM363K, AM364K and 1 male- SM065K) underwent a well-established surgical procedure that involved placing an obstructing clip on the renal artery to 1 kidney (2-kidney 1-clip (2K1C) procedure), resulting in a significant reduction of blood flow to one kidney thereby inducing renovascular HT. Following surgery, blood pressure (BP) was measured biweekly using electronic oscillometry and blood was collected at various time points for analysis. BP measurements and blood values were compared to those from a male spontaneously HT monkey (AM379) in which BP was measured monthly over 5 months and clinical chemistry and complete blood counts were obtained via femoral artery puncture at euthanasia.
RESULTS: Over the course of a year, BP in 2K1C monkeys ranged from 116-235 mmHg systolic and with a mean increase of ~23 mmHg from baseline. AM379 had spontaneously occurring elevations in blood pressure indicative of severe hypertension (ranging from 163-184). Total Cholesterol, Potassium, Sodium, and Chloride were above normal limits in the 2K1C and the spontaneous HT monkey while total protein was lower than normal limits.
CONCLUSIONS: Monkeys who underwent 2K1C procedure became hypertensive and showed similar changes in blood chemistries to that of a monkey with spontaneously HT. Brain tissue from prefrontal cortex, an area known to be susceptible to HT and aging, is being analyzed with immunohistochemical methods in comparison with and normotensive age-matched controls. Markers being assessed include microglial reactivity (using antibodies against Iba1 and LN3) and cerebrovascular stiffness (using antibodies against collagen IV). Based on rodent studies, we hypothesize that immunohistochemical analysis of markers of neuroinflammation and vascular stiffening will be elevated in the HT monkeys compared to age-matched controls. These results will provide a basis for future studies of the effects of HT on markers of oxidative stress (8OHG and 4HNE), myelin damage, and how they may underly cognitive decline.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Program #/Poster #: P189.03

Topic: C.01. Brain Wellness and Aging

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Title: Aging-related cerebral microvascular changes visualized using Ultrasound Localization Microscopy in the living mouse

Authors: M. LOWERISON[1,2], **N. CHANDRA SEKARAN**[2,3], W. ZHANG[4], Z. DONG[1,2], X. CHEN[1,2], D. A. LLANO[2,3], P. SONG[1,2];
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Abstract: Aging-related cognitive decline is an emerging health crisis; however, no established unifying mechanism has been identified for the cognitive impairments seen in an aging population. A vascular hypothesis of cognitive decline has been proposed but is difficult to test given the contradictory radiologic needs of high-fidelity microvascular imaging resolution and a broad and deep brain imaging field of view. Super-resolution ultrasound localization microscopy (ULM) offers a potential solution by exploiting circulating microbubbles to achieve a vascular resolution approaching the capillary scale without sacrificing imaging depth. In this report, we apply ULM imaging to a mouse model of aging and quantify differences in cerebral vascularity, blood velocity, and vessel tortuosity across several brain regions. We found significant decreases in blood velocity, and significant increases in vascular tortuosity, across all brain regions in the aged cohort, and significant decreases in blood volume in the cerebral cortex. These data provide the first-ever measurements of subcortical microvascular dynamics *in vivo* and reveal that aging has a major impact on these measurements.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Program #/Poster #: P189.04

Topic: C.01. Brain Wellness and Aging

Support: CONACyT grants No. 736339 and 701506
CONACyT No. PN 2015-01-465
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INFR-281265

Title: Characterization of a mouse model of chronic hydrocephalus induced by partial occlusion of the aqueduct of Sylvius in the adult brain

Authors: *T. CAMPOS ORDOÑEZ[1,2], M. EUDAVE-PATIÑO[3], P. PRADO[1], V. HERRANZ-PEREZ[4], E. LIRA-DIAZ[1,2], J. BURITICA[3], J. GARCIA-VERDUGO[4], O. GONZALEZ-PEREZ[1];

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Abstract: Hydrocephalus is a neurologic disturbance produced by the abnormal production, circulation, and absorption of cerebrospinal fluid (CSF), which expands the ventricular system. The aqueduct of Sylvius is the narrowest portion of the entire ventricular system that communicates the third ventricle with the fourth one. The occlusion of this structure or severe stenosis is considered as a predisposing factor for hydrocephalus development. Late-onset idiopathic aqueductal stenosis induces normal pressure hydrocephalus (NPH) in adults. To date, no animal model replicating chronic NPH is available to study the pathophysiological changes observed in these subjects. Herein, we characterize an experimental model that induces chronic hydrocephalus in the adult mouse brain by producing a pre-aqueductual semiobstruction into the atrium of the aqueduct of Sylvius. This model generates a long-term ventricular enlargement with normal intracranial pressure and moderate glial reactivity. Importantly, this mouse model allows the reversibility of the ventricular enlargement after the removal of the obstructive film from the brain. This animal model may be useful to study the long-term cerebral alterations that occur during NPH or after its surgical resolution.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Program #/Poster #: P189.05

Topic: C.01. Brain Wellness and Aging

Support: HMRF 04151216

Title: Cytokines play a pivotal role in modulating the risk of both periodontitis and Alzheimer's disease

Authors: *R. P.-H. WANG[1], W.-K. LEUNG[2], T. GOTO[4], J. Y.-S. HO[5], R. C. CHANG[1,3];
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Abstract: Periodontitis is a common health problem in the elderly, which can induce chronic systemic inflammation. We have been studying how systemic inflammation affects the brain immune responses, which can then affect progression of AD. We aimed to define the roles of cytokines in the pathogenesis of periodontitis and AD. By employing Micro-CT (micro-computed tomography) scan, our data revealed that in comparison to young mice, aged mice displayed significantly increased periodontal bone loss. The increased periodontal bone loss observed in aged mice was also accompanied by elevated levels of

inflammatory cytokines in the gums and the brain. The age-dependent increase in periodontal bone loss and elevated levels of cytokines in the gums and the brain of WT mice led us to further question whether cytokines play a key role in modulating the risk of periodontitis and AD. To address the question, female WT mice were injected with heat-killed *Porphyromonas gingivalis* bacteria into their buccal mucosa three times per week every other week for a total of 5 weeks to induce periodontitis. It was found that mice injected with heat-killed bacteria displayed worsened long-term memory functions. Bacterial-induced periodontitis also significantly increased periodontal bone loss and inflammatory cytokine levels in the gums of WT mice. In addition, bacterial-induced periodontitis led to significant elevated levels of inflammatory cytokines in the liver as well as different brain regions. Immunostaining and western blot analysis revealed significant increased levels of phospho-tau in WT mice injected with heat-killed bacteria. To further demonstrate the importance of inflammatory cytokines in modulating the risk of periodontitis and AD, another group of female WT mice were injected with IL-1β and TNF-α into their buccal mucosa three times per week every other week for a total of 5 weeks. It was found that mice injected with cytokines displayed hyperactivity and worsened short-term memory functions. Injections of IL-1β and TNF-α also induced periodontal bone loss in mice, which was accompanied by elevated levels of inflammatory cytokines in the liver as well as different brain regions. Taken together, our current study revealed that increased cytokine innate immune response in the gums led to periodontal bone loss and modulated the cognitive functions of mice. This research demonstrated that cytokines play a crucial role in the process of aging as well as the pathogenesis of periodontitis and AD.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Topic: C.01. Brain Wellness and Aging

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Title: Timp2 regulates hippocampus-dependent cognitive function

Authors: *A. FERREIRA[1], A. PHAN[1], J. D. ZHU[1], Y. WANG[1], B. M. HEMMER[1], A. K. FAKIRA[2], R. D. BLITZER[2], J. M. CASTELLANO[1];
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Abstract: Aging, which acts as the major risk factor for Alzheimer's disease (AD) and other neurodegenerative diseases, results in deleterious changes in the brain. Emerging data has demonstrated that exposure to youthful-blood factors counteracts age-related decline in brain function. Specifically, the blood-borne, youth-associated factor tissue inhibitor of metalloproteinases-2 (TIMP2) was shown to revitalize aged mouse hippocampus and to be necessary for human plasma-induced synaptic plasticity and memory improvements in aged mice. Moreover, local depletion of TIMP2 impairs hippocampal long-

term potentiation (LTP), arguing for an unexplored critical role in hippocampal function. However, its mechanism of action in the hippocampus under normal conditions remains unclear. To begin to examine how TIMP2 regulates hippocampus-dependent function, we deleted TIMP2 and evaluated performance of the resulting mice in novel location recognition, contextual fear-conditioning, and Barnes maze tasks. We observed striking memory deficits in TIMP2 mutant mice and in a manner that is unrelated to perturbations in motor function. To examine molecular processes within the brain that are disrupted by TIMP2 deletion, we examined networks of transcriptomic changes within hippocampus, as assessed by RNAseq. We find changes in networks related to synapse organization, memory, and neurogenesis. To link these transcriptomic changes to changes in the hippocampal cellular microenvironment, we examined adult hippocampal neurogenesis, neuroinflammation, and other markers of plasticity. We find cellular changes that are consistent with the cognitive deficits we observed with TIMP2 deletion. We find that levels of TIMP2's canonical target, MMP2, are perturbed in hippocampi from TIMP2 mutant mice, suggesting that TIMP2 may alter function through regulation of the extracellular matrix. Ongoing work is focused towards further isolating the molecular events tying TIMP2 to hippocampal function. Together, our data define novel putative mechanisms through which TIMP2 regulates hippocampus-dependent function under normal conditions, potentially informing novel targets for aging and AD-associated therapies.

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Poster

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Topic: C.01. Brain Wellness and Aging

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NIH Grant P20GM109091 to JAM
NIH Grant K01AG061263 to JAM

Title: Age-associated peripheral glucose dysregulation coincides with changes to glycolytic enzyme levels in hippocampal synapses

Authors: P. W. BRAUNSTEIN[1], N. M. RUGGIERO[1], A. HAMPTON[2], S. N. BURKE[2], L. A. NEWMAN[3], **J. A. MCQUAIL**[1];

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Abstract: Aging is associated with abnormalities in circulating glucose, altered secretion of glucocorticoids, and synaptic changes within the hippocampus, a brain region involved in cognition and regulation of homeostasis. These disturbances are particularly evident in Alzheimer's disease (AD), supporting a theory wherein age-related deficits in neural glucose metabolism underlie bioenergetic disruptions that contribute to memory loss and dyshomeostasis in AD. With the goal of elucidating the precise features of brain aging that could feasibly mediate this relationship, we evaluated differences in peripheral glucose regulation and central expression of glucose metabolizing enzymes in young adult (6 months) and aged (24 months) male F344×Brown Norway F1 hybrid rats. First, we observed blood glucose levels were significantly elevated in aged rats, but insensitive to modulation by glucocorticoids released when challenged with an acute stressor. Further, age-related differences in glucose modulation occurred in the absence of significant differences in liver glycogen content, measured after overnight fast. Second, level of phosphofructokinase-1 (PFK-1), which is the rate limiting enzyme of glycolysis, was marginally greater in aged hippocampal synapses whereas level of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), another glycolytic enzyme, tended to decrease with age. Third, age-related changes to metabolic signatures in hippocampal synapses may be specific to glycolysis as we observed no difference in protein levels of representative enzyme subunits that comprise the mitochondrial electron transport chain, which are required for oxidative phosphorylation. Our initial findings exhibit how normally aging rats are a translationally useful model to examine the antecedents and consequences of glucose dysregulation. During aging, differences in peripheral glucose metabolism coincide with changes to glycolytic enzymes in hippocampal synapses without affecting mitochondrial abundance. Ongoing experimentation will examine the degree to which age-related alterations in peripheral and central glucose metabolism relate to memory function and whether variations in expression or trafficking of neural glucose transporters contribute to the metabolic insufficiency of aging synapses.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

Location: Virtual Only

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Program #/Poster #: P189.08

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University of South Carolina Office of Vice President of Research ASPIRE Award to JAM
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Title: Ketogenic diet improves memory and mitochondrial function in hippocampus of aging female rats

Authors: *T. J. COX[1], E. GORMAN-SANDLER[1], D. J. HOROVITZ[1], K. VELAZQUEZ[2], R. T. ENOS[2], F. HOLLIS[1], J. A. MCQUAIL[1];
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Abstract: Metabolic irregularities of the aging brain are linked to severity of cognitive symptoms in the age-associated neurological disorder Alzheimer's disease (AD). Age- and disease-related defects in cerebral glucose utilization are proposed to limit metabolically demanding neural processes, such as synaptic neurotransmission, that are essential for normal memory function. Under circumstances of limited glucose, neurons can effectively metabolize fat-derived ketone bodies to replenish cellular energy needs. Unlike glucose, ketone bodies can cross cell membranes and directly fuel oxidative phosphorylation by mitochondria to produce ATP. This leads to the hypothesis that feeding a "ketogenic" diet, which elevates ketone bodies whilst attenuating blood glucose, could rescue memory in aging through a mechanism that involves improved function of synaptic mitochondria in the hippocampus. To test this hypothesis, we fed young adult (6 months) and aged (24 months) F344 × Brown Norway F1 hybrid rats a ketogenic (KETO) diet, enriched with medium-chain triglycerides, and evaluated behavioral and metabolic changes relative to identically aged rats fed a calorie-matched control diet that provided most energy in the form of carbohydrates. Weekly blood metabolite testing determined that all KETO-fed rats, regardless of age, entered ketosis within 1-2 weeks and maintained similar levels throughout the duration of the study. In the 6th week of diet, cognition was tested in the spatial reference memory-version of the Morris water maze. Consistent with prior work, aging impaired spatial learning and accuracy of spatial search was lower in females compared to males. KETO diet improved cognition in young and aged females relative to age-matched females consuming control diet; KETO produced no effect in males of any age. In the 8th week of diet, mitochondrial function in isolated hippocampal synaptic terminals was evaluated using substrate stimulated respirometry. In line with our behavioral results, we observed that respiration and spare capacity of mitochondria from aged females was lower than aged males maintained on a control diet and this effect was reversed in aged females who consumed the KETO diet. KETO diet had no effect on male hippocampal mitochondrial respiration at any age. These findings support our hypothesis that a ketogenic diet can improve memory by augmenting mitochondrial function in aging synapses, but also demonstrate that enhancing effects on brain and memory are most pronounced in females. Collectively, KETO may be a viable strategy to protect neural health, especially in aging women.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Title: Excitatory and inhibitory synapses in dorsal CA3 distinguish cognitive reserve from decline in normal aging

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Abstract: Aging is characterized by declining memory and escalating risk for Alzheimer's disease (AD). Anomalous patterns of hippocampal activity manifest in prodromal AD, wherein a shift in the excitatory-inhibitory (E/I) dynamic signals the transition from normal brain aging to neurological disease. E/I imbalance is most evident within the dentate gyrus (DG)-CA3 network and is proposed to underlie age-related deficits in spatial learning that are ascribed to the dorsal, but not the ventral, hippocampus. Collectively, these observations indicate that a neuroanatomically precise characterization of changes to excitatory and inhibitory hippocampal synapses could elucidate the circuit basis of memory changes that confer age-associated risk for AD. Consequently, we quantified changes to VGluT1, a marker of glutamatergic synapses, and VGAT, a marker of GABAergic synapses, in hippocampal sections from young 6-months old F344×Brown-Norway F1 rats relative to strain-matched 24-months old rats that were rated as spatial-learning unimpaired (24M-U) or impaired (24M-I) based on performance in the Morris water maze. We identified significantly higher VGAT in the dorsal CA3 and CA1 of 24M-U rats compared to 24M-I rats. We also observed a significant decline of VGluT1 levels in the dorsal CA3 of 24M-I rats compared to 6M rats. Using a follow-up approach that leverages the full range of individual differences in spatial learning, correlational analyses applied across the entire spectrum of aged performance revealed significant relationships between spatial learning decrements and lower level of VGAT in multiple synaptic layers of the dorsal CA3 and CA1, including the strata radiatum (SR) and lacunosum moleculare (SLM). VGluT1 levels, however, were only correlated with SLM of the dorsal CA3. Further, we did not detect evidence for significant changes to E/I balance ventral hippocampal subregions or adjacent neural structures including the entorhinal and perirhinal cortices or the basolateral amygdala. These new findings are consistent with our hypothesis that E/I disruption centered on dorsal DG-CA3 network is of special relevance to age-related memory loss. More specifically, distributed augmentation of inhibitory synapses is associated with preserved spatial memory in aging whereas comparatively targeted deterioration of glutamatergic terminals synapsing upon apical dendrites of CA3 pyramidal neurons is indicative of memory loss. Overall, these data identify potential, complementary mechanisms that contribute to different rates of cognitive changes over the lifespan.

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Poster

P189. Systemic Factors in Brain Function and Cognitive Decline

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Program #/Poster #: P189.10

Topic: A.03. Stem Cells and Reprogramming

Support: NIH 5R21NS111249-02

Title: Periventricular alterations and neuroinflammation in juvenile pigs with hydrocephalus

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Abstract: Background Ventriculomegaly, white matter injury, inflammation, edema, and gliosis are the common neuropathologies in hydrocephalus in humans and experimental models. Our group has developed a large animal model of acquired hydrocephalus in juvenile pigs to evaluate the current treatments. We hypothesized that hydrocephalus is associated with subventricular and periventricular alterations and neuroinflammation that could mimic the neuropathology described in humans.
Methods Hydrocephalus was induced by percutaneous intracisternal kaolin injections in 35-day old pigs (n=7). Age-matched sham controls received saline injections (n=6). At 30-days post-induction, MRI, immunohistochemistry, flow cytometry, and cerebrospinal fluid (CSF) protein analyses were performed.
ResultsVentriculomegaly was especially pronounced in the body of the lateral ventricle (mean 2237 ± SD 1590 mm^3) compared with controls (2251 ± 86.8 mm^3), where ependymal disruption occurred. In this area, the periventricular white matter showed a 44% increase in cell death ($p<0.05$) and a 67% reduction of oligodendrocytes ($p<0.01$). In the subventricular zone (SVZ), the number of proliferative cells and oligodendrocyte progenitors decreased by 75% and 57% respectively ($p<0.01$). The SVZ size reduced when the ventricular volume increased ($R^2=0.6065$, $p<0.03$). Neuroinflammation occurred in the hydrocephalic pigs with an increase of astrocytes and microglia in the periventricular white matter ($p<0.02$), and high levels of inflammatory interleukins IL-6 and IL-8 in the CSF ($p<0.01$). Reactive microglia were prevalent showing reduced filament volume and length, and the number of branches ($p<0.03$).
Conclusion Acquired hydrocephalus produced changes in the periventricular white matter, reduced cell proliferation in the SVZ, and neuroinflammation. These findings mimic those found in human hydrocephalus, demonstrating that the pig model can be a useful tool for preclinical studies of the pathophysiology of hydrocephalus.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

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Program #/Poster #: P202.01

Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Repurposing BT-11 for Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disease with annual costs of over $300 billion. AD is characterized by the accumulation of amyloid plaques and tau neurofibrillary tangles, as well as chronic neuroinflammation, loss of neuronal connections, and neuronal cell death. Therapeutic strategies aimed at treating two of these key hallmarks of AD, i.e. amyloid plaques and tau tangles, have so far been unsuccessful at halting or reversing disease progression. Research points towards the pathology of neuroinflammation as an important target for treatment of AD. BT-11 is an orally active lanthionine synthetase C-like 2 (LANCL2) binding compound that has potential to treat AD based on clinical trials in Irritable Bowel Disease (IBD), demonstrating its immunomodulatory properties. This BT-11 benefit is relevant to AD, as AD is characterized by an imbalance in pro-inflammatory and anti-inflammatory signaling, allowing inflammation to go unchecked. Based on its ability to modulate inflammation through targeting LANCL2, and on in silico studies, BT-11 is a drug that could be repurposed to treat AD. Our studies utilized a transgenic rat model (TgF344- AD) that is unique as it exhibits hippocampal-dependent spatial learning and memory deficits, as well as hippocampal AD pathology in a progressive age-dependent manner that mimics the pathology exhibited by AD patients. BT-11 was administered orally to a cohort of WT and Tg-AD rats for 6 months, beginning at 5 months of age (pre-pathology) to 11 months of age (full AD-pathology). Age-matched, non-treated WT and Tg-AD rats were included as controls. At 11 months of age, spatial learning and memory were evaluated with an active place avoidance task that is hippocampal-dependent. At 11 months of age, untreated male Tg rats showed significant spatial learning and memory deficits compared to male WT rats. BT-11 treatment mitigated these deficits and showed learning improvements in Tg rats as compared to untreated Tg rats. Our results support that BT-11 is a potential drug candidate for AD treatment.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: N-acetylneuraminic acid links obesity to Alzheimer's disease via immune dysfunction

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Abstract: Systemic immune dysfunction can catalise onset of Alzheimer's disease. Obesity, one of the strongest risk factors for AD, causes profound metabolic and immune perturbations. Here we hypothesized that changes in circulating metabolites associated with obesity might impair the ability of the immune system to cope with disease. To approach this, we used AD-prone 5xFAD mice, and wild-type controls, fed with high-fat diet (HFD), or control diet (CD). Using the novel object recognition assay, we found that the HFD impaired cognition specifically in 5xFAD mice. The worse cognitive performance was associated with increased neuronal loss and astrogliosis compared to CD-fed 5xFAD mice. Using a combination of flow cytometry and mass cytometry (CyTOF), we found that the HFD induced immune perturbations specifically in 5xFAD mice. In particular, we found increased frequencies of immune suppressive regulatory T cells and CD4+ effector memory T cells expressing markers of exhaustion. Next, we sought to characterize the metabolites that might be associated with the observed cognitive and immune changes. To this end, we performed non-targeted metabolomics of the blood and identified N-acetylneuraminic acid, or NANA, as the metabolite that was most strongly correlated with the obese-AD comorbid state. On a single-cell transcriptomic level, we found that the diet and AD pathology independently affected the hippocampal cell fate, thus suggesting a compound effect on brain cell vulnerability of both conditions. Interestingly, single-cell analysis of the visceral adipose tissue revealed increased proportions of macrophages expressing the gene Neu1 in the obese state. Neu1 codes for an enzyme that generates NANA. Therefore, increased NEU1 enzymatic activity in the adipose in obese condition might be one of the sources of increased NANA in the circulation. To mechanistically connect NANA to immune dysfunction, we injected NANA in regularly-fed WT mice, and found that NANA recapitulated the same immune perturbations observed in obese 5xFAD mice. Finally, using human T cell cultures, we found that NANA impaired T-cell proliferation and altered several transcriptional programmes associated with T-cell differentiation. To sum up, our results are in line with the notion that AD not only is a brain disease, but also an immune disease, and that the brain and immune aspects of the pathology are connected. In particular, we identified NANA as an obesity-induced modifying factor of AD through immune-exhausting effects. Finally, our findings imply that restoring T-cell function and targeting NANA might be applicable approaches to fight AD.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

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Program #/Poster #: P202.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-R01-AG056303
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Cure Alzheimer‘s Foundation

Title: A genetic absence of microglia promotes cerebrovascular pathology and premature mortality in 5xfAD mice which can be partially rescued by microglial transplantation

Authors: *S. KIANI SHABESTARI[1], S. MORABITO[1], E. DANHASH[1], A. MCQUADE[1], E. MIYOSHI[1], J. CHADAREVIAN[1], C. CLAES[1], M. COBURN[1], J. HASSELMANN[1], A. MARTINI[1], J. R. SANCHEZ[1], E. HEAD[1], D. HUME[2], C. PRIDANS[3], H. DAVTYAN[1], V. SWARUP[1], M. BLURTON-JONES[1];
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Abstract: Aims:Microglia are strongly implicated in the development and progression of Alzheimer’s disease (AD). To further understand how microglia impact AD pathology, we crossed 5xfAD mice with ‘FIRE’ mice, a novel model that genetically lacks microglia. Compared to other genetic or pharmacological methods, this new approach allows one to understand how a consistent absence of microglia impacts disease progression. The resulting empty microglia niche also enables the robust repopulation of microglia from genetically modified donors. Methods:‘FIRE’ mice harboring a deletion in the fms-intronic regulatory element of CSF1R and lack microglia were backcrossed with 5xfAD mice. Immunohistochemical and biochemical analysis was used to determine the impact of microglial absence on disease pathology. In addition, transplantation of wild-type donor microglia was performed to determine the impact of microglial replacement on these endpoints. Results:Pharmacological depletion of microglial has not been reported to effect AD mouse mortality. In contrast, we found that FIREKO-5xFAD mice that genetically lack microglia, exhibit a significantly shortened lifespan, with few mice reaching 6 months of age. Interestingly, this increased mortality is accompanied by a significant reduction in parenchymal beta-amyloid plaques intensity, but a dramatic increase in cerebral amyloid angiopathy (CAA) and other signs of blood brain barrier (BBB) pathology and disruption. Remarkably, transplantation of Wild Type donor microglia rescues many, but not all, of these changes. Conclusion:The FIREKO-5xFAD model provides a novel platform to determine how microglia influence the relationship

between plaque formation and blood vessel pathology and the impact of varying microglial donor cells on these outcomes.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

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Program #/Poster #: P202.04

Topic: C.02. Alzheimer's Disease and Other Dementias

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U54GM128729

Title: Asthma induced by house dust mite exacerbates Alzheimer’s-associated changes in App^{NL-G-F} mice

Authors: *B. SAHU, A. M. FLODEN, S. NOOKALA, C. K. COMBS;
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Abstract: Alzheimer's disease (AD) is a progressive age-related neurodegenerative disorder affecting approximately 35 million individuals worldwide. AD is a leading cause of death in the USA, with an estimated 5.8 million affected. There are several well-established genetic and environmental factors hypothesized to contribute to AD pathophysiology. Besides aging, various comorbid conditions also increase the risk of AD, including obesity, diabetes, air pollution, and asthma. Epidemiological studies have reported a 2.17-fold higher risk of dementia in asthmatic patients >45 years old and 1.27-fold in asthmatic patients ≥20 years old. However, the molecular mechanism(s) underlying this asthma-associated AD exacerbation is not known. This study was designed to explore the effects of house dust mite-induced asthma on AD-related brain changes using the App^{NL-G-F} transgenic mouse model of disease. Male and female C57BL/6 wild type and App^{NL-G-F} mice (8-9 months old) were exposed to either saline vehicle or house dust mite at a dose of 833μg/kg every alternate day for 16 weeks. Mice were sacrificed to collect bronchoalveolar lavage fluid (BALF), blood, and brains at the end of the experiment. BALF was analyzed for immune cell markers, cytokine levels, and overall protein content. Immunohistochemistry for Aβ was performed on fixed brain sections. Aβ ELISAs and cytokine arrays were performed on frozen hippocampal and cortical lysates and serum. As expected, asthma increased BALF inflammatory cells, several inflammatory and Th_2 cytokines, and pulmonary vascular permeability compared to the vehicle controls. Interestingly, asthmatic App^{NL-G-F} mouse hippocampi had a higher Aβ plaque load. Additionally, the cytokines TNF-α, IL-1β, IL-6, IFN-γ, and IL-5 were elevated in the cortices of dust mite exposed mice compared to vehicle controls, both in wild type and App^{NL-G-F} mice. Serum cytokines such as TNF-α, IFN-γ, IL-5, and IL-13 were also elevated in dust mite exposed wild type and

App^{NL-G-F} mice. Furthermore, soluble Aβ 1-42 was increased significantly in the serum of dust mite exposed *App*$^{NL-G-F}$ mice. Overall, our data suggest that chronic house dust mite exposure exacerbates AD pathophysiology potentially by increasing Aβ levels and inflammatory mediators systemically and in the brain. Understanding a mechanistic relationship linking AD and asthma progression may provide novel therapeutic interventions for both chronic diseases.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

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Program #/Poster #: P202.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Brain translocator protein 18kDa (TSPO) levels are associated with sex-dependent cognitive function deficits in the 5XFAD animal model of Alzheimer's disease

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Envrn. Hlth. Sci., Robert Stempel Col. of Publ. Hlth. & Social Work Florida Intl. Univ., Miami, FL

Abstract: Alzheimer’s disease (AD) is an irreversible neurodegenerative condition leading to dementia affecting the performance of daily tasks. Neuroinflammation is thought to play an important role in AD pathogenesis. Here, we used the 5XFAD transgenic mouse model of AD that expresses five of the human familial mutations and recapitulates features of the human disease including cognitive function deficits and amyloid pathology. Cognitive function was assessed in male and female wildtype (WT) and 5XFAD mice at 7 months (7M) of age using the Barnes Maze. We observed no significant differences in cognitive function between WT and 5XFAD male mice ($F_{1,15}$=1.646, p=0.219), but a highly significant impairment in 5XFAD female mice relative to WT ($F_{1,15}$=18.170, p=0.001) consistent with the gender differences observed in humans. TSPO is a validated neuroimaging biomarker of neuroinflammation that is widely used to study animal models of human neurological disease and neurodegenerative disorders including AD. To assess the level of neuroinflammation in the brain of 7M male and female WT and 5XFAD mice, we performed quantitative autoradiography using the TSPO-specific radioligand [^{3}H]-DPA-713. Brain regions analyzed included the cerebral cortex, striatum, septal nuclei, amygdala, hippocampus, thalamus, and hypothalamus at two different levels of the brain. That is, at +0.48 mm (level 1) and -3.3 mm (level 2) from Bregma based on the Paxinos and Watson mouse brain atlas. Two-way ANOVA of TSPO autoradiography in male mice indicates significant increases in TSPO levels by genotype [$F_{1,70}$=11.9, p=0.001] and brain region [$F_{7,70}$=3.87, p=0.0013] with no genotype x region interaction [$F_{7,70}$, p=0.59]. In female mice, we also found highly significant differences in TSPO levels by genotype [$F_{1,61}$=59.2, p<0.0001], brain region [$F_{7,61}$=5.4, p<0.0001] with no significant genotype x brain regions interaction [$F_{7,61}$=1.26, p=0.285]. The increases in [^{3}H]-DPA-713 specific binding to TSPO ranged from 0-52.8% in male 5XFAD mice and 31.4-134.9% increases in female 5XFAD compared to sex-specific WT mice. The results indicate that brain TSPO levels are inversely associated with cognitive performance in female 5XFAD mice at 7M. The findings in 7M male 5XFAD mice indicate that brain TSPO levels are

significantly increased prior to deficits in cognitive function. These results suggest that brain TSPO levels may be an early biomarker of declining cognitive performance in the 5XFAD mouse model of AD. Future studies will examine the association of brain TSPO levels with cognitive function, amyloid load, and the glial sources of the TSPO response using a life-course approach.

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Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

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Topic: C.02. Alzheimer's Disease and Other Dementias

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NINDS/NIA R01NS110749
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Title: Sex Differences in Metabolic and Hypothalamic Disturbances in the 3xTg-AD Mouse Model of Alzheimer’s Disease Across the Lifespan

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Abstract: Alzheimer’s disease (AD) is often associated with cognitive decline and impaired function of hippocampal and cortical areas; however, several other domains and corresponding brain regions are affected. One such brain region is the hypothalamus, shown to atrophy and develop amyloid and tau pathology in AD patients. The hypothalamus controls several functions necessary for survival, including energy and glucose homeostasis. Changes in appetite and body weight are common in AD, often seen prior to the onset of cognitive symptoms. Therefore, altered metabolic processes may serve as a biomarker for AD and/or a target for treatment, considering they are likely both a result of and contributor to disease progression. Previously, we reported sex differences in metabolic disturbances in ~7-month-old 3xTg-AD mice, accompanied by systemic and hypothalamic inflammation. In the current study, we investigated metabolic outcomes and hypothalamic inflammation in 3xTg-AD males and females at 3, 6, 9, and 12 months of age to determine when these sex-specific metabolic phenotypes emerge. In agreement with our previous study, AD males displayed reduced weight gain and adiposity, as well as reduced blood glucose levels following a glucose challenge, compared to females by 6 months of age. Additionally, we note increased expression of inflammatory markers (Iba1, GFAP, TNF-a, and IL-1B) in the hypothalamus of AD males at 6-9 months. These findings provide additional evidence for sex-dependent effects of AD pathology on altered metabolism, which may be linked to hypothalamic inflammation.

Disclosures: L.S. Robison: None. **O.J. Gannon:** None. **A. Salinero:** None. **D.A. Riccio:** None. **R.D. Kelly:** None. **C. Abi-Ghanem:** None. **K.L. Zuloaga:** None.

Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P202.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CTSI at University at Buffalo

Title: Memory enhancing effect of phosphodiesterase 2 inhibitor: involvement of cAMP and cGMP dependent antioxidant stress and neuronal remodeling

Authors: S. GAO[1], X. ZHU[2], J. O'DONNELL[1], ***Y. XU**[1];
[1]The State Univ. of New York at Buffalo, Buffalo, NY; [2]Case Western Reserve Univ., Cleveland, OH

Abstract: Memory enhancing effect of phosphodiesterase 2 inhibitor Bay 60-7550: involvement of cAMP/cGMP-dependent antioxidant stress and neuronal remodeling
Shichao Gao[1], Xiongwei Zhu[2], James M. O'Donnell[1], Ying Xu[1] 1. Department of Pharmaceutical Sciences, School of Pharmacy & Pharmaceutical Sciences, University at Buffalo, The State University of New York, Buffalo, NY 142142. 2. Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106
Phosphodiesterase 2 (PDE2) mainly catalyzes the hydrolysis of the second messengers cyclic AMP (cAMP) and cyclic GMP (cGMP), which play crucial roles in learning and memory processes. Previous studies suggested that inhibition of PDE2 by Bay 60-7550 ameliorates memory loss upon exposure to oxidative stress. However, whether PDE2 inhibition ameliorates memory deficits associated with Alzheimer's disease by enhancing antioxidant function and neuronal remodeling, are largely unexplored. This study investigated how Bay 60-7550 rescues the dysregulated cAMP/cGMP-related oxidative stress in Aβ oligomers (AβO)-treated neuronal cells and regulates memory behavior in Alzheimer's disease mouse model. The results suggested that exposure of SH-SY5Y cells to AβO resulted in time- and concentration dependent increases in PDE2 expression, which are parallel to increased oxidative parameter malondialdehyde (MDA) level and cellular apoptosis. However, this AβO-induced oxidative stress was blocked by pretreatment with protein kinase A or G inhibitor H89 or KT5823, suggesting the involvement of cAMP/cGMP-dependent signaling. The subsequent *in vivo* study suggested that microinjection of AβO into prefrontal cortex of mice increased MDA level; while Bay 60-7550 treatment reversed this effect and increased antioxidant and antiapoptotic factors' levels. Bay 60-7550 also rescued AβO-induced neuronal atrophy and working memory performance in the eight-arm maze and novel object recognition tests, which were also prevented by either H89 or KT5823. These findings suggest that inhibition of PDE2 contributes to antioxidant defense and neuronal remodeling in AD mouse model, indicating that PDE2 may be a potential target for the treatment of AD dementias.

Disclosures: S. Gao: None. **X. Zhu:** None. **J. O'Donnell:** None. **Y. Xu:** None.

Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P202.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Simultaneous RNA and protein imaging using a spatial omics platform reveals cellular composition changes in Alzheimer's Disease mouse models

Authors: N. KOTOVA, R. YIN, I. OH, T. AWAD, ***M. OTERO-GARCIA**;
Rebus Biosystems, Santa Clara, CA

Abstract: Cell-type composition and expression of immune response genes are two key variables in neurodegeneration mouse model studies, but using Single-cell RNA sequencing to measure them sacrifices important anatomical and morphological information. Here we present a methodology which allows accurate gene expression quantification without compromising spatial resolution. Using Rebus' automated high-throughput spatial omics platform, we quantified the expression of 30 target genes at the single-cell level, in addition to two proteins of interest, in the hippocampus of two disease models plus a wild-type control mouse. We were able to define the major neuronal and glial cell types, anatomical structures, and quantify expression changes in disease-related genes. We measured changes in the relative abundances of the defined cell types and their spatial relationships between disease conditions. We also explored the relationship between these pathological gene-expression changes and the presence of proteins of interest. These results demonstrate the ability of the Rebus Esper spatial omics platform to yield high-throughput spatial omics data with single cell resolution. The combination of large imaging area, high-plex RNA quantification, and protein imaging offers a unique and powerful tool to explore complex tissues with an unprecedented level of detail.

Disclosures: N. Kotova: None. **R. Yin:** None. **I. Oh:** None. **T. Awad:** None. **M. Otero-Garcia:** None.

Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

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Program #/Poster #: P202.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: HKU Seed Funding for Basic Research 202011159177

Title: Il-1bas a key cytokine to regulate infiltration of monocytes/macrophages in the brain in systemic inflammation

Authors: *R. C. C. CHANG[1,2], X. K. CHEN[1], A. C. H. MA[3];
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Abstract: Our previous studies have shown that laparotomy of the intestine in laboratory mice stimulates cytokine production and activation of microglia in the brain. However, it is unclear whether activation of systemic monocytes/macrophages can migrate into the brain. Since it is easy to prepare gene knockout and mutation in zebrafish, we extend our study to zebrafish by using tail amputation as a model of traumatic injury. Tg(coro1a:DsRed) transgenic zebrafish was used to monitor microglia and macrophages. Tg(mpx:mCherry) was used for monitoring neutrophils, Tg(mepg1:GFP) was used for monitoring macrophages. We have used TALEN method to make knockout or mutation of IL-1β in zebrafish. Quantitative PCR and immunohistochemical staining were used for examination. Acridine orange and TUNEL were employed for labeling apoptotic cells. Tail amputation was performed at day 3 of embryos under anesthetization with tricaine. Tail amputation recruited accumulation of monocytes/macrophages into the wound site in zebrafish tail. Surprisingly, an increased number of macrophages and microglia were also found in the brain, which was tissue-specific as no other organs showed a similar phenomenon. The expression of mRNA for different cytokines was examined in the brain. Among these, IL-1β was significantly increased. Therefore, we prepared IL-1β knockout and mutated zebrafish. After amputation, the number of macrophages in the brain did not show any significant increase. To further understand why monocytes/macrophages migrate into the brain after peripheral wound injury, we found an increased number of apoptotic cells in the brain after wound injury. IL-1β had a key role in regulating the migration of monocytes/macrophages. Our study demonstrated that zebrafish is a good animal model to investigate how peripheral wound injury triggers neuroimmune responses. IL-1β is a key player to regulate the migration of monocytes/macrophages into the brain.

Disclosures: R.C.C. Chang: None. **X.K. Chen:** None. **A.C.H. Ma:** None.

Poster

P202. Alzheimer's Disease: Neuroinflammation and Immune Actions: In Vivo Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P202.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant HL142752

Title: Sex-dependent effects of chronic intermittent hypoxia exposure in the 5xFAD mouse model of Alzheimer's disease

Authors: *A. C. EWALD[1], K. M. MARINO[2], A. B. RADCLIFF[3], P. Z. ROMERO[3], E. C. MCCANN[3], T. K. ULLAND[2], T. L. BAKER[3], J. J. WATTERS[3];
[1]Comparative Biosci., Univ. of Wisconsin, Madison, Madison, WI; [2]Pathology and Lab. Med., [3]Comparative Biosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: Neurodegenerative diseases strongly correlate with the incidence of sleep apnea in humans. However, whether the neurodegeneration leads to sleep apnea or vice versa is not yet clear. To address this, we utilized a genetic mouse model of Alzheimer’s disease (AD; hemizygous 5xFAD) and exposed

them to chronic intermittent hypoxia (CIH), a hallmark of sleep apnea. This model mimics daily, untreated sleep apnea throughout a lifetime, beginning before disease symptom onset, to identify the impact of CIH on neurodegenerative decline. Male and female WT and 5xFAD mice received CIH (90s alternating 6.5%/21% O_2) or normoxia (90s alternating 21%/21% O_2) for 12 hrs/day during their sleep cycle from age 4 months to 10 months. Prior to, and every two months during CIH exposure, prefrontal cortex- and hippocampal-dependent behavioral testing was performed to assess disease-related decline. Preliminary behavioral data in both male and female 8-month-old animals demonstrated decline in cognitive function of control (normoxia) 5xFAD animals. Interestingly, CIH WT animals exhibited cognitive dysfunction at this time point, and the 5xFAD animals had exacerbated decline in conjunction with CIH. After final behavioral testing, brains were harvested for immunohistochemistry analysis and immunomagnetic microglial isolation. Imaging analysis demonstrated sexually dimorphic alterations in amyloid-beta plaque quantity and intensity. Studies are underway to analyze microglial immune responses, inflammatory and intercellular communication gene expression by RNA-sequencing. Together, these data suggest that CIH, prior to AD cognitive symptom onset, may exacerbate neurodegenerative disease that correlates with altered microglial function, in a manner that differs by sex. These observations have implications for individuals with sleep apnea and AD progression.

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Poster

P411. Somatosensory Thalamic and Cortical Processing

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P411.01

Topic: D.04. Somatosensation – Touch

Support: Swiss National Science Foundation

Title: Dynamic stimulus representation by somatosensory cortical circuits during sensory discrimination learning

Authors: *T. BAWA[1], R. CHÉREAU[1], S. PAGÈS[1,2], A. HOLTMAAT[1];
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Abstract: Cortical networks are constantly remodelled to retrieve and encode new information. During sensory learning, the cerebral sensory cortices integrate sensory information that is fed forward from the thalamus with feedback information coming from higher-order cortical or thalamic areas. Previously, our lab and others have shown that in this process, pyramidal neurons (PN) in the mouse primary somatosensory cortex (S1) can adapt their response selectivity for sensory stimuli depending on the associated reward contingencies. Changes in such responses are thought to be the result of plasticity that ultimately promotes synapses activated by stimulus-driven feedforward signals. Other studies in our lab have revealed that feedback signals from the higher-order posteromedial (POm) thalamic nucleus of the somatosensory system mediate long-term potentiation of PNs in S1. Disinhibition through the activation

of vasoactive intestinal peptide-expressing (VIP) interneurons (IN) was identified as an important circuit mechanism for this form of plasticity. We sought to investigate whether the dynamic perceptual feature selectivity of PNs during learning is associated with changes in the stimulus-evoked responses of thalamocortical projections from POm or local VIP INs during sensory discrimination learning. We hypothesise that both POm and VIP INs, exhibit a transient change in their responses during sensory learning, which would forecast alterations in PN selectivity and the animal's discrimination performance. We use *in vivo* calcium imaging to longitudinally monitor the responses of individual layer 1 (L1) POm axonal boutons, and L1 and L2/3 VIP INs during reward-based and whisker-mediated texture discrimination learning. We observe that both POm axons and VIP INs are active during texture discrimination and both display an increase in texture selectivity as the animal learns. As observed with PNs, feature selectivity of POm projections and VIP INs is highly dynamic during the learning process. POm projections show distinctive responses for combinations of stimulus features and reward contingencies, while the selectivity of VIP INs tends to reflect more the stimulus contingencies. We are currently investigating whether the POm projections and VIP INs exhibit specific responses during the transition between the naïve and expert phases of learning. Altogether, our study suggests that the POm and VIP INs in S1 convey sensory discrimination information to L2/3 PNs, implying that they play an important role during sensory perception and learning.

Disclosures: T. Bawa: None. **R. Chéreau:** None. **S. Pagès:** None. **A. Holtmaat:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

Location: Virtual Only

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Topic: D.04. Somatosensation – Touch

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McKnight Technological Innovations Award in Neuroscience
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NINDS NS094184
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NEI EY028812

Title: Morphological analysis of driver inputs from layer 5 corticothalamic axons in higher order posterior medial nucleus of thalamus.

Authors: *V. SAMPATHKUMAR[1], A. J. MILLER[2], S. SHERMAN[3], N. B. KASTHURI[2];
[2]Neurobio., [1]Univ. of Chicago, Chicago, IL; [3]Dept Neurobiol, Univ. Chicago, Chicago, IL

Abstract: Driving afferents to the thalamus, such as that from layer 5 of cortex, are generally subserved by inputs with large terminals forming onto more proximal dendritic locations. We combined large volume serial electron microscopy (EM) in Rbp4-cre transgenic mice to label differentially layer 5 axons and terminals from the somatosensory (S1) and motor (M1) cortices. With such an approach, we recently demonstrated that layer 5 inputs to neurons of the posterior medial (POm) nucleus of the thalamus indeed

commonly produce such synaptic inputs, but the population of such afferent terminals include some that are smaller and/or that terminate more distally on dendrites. We asked whether the variability in such terminal morphology was seen with input from individual layer 5 axons or whether such axons individually produced less variable terminal morphology. That is, does the variability in terminal morphology seen in layer 5 inputs exist within single axons or is it a feature of variability among axons? To address this, we reconstructed 34 layer 5 corticothalamic axons from S1 and 17 axons from M1 in POm in two mice. We found no evidence of distinct populations of axons with regard to terminal morphology and instead commonly found that individual axons from both M1 and S1 mostly formed large terminals that contact proximal dendrites but also produce a minority of smaller terminals that form more peripherally onto dendrites. Furthermore, despite the relatively low frequency of synapses along axons, we found commonly that individual S1 axons will synapse multiple times with the same postsynaptic POm neuron. That is, of 11 S1 axons found to innervate five different POm neurons, seven of these axons made multiple synapses onto the same cell. Only one of the five POm neurons did not receive multiple synapses from the same axon. Future studies will ask similar questions about the arborization patterns of POm neurons axons in secondary somatosensory cortex. These experiments suggest that the variability in the morphology of driver inputs from layer 5 is not due to subpopulations of afferents with variable morphology.

Disclosures: V. Sampathkumar: None. **A.J. Miller:** None. **S. Sherman:** None. **N.B. Kasthuri:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

Support: NIH Grant NS094184-01A1
NIH/NEI Grant RO1 EY022388
NIH Grant F31 EY031965

Title: A transthalamic pathway via the posterior medial nucleus is necessary for whisker discrimination

Authors: *C. MO, C. MCKINNON, S. M. SHERMAN;
Neurobio., Univ. of Chicago, Chicago, IL

Abstract: In sensory systems, pathways from primary cortex to secondary cortex can arrive directly (cortico-cortical) or indirectly through higher order thalamus (cortico-thalamo-cortical). The function of the transthalamic route is unknown, despite its ubiquity and driver-type glutamatergic synapses. In the somatosensory system in the mouse, we optogenetically inactivated the transthalamic pathway at its cortico-thalamic terminals and found that this projection is essential to drive specific cells in secondary cortex and for performance in whisker-based texture discrimination. To label layer 5 cortico-thalamic terminals, AAV8-CAG-FLEX-JAWS-KGC-tdTomato-ER2 was injected into primary somatosensory cortex (S1) of 9-11 week old Rbp4-Cre x Thy1-GCAMP6S mice. Two weeks later, a 4mm diameter glass window was installed over left S1 and secondary somatosensory cortex (S2). An optic fiber was also

implanted 3.2mm deep at 8° vertical into the posterior medial nucleus (POm) of the thalamus. Jaws-tdTomato expression was visualized through the window as confined to S1 barrels, which were located by intrinsic signal optical imaging. Mice were trained in a head-fixed, delayed go/no-go task to discriminate between texture panels presented to the right whisker field. A panel with a coarse grating (P60) on a foil background was the go stimulus, and a panel with foil alone was the no-go stimulus. A 1sec delay separated the end of the texture presentation period and the response period, signaled by an 8kHz tone. Once mice reached >70% correct for 2 days, 4 other gratings of variable coarseness were added to test psychometric performance. A 633nm laser inactivated cortico-thalamic Jaws-expressing terminals in POm. We found effects depending on the period of task processing. Inhibition during the texture period severely impaired discrimination performance, and, inhibition during the delay period increased the threshold of discriminability (n=5 mice). We also imaged GCAMP6S activity in layer 2/3 of either S1 or S2 during performance and found that S2 cells could discriminate texture trials better than S1 cells and laser inhibition suppressed texture-responsive S2 cells more than S1 cells. TdTomato-expressing mice (n=2) and Jaws-expressing mice with a fiber implanted away from POm (n=2) did not show any effects of laser activation. Our results suggest that the layer 5 S1 - POm - S2 transthalamic pathway propagates complex sensory information such as texture features.

Disclosures: C. Mo: None. **C. McKinnon:** None. **S.M. Sherman:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

Support: Vici NWO 865.13.007 to M.H.P.K

Title: Demyelination impairs layer 5 corticothalamic feedback in the somatosensory system

Authors: *N. JAMANN[1,2], J. S. MONTIJN[1], S. DRIESSENS[1], J. A. HEIMEL[1], M. H. P. KOLE[2,1]; [1]Netherlands Inst. for Neurosci., Royal Netherlands Acad. of Arts and Sci., Amsterdam, Netherlands; [2]Cell Biology, Neurobio. and Biophysics, Dept. of Biology, Fac. of Sci., Univ. of Utrecht, Utrecht, Netherlands

Abstract: Myelination is essential for temporally precise and rapid action potential (AP) propagation. There is emerging evidence that myelin sheath properties differ widely across brain regions and can be altered activity-dependently to fine tune and adjust temporal delays. In the somatosensory whisker system, the information transfer via projections from layer 5 (L5) pyramidal neurons to the posteromedial nucleus of the thalamus (PoM) plays a powerful role in providing feedback information to thalamic neurons, who act as coincidence detectors for synchronized activity. Here, we studied the role of L5-to-PoM myelination in precise timing of corticothalamic feedback in vitro and in vivo. Using a retrograde AAV targeting approach in combination with a L5-specific Cre-driver mouse line (Rbp4-Cre) and immunofluorescent stainings against nodal compartments (Caspr, Ankyrin G), we investigated morphological parameters of nodes of Ranvier (noR) and internodes along the axonal projections within

the cortex, corpus callosum, striatum and thalamus. After 6 weeks of cuprizone-induced demyelination, we observed a diverse pattern of disassembly of nodal compartments. NoR either lacked one or both paranodes, most prominently in the cortex (~20% of the noR). In the white matter regions, paranode lengths were significantly increased, indicating impaired node clustering. To test how these changes in axon architecture associate with information transmission we used optogenetic stimulation of L5-to-PoM axons in acute brain slices in combination with whole-cell patch-clamp recordings of PoM neurons. The results showed a reduced conduction velocity in demyelinated L5-to-PoM axons (1 m/s vs 0.2 m/s, $P < 0.05$, $n = 8$) and a significant and frequency-dependent impairment of synaptic transmission (at 20 Hz, 30% reduction, $P < 0.01$). Furthermore, to understand how information transfer is affected in vivo we employed extracellular recordings with Neuropixels probes to record at high-density and simultaneously both whisker- and optically-evoked activity in S1 and PoM. Preliminary data suggests that demyelination increases the delay to spike triggering in PoM, as well as the jitter and failure rates. In vivo patch-clamp recordings will be utilized to identify whether L5-to-PoM projections are affected at the supra- and subthreshold levels. Taken together, demyelination disrupts the proper function of corticothalamic loops, which are key to sensory processing. Our findings demonstrate the crucial role of myelination for precisely timing the information transfer between neurons in distant brain-regions.

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Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

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Swiss National Science Foundation Postdoctoral Fellowships P2ELP3_168506

Title: Synchrony dependent corticothalamic gating of thalamocortical sensory encoding

Authors: *E. DIMWAMWA, A. PALA, G. B. STANLEY;
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Abstract: Amid the more canonically studied feedforward neuronal pathways that enable us to perceive the world through our senses, there are numerous feedback processes. Corticothalamic feedback neurons from layer 6 of the cortex (L6CT) is one such process that provides extensive inputs back to the thalamus. Despite corticothalamic projections outnumbering thalamocortical (TC) projections 10:1 (Deschênes, P. et al., 1998), the function of L6CT neurons remains elusive. L6CT neurons are well-positioned to play an important role in TC sensory signaling and our objective is to elucidate this role. Using the vibrissal

system of awake, NTSR1-cre mice selectively expressing ChR2 in L6CT neurons, we conduct simultaneous extracellular recordings of populations of individual neurons in the primary somatosensory cortex (S1) and Ventral Posteromedial nucleus (VPm) of thalamus. While optically driving the spiking activity of ChR2-expressing L6CT neurons, we investigate how L6CT neurons modulate thalamic and cortical neuronal activity. We find that firing rates of VPm neurons can be enhanced or suppressed depending on the synchrony of the L6CT inputs. More specifically, while a constant optical input decreases VPm firing rates relative to baseline, a noisy optical input to increase L6CT synchrony (while accounting for firing rate) in turn enhances VPm firing rates. In addition to providing monosynaptic excitation via direct projections to VPm, L6CT neurons also provide disynaptic inhibition via projections to the inhibitory Thalamic Reticular Nucleus (TRN). Interestingly, preliminary recordings in TRN show comparable, enhanced firing rates under both conditions. Taken together, we hypothesize a synchrony dependent L6CT excitatory window of integration (WOI) as the underlying mechanism gating net enhancement/suppression of VPm. This is akin to the well-characterized TC WOI in the feedforward pathway, and thus may emerge as a fundamental principle underlying sensory processing throughout the sensory hierarchy.This WOI can have important implications for the representation of sensory stimuli, which we explore. In preliminary results, we find that asynchronous L6CT input shifts both the pre-stimulus and sensory evoked response of both thalamic and cortical neurons to brief, punctate whisker deflections. These shifts increase the theoretical detectability of sensory stimuli; ongoing work will establish whether synchronous L6CT inputs further shift detectability of stimuli. Success of this work will illuminate a relevant context for the study of L6CT as well as provide a functional link between L6CT and sensory encoding.

Disclosures: E. Dimwamwa: None. **A. Pala:** None. **G.B. Stanley:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

Support: NIH/NINDS BRAIN R01NS104928
Georgia Tech-Emory-PKU Global Biomedical Engineering Research and Education Fellowship

Title: The timescale of adaptive dynamics in the thalamocortical circuit

Authors: *Y. LIEW[1], N. C. WRIGHT[1], Y. ZHANG[2], G. B. STANLEY[1];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Hlth. Sci. Ctr., Peking Univ., Beijing, China

Abstract: Sensory processing requires efficient transmission of sensory information across multiple brain regions, and flexible neural representation is often required to capture changes in the environment across a range of timescales, from seconds to minutes. When the brain is presented with persistent stimuli, neurons adapt their spiking responses accordingly to match the statistics of their inputs. Although sensory adaptation has been shown to be a vital mechanism for sensory encoding beyond just the loss of

sensitivity in response to persistent stimulation, the neural basis of sensory adaptation across timescales remains underexplored. While nearly all studies of adaptation focus on a single, relatively short timescale of seconds, here we ask how the effects of persistent stimulation depend on the duration of exposure, spanning multiple timescales. Specifically, we take advantage of the well-known anatomical and functional organization of the rodent whisker pathway to perform in vivo anesthetized, large-scale recordings from the ventroposteromedial nucleus of the thalamus (VPm) and layer 4 of primary somatosensory cortex (S1) to understand the effect of prolonged exposure to persistent stimuli on thalamic neurons and their downstream cortical targets. We presented punctate whisker deflection trains to individual whiskers and quantified the adaptive effects on VPm and S1 as a function of stimulus duration. Our preliminary results demonstrate that the degree of neuronal adaptation in both the thalamus and cortex increases with stimulus duration, and importantly, neurons adapt well beyond a single, short timescale that is typically described in the literature. In general, adaptation of response amplitudes and latencies of VPm and S1 neurons increased with time. Compared to VPm, adaptation was on average more variable across neurons in S1, likely due to the complex integration of feedforward thalamic and intracortical synaptic inputs to cortical neurons. Preliminary results also show that recovery from adaptation depended on the duration of the adapting stimulus. Finally, the synchronization of thalamic spiking adapted with persistent sensory stimulation, though the relationship with stimulus duration is complex and warrants further investigation. Although to what extent prolonged adaptation can cause a switch from reversible neuronal change to a permanent one remains unclear, here we found preliminary evidence that suggests distinct adaptive circuit motifs can emerge across multiple timescales.

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Poster

P411. Somatosensory Thalamic and Cortical Processing

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Program #/Poster #: P411.07

Topic: D.04. Somatosensation – Touch

Support: NIMH-IRP

Title: Higher-order thalamic nucleus contributes to sensory perception during active sensing in mice

Authors: *J. QI, C. YE, A. R. INACIO, S. LEE;
Natl. Institue of Mental Hlth., Bethesda, MD

Abstract: The higher-order thalamic nucleus in rodent somatosensory, the posteromedial thalamic nucleus (POm), is a critical network hub integrating sensory-motor processing. While POm has dense cortical and subcortical projections, POm neurons weakly respond to sensory stimulation, and the role POm plays in sensory perception during active sensation remains unclear. Here, we investigated the role of a higher-order thalamic nucleus in perceptual decision during active sensation in the vibrissa-related somatosensory system. We first develop a whisker-dependent, self-initiated, two-alternative forced-choice (2AFC) sensory perception task in freely moving mice to probe the circuit mechanisms of POm in context-dependent sensory processing. We demonstrate that chemogenetic suppression of POm activity

significantly impairs the behavioral performance in the whisker-dependent sensory discrimination task, leading to a progressively extensive impairment as the difficulty of the task increased. By combining optogenetic manipulation of the projections from the sensory cortex, motor cortex, or the brain stem to POm, we find that the corticothalamic projection from the layer 5 neurons in the primary somatosensory cortex is critical the contribution of POm to sensory perception. Our results suggest that 1) the POm thalamic nucleus significantly contributes to sensory perception during active sensing, and 2) the role of POm in sensory perception is mainly inherited from the primary somatosensory cortex but not from motor cortical projections or brainstem ascending pathway.

Disclosures: J. Qi: None. **C. Ye:** None. **A.R. Inacio:** None. **S. Lee:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

Support: NIH R01 NS094659
NIH R01 NS069679
NIH T32 EY013933

Title: Effects of arousal and movement on secondary somatosensory and visual thalamus

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Abstract: All neocortical sensory areas have an associated primary and secondary thalamic nucleus. While the primary nuclei encode sensory information for transmission to cortex, the nature of information encoded in secondary nuclei is poorly understood. We recorded juxtasomally from neurons in secondary somatosensory (POm) and visual (LP) thalamic nuclei of awake head-fixed mice with simultaneous whisker tracking and pupilometry. POm activity correlated with whether or not a mouse was whisking, but not precise whisking kinematics. This coarse movement modulation persisted after unilateral paralysis of the whisker pad and thus was not due to sensory reafference. POm continued to track whisking even during optogenetic silencing of primary somatosensory and motor cortex and after lesion of superior colliculus, indicating that motor efference copy cannot explain the correlation between movement and POm activity. Whisking and pupil dilation were strongly correlated, raising the possibility that POm may track arousal rather than movement. LP, being part of the visual system, is not expected to encode whisker movement. We discovered, however, that LP and POm track whisking equally well, suggesting a global effect of arousal on both nuclei. We conclude that secondary thalamus is a monitor of behavioral state, rather than movement, and may exist to alter cortical activity accordingly.

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Poster

P411. Somatosensory Thalamic and Cortical Processing

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Topic: D.04. Somatosensation – Touch

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Title: Layer 6 corticothalamic neurons in the barrel cortex are not a homogenous population: distinct functional subtypes revealed through targeted recordings in awake behaving mice

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Abstract: Layer 6 corticothalamic (L6 CT) neurons are in a strategic position to control thalamocortical transmission and sensory responses in the cortex, yet we understand very little about their function during behavior. Apart from studying their anatomical, physiological and synaptic properties, most recent efforts have focused on the activity-dependent influences CT cells can exert on thalamic and cortical neurons through causal optogenetic manipulations. However, very few studies have attempted to study them during ethological relevant behaviors. In an attempt to address this gap, we performed targeted juxtacellular recordings from optogenetically identified CT neurons in vibrissa primary somatosensory cortex (vS1) of awake, head-fixed mice free to rest quietly or self-initiate bout of whisking and locomotion. We found a rich diversity of response profiles exhibited by L6 CT cells. Broadly, their spiking patterns were either modulated by whisking behavior (~33%) or not (~66%). Whisking-related CT neurons exhibited both increases as well as decreases in firing rates. We also encountered CT cells with preceding (putatively motor-related) modulations in firing rate before whisking onset. Overall, whisking better explained these changes in firing rates than overall changes in arousal. The CT cells that showed no whisking-related activity had low spontaneous firing rates (<0.5 Hz), with many all but silent. Remarkably, this relatively silent CT population generated precisely timed spikes during pupil constriction, corresponding to a transition from low to high delta cortical network state. Thus, our results demonstrate that L6 CT neurons in rodent vS1 show diverse activation patterns, perhaps subserving distinct functional roles related to precisely timed responses during complex behaviors and transitions between discrete waking states.

Disclosures: S. Dash: None. **D.M. Autio:** None. **S.R. Crandall:** None.

Poster

P411. Somatosensory Thalamic and Cortical Processing

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Title: Thalamic control of the cortical excitatory-inhibitory ratio and implications for cortical sensory representations

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Abstract: Inhibition has long been known to play a key role in the early sensory pathway, by balancing synaptic excitation to gate the sensory-evoked output of relay neurons. For example, parvalbumin-positive (PV) interneurons in cortical layer 4 (L4) provide dampening inhibition that shapes both the rate and timing of L4 firing evoked by synaptic excitation. This excitation-inhibition (E-I) balance is often considered to be a static property of anatomy, but recent work has demonstrated rapid changes in the L4 E-I ratio across states of wakefulness (Yu et al. 2016; Stringer et al. 2016). While this may involve a range of mechanisms that shape the E-I ratio across cortical sensory areas, layers, and timescales, one intriguing possibility is that the L4 E-I ratio is rapidly and focally altered via differential drive of excitatory and inhibitory neurons by primary sensory thalamus (Yu et al. 2016). This has profound implications for the shaping of L4 sensory representations via changes in feedforward inhibition and large-scale cortical activity, or "state" (Isaacson and Scanziani 2011; Stringer et al. 2016), but these predictions have yet to be directly tested. To determine the ability of thalamus to alter the L4 E-I ratio and thereby shape cortical sensory representations, we recorded spiking activity in primary somatosensory (S1) cortex and the upstream ventral posteromedial (VPm) thalamic nucleus in the vibrissa pathway of the awake, head-fixed mouse, while optogenetically manipulating baseline VPm rates and presenting precise whisker stimulation. We estimated the E-I ratio using the firing rates of cortical regular-spiking (RS, putative excitatory) and fast-spiking (FS, putative inhibitory) interneurons. We found that spontaneous, sensory-driven, and light-driven elevation of baseline VPm rates differentially elevates FS rates and alters spectral properties of the cortical local field potential (a descriptor of cortical state). A model network reproduces this decrease in the E-I ratio via differential thalamocortical connectivity to excitatory and inhibitory neurons. Further, such shifts in the baseline E-I ratio impact representations of simple stimuli, as RS responses to punctate whisker deflections are smaller when pre-stimulus FS rates are relatively elevated. Taken together, these results suggest that primary sensory thalamus can indeed shape cortical sensory representations in part by rapidly modulating the E-I ratio. Next, we plan to explore the implications for representations of more temporally rich sensory stimuli.

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Poster

P483. Representation of Objects and Scenes II

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Topic: D.07. Vision

Support: FWO Vlaanderen G088418N
KU Leuven C14/17/109

Title: Comparison of statistical learning signals between macaque inferotemporal and prefrontal cortex

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Abstract: Many species are sensitive to temporal regularities in their environment. Such extraction of statistical regularities is referred to as "statistical learning". Studies in macaque inferotemporal (IT) showed stronger spiking activity to images that violated a learned image sequence ("deviants"; e.g. Meyer and Olson, 2011; Kaposvari et al., 2016; Schwiedrzik and Freiwald, 2017). However, it is unknown whether this enhancement originates within IT. One candidate origin is ventrolateral prefrontal cortex (VLPFC), connected with IT, and which may detect the difference between predicted and observed stimuli. We assessed whether VLPFC shows a different response to deviant versus predicted images and compared the time course of the deviant response between VLPFC and IT. We performed multi-site linear array recordings of spikes and local field potentials (LFPs) in IT and VLPFC simultaneously after exposing the 2 female rhesus monkeys for weeks to 5 triplets of images of animals for which within-triplet (S1-S2-S3) image order was fixed. Triplets were shown during passive fixation without interstimulus interval and stimulus duration of 500 milliseconds followed by a reward. During recordings, 16% of the second stimuli (S2) of the triplets were deviants, i.e. originated from another triplet. As IT, VLPFC showed enhanced LFP power to the deviant image for gamma frequencies, while beta frequency power was suppressed. The multi-unit activity (MUA) of each individual monkey in both IT and VLPFC demonstrated the enhancement to the deviant images. These effects were present for the LFP power and MUA for both the second (S2; =deviant) and third image (S3) of a triplet, indicating coding of only adjacent stimulus dependencies not only in IT (Meyer and Olson, 2014; Kaposvari et al., 2016), but also in VLPFC. The deviant response occurred approximately 33 milliseconds earlier in IT than VLPFC in both monkeys. Furthermore, cross-temporal decoding analysis (linear SVM) using the high gamma power showed no evidence of predictive stimulus coding in IT during the presentation of S1 and S2. These data suggest that at least the early part of the deviant response in IT does not originate from a prediction error signal in VLPFC.

Disclosures: H. Esmailpour: None. **R. Vogels:** None.

Poster

P483. Representation of Objects and Scenes II

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Topic: D.07. Vision

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Title: A gravitational reference frame for stable vision across head tilt

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Abstract: We obtain visual information in a retinal reference frame, which is frequently tilted laterally, with the head, up to 45° or more during normal physical activity or at rest. Yet head tilts in this range (which are compensated only ~20% by ocular counterrotation) have little effect on visual function or the perceived orientation of the world. Here, we report that the brain transforms visual information into a gravitational reference frame, which would remain stable across head tilts. We measured neural tuning for object orientation in the final stage of ventral pathway object vision, in inferotemporal cortex (IT) of macaque monkeys, during combined body/head tilts of +/-25°. Test objects were high-response abstract 3D shapes (discovered through an initial search process) rendered photo-realistically with Blender, on a blank background in a dark room. Object tilt was sampled across a range of 200° centered on the original orientation of the high-response stimulus. Responses to this range of object tilts were sampled in 2 conditions, in which the monkey was tilted either 25° clockwise or 25° counterclockwise, around a sagittal axis bisecting the line between the two pupils and running through the fixation point on the screen. The video eye-tracking system rotated with the monkey and confirmed that there was no change in eye position during fixation after rotation. Object coding in a retinal reference frame predicts that the closest correspondence between responses in the two monkey tilt conditions would exist for object tilts shifted by 50°. Object coding in a gravitational reference frame predicts closest correspondence between objects at the same object tilt, regardless of monkey tilt. Many IT neurons showed strong correspondence in the gravitational reference frame (low mean squared error between response rates for identical object tilts) and low correspondence in the retinal reference frame (high mean squared error between response rates for object tilts shifted by 50°). The converse pattern was rare. We also modeled responses for each neuron as a weighted mixture of the two reference frames, and again the gravitational reference frame was dominant. Thus, IT neurons provide clear and easily extracted information about object shape in the gravitational reference frame, which could support stable perception of object structure, balance, and potential energy during real world vision with variable head tilt.

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Poster

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CEA PE Bottom Up 2020 (20P28)

Title: Submillimeter fMRI reveals an extensive and fine-grained scene-processing network in monkeys

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Abstract: Humans and monkeys are endowed with a dedicated cortical network for processing visual scene information, which is critical for navigation and object retrieval (Epstein & Baker, 2019). Given the intrinsic high dimensionality of complex scenes and large within-category variability, one may expect the contribution of many processing modules representing scenes, at least compared to faces and bodies. Currently available data, however, refute this hypothesis. For example, in macaques, about 6-7 occipito-temporal face-selective patches are consistently found, versus only 3-4 consistent scene-selective patches (Kornblith et al., 2013; Nasr et al., 2011; Verhoef et al., 2015). Hypothetically, smaller sized scene-processing modules may be difficult to identify with conventional-resolution fMRI. To overcome this limitation, we scanned monkeys viewing scenes and control stimuli with submillimeter resolution (0.22 mm3 voxels) contrast-agent enhanced fMRI, using implanted phased array receive coils (Janssens et al., 2012; Li et al., 2019). We performed two experiments using entirely different stimuli, aimed to control several high- and low-level features. For example, we included images of scenes familiar and unfamiliar to the monkeys, which appeared to be a surprisingly important determinant of scene-selective activations. Moreover, spatial frequency distributions were made indistinguishable between a mosaic face condition versus scenes. Also, we presented fractured scenes to control for local scene features, such as long lines and indoor textures. Our results revealed a robust, fine-grained, yet three-fold more extensive scene-processing network than previously documented. The core scene-selective network consists of eleven cortical patches distributed over occipito-temporal, parietal, and frontal cortex. Five additional non-core scene-selective patches show similar selectivity relative to all non-scene controls, but only for familiar spaces. Furthermore, the core scene selective patches form not only a functionally connected, but also a functionally relevant network, largely segregated from face and body networks. Functional scene responses correlated dominantly with functional connectivity fingerprints derived from the scene network than from patches from face and body systems. In general, our results invite to revisit the mesoscale functional architecture of all category-selective networks in human and non-human primates.

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Poster

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Title: Things-fmri/meg: a densely sampled-multimodal neuroimaging dataset of brain responses to a broad range of natural object images

Authors: *O. CONTIER[1], M. N. HEBART[1,2], A. H. DICKTER[2], L. TEICHMANN[2], A. KIDDER[2], A. CORRIVEAU[2], C. ZHENG[3], M. VAZIRI-PASHKAM[2], C. I. BAKER[2];
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Abstract: A detailed understanding of object representations in brain and behavior strongly benefits from large-scale neuroimaging datasets for training and testing computational models. Most existing datasets focus on maximizing the number of presented stimuli. For the purpose of studying object representations however, another important dimension is object space coverage, i.e. extensive and representative sampling of objects. Furthermore, most previous large-scale efforts focus on spatial responses, leaving details about temporal response profiles largely unaccounted for. Towards the aim of object space coverage, we recently developed THINGS, a database of more than 26,000 images of 1,854 object concepts sampled from the American English language (Hebart et al., 2019). Here, we present THINGS-fMRI and THINGS-MEG, two large-scale neuroimaging datasets using functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). These datasets are part of the THINGS-initiative, a multidisciplinary effort to study object recognition in several modalities by working on a shared set of objects. The two datasets comprise 7 participants (fMRI: n = 3, MEG: n = 4). Each participant viewed images from the THINGS database (fMRI: 8,740 images of 720 concepts, MEG: 22,448 images of 1,854 concepts) over the course of 12 sessions while performing an oddball detection task. Participants wore custom head casts in order to reduce head motion. We recently demonstrated the general quality, reliability, and validity of these two datasets, as indicated by head motion parameters, noise ceilings, split half reliability and a replication of the effect of object animacy. Building upon these efforts, we are presenting several extensions to the THINGS-fMRI/MEG dataset. First, we further validated the MEG data by showing that object concept and object image identity can be decoded from MEG recordings. Next, we developed a denoising strategy for the fMRI data based on semi-automated classification of independent components. Finally, we extracted single trial response estimates for the fMRI data which drastically decreases computational cost for subsequent analyses (compared to time-series data) and enables more data driven analysis approaches. Thereby, we hope to further increase the value of the data to the research community and facilitate its use. By covering a broad, representative, and multimodal sample of neural object representations, we hope that these datasets may be of use for visual neuroscience and computational vision research alike and will provide a basis for the extensive evaluation of object recognition in the human brain.

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Poster

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Topic: D.07. Vision

Support: National Eye Institute R01 EY029724

Title: The occipital place area responds to visual information about walking, not crawling

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Abstract: The occipital place area (OPA) - a cortical region supporting "visually-guided navigation" (i.e., finding our way through the immediately visible environment) in adulthood - has recently been found to be late developing, not fully developed until around 8 years old. But how is this prolonged development possible given that we move through our local environment long before 8 years old, beginning with crawling followed by "toddler" and "preschool" walking? One possibility is that OPA represents only the visual information from an "adult-like" walking perspective, and not from the other perspectives encountered during early development. To directly test this hypothesis, using fMRI in 15 human adults, we measured the responses in OPA to videos depicting the actual first-person visual experience of navigating the immediate environment - from either a "walking" or "crawling" perspective, as well as two baseline perspectives (i.e., an aerial "flying" perspective and a "scrambled" version of the walking videos). Consistent with our hypothesis, we found that OPA responded significantly more to the walking videos compared to the crawling, flying, and scrambled ones. Critically, we also found that OPA responded similarly to the crawling, flying, and scrambled videos, indicating that OPA does not respond to crawling information any more than either a perspective by which humans do not navigate ("flying") or a non-navigable perspective all together ("scrambled"). This pattern of results was unique to OPA, and was not found in other scene-selective regions, motion-selective cortex, or primary visual cortex - ruling out any general attentional, motion, or low-level visual information accounts. Collectively, these results 1) reveal that OPA is "tuned" to visual information about adult-like walking, not crawling, consistent with its prolonged development hypothesis, and 2) raise the intriguing question of whether crawling (and early walking even) is a mode of visually-guided navigation at all, or is processed by a different neural system all together.

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Poster

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Topic: D.07. Vision

Title: Understanding the development of attention and temporal binding

Authors: *J. KLEIN[1], A. COOK[1], H. ALLEN[2], J. CLIBBENS[1], V. AMANATIDOU[1], E. MAVRITSAKI[1];

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Abstract: To achieve the task at hand the brain relies on attention to select and process the most relevant information. Here, we compare how attention and perception interact to produce goal-oriented behaviour in children compared to adults. A total of 77 children (mean age 9.7 years) and 78 adults (mean age 20.72 years) were tested on four visual search conditions each with two display sizes (4 and 8), where the target item was always a blue letter "H." The first two baseline conditions were standard single-feature and conjunction searches (Treisman et al., 1980). Distractors were blue letter "A"s and a mixture of blue letter "A"s and green letter "H"s, respectively. The third condition was a standard preview search, where one distractor set (green letter "H"s) was displayed for 750 msec before the second set and target item appeared alongside. The standard preview search task has been found to generate a 'preview benefit,' where search slopes can become as efficient as a standard single-feature search (Watson et al., 1997). The final condition was a preview gap search. In this last condition, the first distractor set (green letter "H"s) was displayed for 750 msec, followed by a white, 250 msec 'gap' display. After the gap, the first set of distractors reappeared in their original positions alongside the second blue "A" distractors and blue "H" target item. The preview gap search has been shown to completely abolish the preview benefit in adults (Watson et al., 1997). A recent computational modelling study has shown this effect is due to the disruption of temporal binding by common onset in adults (Mavritsaki et al., 2016). Here, for the first time, children are tested in this condition. Children and adults showed typical performances in the single feature and conjunction conditions, where single-feature search slopes were significantly faster compared to conjunction search. Slopes in the standard preview search were significantly faster compared to conjunction search for both groups. In the preview gap condition, the preview benefit was abolished, with search slopes significantly slower than those in single-feature search. However, children's search slopes in the preview gap condition were significantly faster than slopes in the conjunction condition. These findings indicate that children have not yet developed the ability to use the common onset as a cue to temporally bind items. Further research should be undertaken to gain a better understanding of when temporal binding develops, and the mechanisms that underlie this process.

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Poster

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Title: Visualization of extra-classical receptive fields that affect visual representation in mouse V1

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Abstract: Visual stimuli which exceed the receptive field (RF) modulate the responses of neurons throughout the visual processing pathways. This surround suppression/facilitation was first reported by using simple artificial stimuli like bars or drifting gratings, and when using natural images as stimuli, the responses of neurons are also modulated to be sparse. Surround suppression becomes the maximum when stimuli presented at the RF and its surround are similar, and it is thought to contribute to sparse and efficient coding by removing spatially redundant visual information. This suppressive surround was not extended uniformly but localized to limited areas of the surround. However, to fully understand the role of surround modulation on neural representations, it is necessary to determine the exact features of natural images that make neural responses sparse. We presented natural images clipped by the two different-size (40 and 90 degrees) circles to lightly anesthetized and sedated adult transgenic (Thy1-GCaMP6s) mice and recorded the visual responses of L2/3 neurons in the primary visual cortex with two-photon calcium imaging. We found that the natural stimuli presented outside the population RFs led to increase in lifetime/population sparseness. Next, we trained convolutional neural networks (CNNs) to predict neural population responses using natural images as input. CNNs could explain neural responses better than linear models, and using these trained neural networks, we visualized images that maximized each output unit of the trained CNNs. The visualized images had the gabor-like structures in most cases. These estimated RFs well predicted preferred orientation calculated from responses to conventional drifting grating stimuli. When the long bars were presented to the network, the trained models showed surround suppression. We identified extra-classical receptive fields structures by visualizing the stimulus features outside the classical RF which minimized the targeted unit responses while keeping stimulus features presented to the classical RF the same. We identified the visual features which make sparser responses in terms of lifetime sparseness. We found the same features also increased population sparseness. These surround structures were robust across training and visualizing initializations and confined to specific positions of the surround, which is consistent with the result of the asymmetric surround of the previous study (Walker et al., 1999). These methods and results can lead to a comprehensive understanding of the relationship between RF and surround structures

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Poster

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Title: Transition between perceptual spaces of low-level features and objects

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Abstract: Elementary features (e.g., color or texture) lie on a continuous scale, while semantic representations (e.g., objects) are often categorical. The transformation of visual signals from elementary features into semantic content may therefore require a qualitative change in the way that information is represented. To probe this process, we developed and implemented a psychophysical paradigm to characterize the geometry of visual representations at several stages of this transformation. In parallel experiments, stimuli were drawn from five domains: (D1) the names of 37 familiar animals (from WordNet), (D2) images of these animals, (D3) pixelated but easily recognizable images of the animals, (D4) texturized images in which the animals were harder to recognize, and (D5) fully scrambled textures. In each experiment, subjects viewed displays consisting of one central reference stimulus and 8 surrounding stimuli. They were asked to rank the surrounding stimuli in order of similarity to the central reference. This rank-order design yielded 5994 unique choice probabilities, and included trials to check for context-dependence, i.e., whether judgments of "Is A (the reference stimulus) more similar to B or to C?" depended on the surrounding stimuli. We found that choice probabilities were consistent across subjects (2M, 6F) and contexts (n=3 for (D1), n=2 for (D2), n=4 for (D3), n=6 for (D4), n=5 for (D5)). To characterize the geometry of the representations of these five domains, we used a variant of multidimensional scaling (MDS). Representations of each domain were modeled by Euclidean spaces, in which points denoted stimuli, and relative distances, along with internal noise, explained choice probabilities. In all domains, five dimensions accounted for the choice probabilities to a large extent, but not completely. Visualizing MDS results showed that the organization of points varied across domains: in the low-level feature spaces (D4 and D5) points were relatively evenly distributed, but in the semantic space (D1) they occupied the periphery of the space. Hierarchical clustering revealed another difference between the domains. Trees obtained from the more semantic domains (D1 and D2) were more balanced than those obtained from the low-level feature domains, and the number of branches from the root of the tree to the individual leaves (objects) was lower in the semantic domains. These findings suggest that points in semantic space are more clustered. Overall, our results demonstrate subtle but systematic differences in the perceptual geometries of semantic and low-level features.

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Poster

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Fiona and Sanjay Jha Chair in Neuroscience (to J.H.R.)

Title: Columnar processing of border ownership in primate visual cortex

Authors: *T. FRANKEN, J. REYNOLDS;
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Abstract: To understand a visual scene, the brain needs to segregate figures from background by assigning borders to foreground objects. Prior studies with single electrodes have discovered neurons in visual cortical areas V2 and V4 that are selective for border ownership (border ownership selectivity, BOS), even if the features that define the object location occur outside of the classical receptive field (cRF; Zhou et al., 2000). It is unknown how BOS is established: a prominent role has been suggested for feedforward inputs (Sakai and Nishimura, 2006), or for horizontal connections and cortical feedback (von der Heydt, 2015; Zhaoping, 2005). Because these pathways have a distinct laminar profile, studying the laminar organization and timing of BOS may give important clues regarding its origin.
Here we investigated the laminar organization of BOS by using 32-channel laminar probes to record from well-isolated units and multiunits in V4 in two behaving male rhesus macaques. By replacing the dura with a transparent membrane we were able to position the probes orthogonally relative to the cortical surface. We presented isoluminant squares on a uniform background to evaluate BOS. We positioned the squares such that only one border overlapped with the cRF. BOS was thus defined by stimulus features outside of the cRF. We used current source density analysis of stimulus-evoked local field potentials to identify the input layer as the current sink with the shortest latency, and locate the units recorded from to superficial, input or deep layers.
We find that border ownership modulation occurs significantly earlier in deep layers than in input and superficial layers. In contrast, spikes evoked by small stimuli centered on the cRF arrive significantly earlier in the input layer than in the superficial and deep layers. BOS units recorded from the same penetration typically share the same preferred side of border ownership, also across layers, suggesting that BOS is organized in columns similar as preferred orientation. When comparing orientation tuning and BOS, we find that BOS can occur for different edge orientations, often far away from the preferred orientation.
Our data argue against the hypothesis that BOS in V4 is simply inherited from upstream visual areas along the feedforward pathway. Instead they are consistent with a model in which deep layer neurons first integrate asymmetric contextual information from a spatially contiguous, often wide area in visual space. Columnar clusters of shared border ownership preference suggest that this afferent contextual information is organized in functionally asymmetric clusters.

Disclosures: T. Franken: None. **J. Reynolds:** None.

Poster

P483. Representation of Objects and Scenes II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P483.10

Topic: D.07. Vision

Support: NEI grant R01EY029724

Title: Using a novel, stimuli-driven approach to uncover a robust image feature that drives human cortical scene selectivity

Authors: *A. CHENG, D. D. DILKS;
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Abstract: Human neuroimaging studies have revealed a dedicated cortical system for visual scene, or place, processing. But what are the stimulus features that characterize visual inputs as a scene, and thereby engage cortical scene processing? While a recent study suggests that concavity is one such feature, it cannot be the only feature that does so. For example, the parahippocampal place area (PPA) and the occipital place area (OPA) respond similarly to both the inside of a building (displaying concavity) and its facade (displaying convexity). So, what are the other stimulus features that characterize visual inputs as a scene, and, perhaps more importantly, given scene images are so variable, how are we even going to identify these other features? Here, we use a novel, stimuli-driven approach to identify another scene-defining stimulus feature. Specifically, we first averaged over thousands of naturalistic images (Study 1), and found that scene images - but not object images - contain a "vertical luminance gradient" (VLG), with the top half of a scene image brighter than the bottom half. Thus, we hypothesized that VLG is a stimulus feature that selectively engages cortical scene processing. In Study 2, using fMRI data from BOLD5000, we then examined the response function of the scene-selective cortical regions, and asked whether VLG systemically increases as neural responses in the scene-selective cortical regions increase. Consistent with our prediction, we found a significant, positive correlation between VLG and the neural responses in the scene-selective cortical regions, but not in an object-selective region or in early visual cortex. To rule out the effects of other potential confounding stimulus features in naturalistic images, in Study 3, we generated tightly controlled VLG stimuli and directly tested the role of VLG in driving cortical scene processing. We found that PPA and OPA responded significantly more to images of VLG over the same, exact images in which VLG was disrupted via image inversion; moreover, no such effect was found in either an object-selective region or in early visual cortex. Taken together, these results reveal that VLG is a visual feature that selectively engages cortical scene processing, and highlight the potential of combining data-driven and hypothesis-driven methods to better understand human cortical processing.

Disclosures: A. Cheng: None. **D.D. Dilks:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.01

Topic: D.08. Visual Sensory-motor Processing

Support: NIH BRAIN Initiative 1R01NS109978
NIH NINDS 1R01NS107968
Whitehall Foundation

GT Neural Engineering Center 1241384

Title: Information content and routing of visuomotor signals in the cortex

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Abstract: Flexible sensorimotor transformations are a hallmark of complex cognitive behaviors. It remains unclear how sensory signals are routed to motor areas of the cortex in the absence of direct connections. In particular, it remains debated if sensory and motor activity relevant for task performance exist locally in relevant cortical areas, or show distributed activation throughout the cortex. By directly and simultaneously measuring neural activity in sensory and premotor areas during a flexible sensorimotor transformation, we can begin to identify principles governing both the information content and the routing of signals relevant for sensorimotor behaviors. We developed a novel behavioral task where head-fixed mice report detection of different visual stimuli with different actions. Mice licked left to report stimuli detected in the central (binocular) visual field, and licked right when detecting stimuli in the right (monocular) visual field. Stimuli were presented in blocks of 15-35 trials in the same location before switching. Behavioral performance varied psychometrically with contrast at each stimulus location (N = 4 mice). We performed acute recordings with Neuropixels probes in primary visual cortex (V1) and anterolateral motor cortex (ALM), and estimated the information content about specific task variables in each area. Peristimulus time histograms from both areas showed clear effects of stimulus location and trial outcome, both as a function of visual stimulus detection (hit vs miss) and non-sensory motor action (false alarm vs correct reject). V1 signals peaked at short-latency (150 ± 53 ms) relative to the reaction time (630 ± 100 ms) and contained significant information about stimulus contrast (9.1 ± 6.3% variance explained), but almost no information about reaction time. Strikingly, in ALM, we also observed information about stimulus contrast (8.1 ± 2.0%) at short-latency (200 ± 16 ms), but with significantly more information about reaction time (15.5± 4.6%) at longer latency (390 ± 27 ms), as expected. To assess the routing of visual information to ALM, we leveraged simultaneous recordings from V1 and ALM. We found a significant delay between V1 and ALM activity on single trials where stimuli were successfully detected in the receptive field of the V1 neurons, with V1 leading ALM by 210 ± 114 ms. We found no such temporal relationship on miss trials where the stimulus appeared in the same position and contrast, or on trials where the stimulus was presented outside of the receptive field. We are currently investigating if visual and motor information is communicated to and maintained in ALM via distinct subpopulations of neurons.

Disclosures: A. Speed: None. **B. Haider:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.02

Topic: D.08. Visual Sensory-motor Processing

Support: Wellcome Trust (209558)

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Simons Foundation

Title: Paradoxical effects of stGtACR2 inactivation of mouse superior colliculus

Authors: *K. Z. SOCHA[1], .. INTERNATIONAL BRAIN LABORATORY[2,1], K. D. HARRIS[1,1], M. CARANDINI[1,1];
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Abstract: [Introduction] Mouse superior colliculus (SC) plays a key role in selecting actions guided by sensory cues (e.g. Huda et al. 2020, Duan et al. 2021, Essig et al. 2021). SC neurons exhibit strongly lateralized activity, responding after contralateral visual cues and before contraversive movements (Steinmetz et al. 2019). A longstanding hypothesis is that SC helps select actions thanks to competitive mechanisms that operate within and across hemispheres. We thus hypothesized that inactivating SC unilaterally would suppress contraversive choices and increase activity in the contralateral SC. [Methods] To test this hypothesis, we inactivated the left SC while recording with a Neuropixels probe in the right hemisphere, in mice that performed a visual discrimination task. We trained head-fixed mice to turn a steering wheel to indicate whether a stimulus appears on the left or right (Burgess et al. 2017, IBL et al. 2021), and we expressed the inhibitory soma-targeting opsin stGtACR2 (Mahn et al. 2018) in deep and intermediate SC layers. The opsin was activated by a laser for 1 s at or before stimulus onset (30% of all trials), through an optic fiber in left SC. In control experiments, we inserted an additional fiber in the right SC. [Results] Unexpectedly, unilateral optogenetic manipulation promoted contralateral choices (n=3 mice), instead of suppressing them. Moreover, it markedly reduced the reaction times, possibly suggesting a different behavioral strategy. Neuropixels recordings revealed that during SC inactivation, units located close to optic fiber in SC were mainly suppressed, but units located in the ipsilateral visual cortex increased spiking. Moreover, units in the opposite hemisphere exhibited a variety of response patterns. [Conclusions] These preliminary results confirm that mouse SC is involved in decision-making and triggers motor actions. However, the effects are opposite to what we expected. They resemble the effects of inactivating projections from anterior cingulate cortex to SC (Huda et al. 2020). Perhaps suppressing SC increases activity in cortex and elsewhere. To test this hypothesis we need further experiments, using different opsins and probing activity in multiple areas.

Disclosures: K.Z. Socha: None. **.. International Brain Laboratory:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.03

Topic: D.08. Visual Sensory-motor Processing

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NIH R01 Grant R01NS104899
NIH R35 Grant R35NS111580

Title: The representation of visual feedback during courtship in Drosophila males

Authors: *N. RANGARAJAN, A. J. CALHOUN, B. R. COWLEY, M. MURTHY;
Princeton Univ., Princeton, NJ

Abstract: Social interactions rely on processing sensory feedback cues from social partners to sculpt ongoing behavior. Here, we investigate how male flies represent visual feedback cues from females as they chase and sing to them during courtship. The *Drosophila* visual pathway contains a large population of visual projection neurons called lobula columnar cells (LCs) that project from the optic lobe to distinct glomeruli in the central brain (Wu et al. eLife, 2016). The LCs are thought to serve as a set of feature detectors for specific behaviors, but how the population functions during natural social behaviors has not been investigated. In fact, male courtship behavior is so far thought to rely primarily on only one LC subset called LC10 (Ribeiro et al. Cell, 2018 and Sten et al. Nature, 2021). To study the LC population, we first used two-photon calcium imaging to record from five different LC subtypes in head-fixed, walking male flies. We presented a wide range of visual stimuli, from simple moving and rotating objects, to more complex fly-like stimuli that mimic the natural motion of the female. We find that all recorded LCs respond to female motion cues, and are additionally modulated by the male's locomotor state. We then built a deep neural network model to recapitulate the sensorimotor transformations that occur within the male nervous system, from processing female visual feedback cues to changes in locomotion and song patterning. We explicitly modeled the LC population within the neural network model by fitting it with neural silencing data and displayed the same stimuli to the model as the real flies. We then validated the model by assessing whether the model predictions matched the neural responses. These data support the idea that males use an LC population code during courtship to track and sing to females.

Disclosures: N. Rangarajan: None. **A.J. Calhoun:** None. **B.R. Cowley:** None. **M. Murthy:** None.

Poster

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Program #/Poster #: P499.04

Topic: D.08. Visual Sensory-motor Processing

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Title: Visual circuit for collision avoidance in walking Drosophila

Authors: *R. TANAKA[1], D. A. CLARK[2,1,3,4];
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Abstract: Visual motion provides animals with rich cues about the spatial relationships between them and their environment, including whether they may be on a collision course with objects in the environment. As an object moves relative to the observer, the size and position of its retinal image change as dictated by geometry. While it has been well studied both at behavioral and neural levels how animals ranging from mammals to insects use apparent size increments (i. e., visual looming) to avoid collision with objects like predators, it has remained relatively unclear whether and how animals use positional cues to detect future collisions. In the present study, we demonstrate that, in walking *Drosophila*, a visual projection neuron type called LPLC1 is necessary and sufficient for slowing caused by small objects moving in the back-to-front direction on their retina. Since back-to-front visual motion predicts that the object is about to cross in front of the observer posing the risk of collision, the slowing behavior likely reflects a strategy for collision avoidance. Using two-photon calcium imaging, we then show that LPLC1 vigorously responds to short objects moving in the back-to-front direction as well as to expanding discs, mirroring our behavioral findings. Combining analyses of a connectomic dataset and optogenetics, we show that LPLC1 implements its response specificity by selectively pooling inputs from both elementary motion detectors and object detectors. In addition, we find spatial bias in the direction selectivity of LPLC1 achieved through glutamatergic inhibition, a potential adaptation to the geometry of collisions. Lastly, we identify a central pathway that conveys LPLC1's signals for the collision avoidance behavior. Overall, our results exemplify how outputs of elementary visual feature detectors can be combined to guide behavior that exploits a universal geometrical constraint of the visual world.

Disclosures: R. Tanaka: None. **D.A. Clark:** None.

Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: ERC grant ERC-2017-STG-759782
FCT grant SFRH/BD/52216/2013

Title: Parallel processing of optic flow signals in central self-motion estimation networks

Authors: *M. ERGINKAYA[1], M. BROTAS[1], K. STECK[2], A. NERN[3], D. BOCK[4], M. B. REISER[3], M. E. CHIAPPE[1];
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Abstract: Sensory experience critically depends on our own movement: the brain must incorporate information about self-movement to guide behavior, or discount self-generated sensory signals to detect external events in the world. How do sensory circuits process self-generated signals in different ways to meet specific demands?
In insects, the pattern of visual motion generated by self-movement, or optic flow, contributes to an

internal estimate of self-motion and is thought to actively control the walking course. Lobula Plate Tangential Cells (LPTCs) of the fly optic system respond to specific patterns of optic flow. LPTCs also receive extra-retinal signals related to head/body movements during locomotion, which suppress or enhance their activity depending on the task. Thus, the LPTC network is suitable to investigate task-dependent processing of self-generated sensory signals for behavioral control. Although some pathways that connect LPTCs to head rotations have been identified, the full extent of the central circuitry that enable optic flow signals to control behavior remains largely unidentified.
Using a complete adult *Drosophila* brain electron microscopy data, we identified synaptic partners of two classes of LPTCs, the Horizontal (HS) and Vertical System (VS) cells. We found that HS and VS cells receive synaptic inputs at their axon terminals located at a premotor center. Interestingly, neurons that receive the strongest convergent input from HS and VS cells are three distinctive classes of GABAergic interneurons that, in turn, provide the majority of synaptic inputs back onto HS and VS cells at their axons, likely modulating LPTC activity. By mapping the inputs and outputs of these key interneurons, we found two major subnetworks that contact distinct populations of central and descending neurons. Functional imaging revealed that these key interneurons are sensitive to specific optic flow patterns that are either induced by forward or turning movements. The same population of cells also respond in darkness, when the fly is either walking forward or turning, respectively.
The combination of the circuit architecture and functional responses suggest that one of the subnetworks can be used to detect voluntary turns and discount the resultant optic flow, whereas the other monitors the angular deviations and elicits turns to maintain a straight course. Altogether, our results reveal two central networks that process complex patterns of optic flow field into translational and rotational directions, which in combination with extra-retinal signals, modulate the activity of visual neurons according to the ongoing task of an animal moving through space.

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Poster

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Program #/Poster #: P499.06

Topic: D.08. Visual Sensory-motor Processing

Support: KCL Marin Studentship
Wellcome Trust Investigator Awards in Science 2016

Title: Diversity and organisation of projection neurons in the optic tectum of the larval zebrafish.

Authors: *R. WILLIAMS, M. GRUBB, M. MEYER;
King's Col. London Sch. of Med. and Dent., London, United Kingdom

Abstract: Background & aims: The optic tectum and its mammalian homologue, the superior colliculus, transform topographically organized visual information from the retina into goal-directed movement in body-centered space.

How the tectum transforms activity in retinotectal coordinates into commands that guide appropriate behavioural responses is not well understood. To address this, we are using the larval zebrafish to determine the identity and organization of cell types that connect the tectum to efferent areas of the brain. **Methods:** At 6 days post-fertilization (dpf) larval zebrafish are small and translucent and so fluorescently labelled neurons can be visualized in their entirety in the intact, living brain. Tectal projection neurons were sparsely labelled by embryonic injection with FoxP2:Gal4/UAS:LYN-tdT. High resolution, 3-dimensional confocal images of 38 labelled neurons were acquired at 6dpf and registered to an anatomical atlas of the zebrafish brain. All non-overlapping, sparsely labelled cells that had a soma within the optic tectum and at least one neurite projecting out of the tectum were imaged and traced. Interneurons, defined as any cells without a neurite projecting out of the tectum, were excluded from analysis. Whole-brain functional activity was recorded using a 2-photon microscope in fish expressing nuclear localised GCaMP6s. **Results:** Preliminary analysis of a novel library of tectal projection neurons suggests their projections are diverse, organised by both dendritic arborisation and soma position along the anterior-posterior axis. The data show that diversity of tectal targets increases along the anterior-posterior axis of the tectum. Functional imaging reveals correlated areas of activity in response to a prey stimulus. **Conclusion:** Topographic visual information from the retina is transformed differentially in the tectum based on both the location and morphology of the tectal projection neurons receiving it. Functional imaging gives insight into how these physical connections underlie correlated activity in the zebrafish brain.

Disclosures: R. Williams: None. **M. Grubb:** None. **M. Meyer:** None.

Poster

P499. Visuomotor Processing: Physiology

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Topic: D.08. Visual Sensory-motor Processing

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Department of Atomic Energy (VT)
NCBS-TIFR graduate student fellowship (SN and AV)

Title: Adaptable internal representations drive cerebellum-mediated predictive control of an innate behavior

Authors: *S. NARAYANAN, A. VARMA, V. THIRUMALAI;
Natl. Ctr. For Biol. Sci., Bangalore, India

Abstract: The brain uses internal models to estimate future states of the environment based on current inputs and to predict consequences of planned actions. Neural mechanisms that underlie the acquisition and use of these predictive models are poorly understood. Using a novel behavioral paradigm coupled with two-photon calcium imaging, we show clear evidence for predictive processing in the larval

zebrafish cerebellum. We find that when presented with repetitive optic flow stimuli, larval zebrafish acquire supra-second internal representations of stimulus timing and modulate their optomotor response. Evidence for such predictive representations appears within two trials, lasts over minute timescales even after optic flow is stopped and readily adapts to changes in the pattern. Results from calcium imaging indicate that the cerebellum through an error feedback loop with sensory areas of the brain plays a central role in acquiring these timing representations. An algorithmic model constrained by our experimental findings acquires timing representations as observed in the fish cerebellum and explains the predictive component of the behavioral response, thereby providing a mechanistic description from sensory input to motor output of how the brain adaptively internalizes rules of the world.

Disclosures: S. Narayanan: None. **A. Varma:** None. **V. Thirumalai:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.08

Topic: D.08. Visual Sensory-motor Processing

Title: Identifying key structural connections from functional response data

Authors: *T. BISWAS[1], L. T. LI[2], J. E. FITZGERALD[3];
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Abstract: Being able to identify key patterns of neural network connectivity that are specifically required to generate functional response patterns is a challenging and aspirational goal in neuroscience. The difficulty, in part, is because we are typically only able to probe a network with a limited number of stimulus conditions, and there exists huge degeneracies in the ways we can connect the neurons to reproduce the observed responses. Here we present a new geometric ensemble modeling approach to this problem. Inspired by whole-brain imaging approaches, we assume that we have access to a finite number of steady state response patterns of all the relevant neurons in a given network, and we then ask if we can identify key excitatory or inhibitory connections that must exist to generate the responses. We assume that the network can be modeled by a recurrent neural network of rectified linear units that receive feedforward inputs. We first analyze a few toy models to illustrate the conceptual content of the theory. We then apply our theory to predict biological connectivity required to generate binocular responses of zebrafish pretectal neurons to various optomotor stimuli, which were previously recorded using whole-brain imaging. We finally present preliminary results trying to leverage the comprehensive connectomic data that now exists in fruit flies to test our theory on the ring attractor network in the fly central complex.

Disclosures: T. Biswas: None. **L.T. Li:** None. **J.E. Fitzgerald:** None.

Poster

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Topic: D.08. Visual Sensory-motor Processing

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Title: Task-dependent representations of population activity in the superior colliculus during sensorimotor transformation

Authors: *E. C. AYAR[1], M. R. HEUSSER[1], N. J. GANDHI[2];
[2]Dept. of Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: For visually guided eye movements known as saccades, neurons in the superior colliculus in the midbrain emit a volley of action potentials to register a visual (sensory) stimulus. They also discharge another high frequency burst of spikes to move the line of sight. Deficits in sensory and/or motor processes are implicated in a number of neurological disorders, so our research is focused on how the context of behavioral tasks impacts patterns of SC population activity during sensorimotor transformation. Specifically, we investigated the representations of sensory- and motor-related activity produced by populations of SC neurons during three paradigms: the gap, visually-guided delayed, and memory-guided delayed saccade tasks. The gap and delayed (visually- and memory-guided) saccade tasks differ in instructing the time to initiate the eye movement, permitting different temporal evolutions of the sensorimotor transformation. The visually-guided and memory-guided delayed tasks differ in whether or not the target is present when the macaque must make an eye movement to it. Dimensionality reduction methods were used to summarize the activity of simultaneously recorded neurons to determine if the population responses in both tasks exhibit similar visual and motor patterns despite differences in event timing and cognitive context. Our analyses suggest that the visual patterns explored during the delayed and gap tasks largely overlap while patterns of motor activity display differences. This also holds true when strictly comparing between the visually-guided and memory-guided delayed saccade tasks. Yet, there is more separability in patterns of motor activity between the visually-guided delayed and gap task than between the visually-guided and memory-guided delayed task. The results imply that downstream structures may differentiate signal processing between behavioral tasks. For instance, these signals ascend through the thalamus to the frontal cortex, which could potentially discern the different cognitive demands of the delayed and gap tasks. Thus, the context of a behavior matters when considering how sensorimotor transformation occurs. The same signals also descend to the saccade generator region in the brain stem. The observation that the motor subspaces associated with the three tasks are not identical, albeit partially overlapping, indicates that the actual motor subspace may be larger than that characterized from an individual paradigm.

Disclosures: E.C. Ayar: None. **M.R. Heusser:** None. **N.J. Gandhi:** None.

Poster

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Topic: D.08. Visual Sensory-motor Processing

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GAANN Fellowship P200A150050

Title: Low-dimensional representations of population activity in the primate superior colliculus during a sensorimotor task

Authors: *M. R. HEUSSER[1,2], U. K. JAGADISAN[1,2], N. J. GANDHI[1,2];
[1]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [2]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a midbrain structure that processes information contained in our visual field and converts it into an appropriate motor command. Neurons in its intermediate layers produce a burst of spikes both when a visual stimulus is presented in their response fields and when an eye movement to that stimulus is initiated. In the intervening time period, these neurons also emit spikes, although the reason for this elevated activity is still unknown. We therefore sought to better understand this "delay period" activity at a population level, aiming to categorize their instantaneous visual- or motor-like representations. To this end, we simultaneously recorded the spiking activity of a small population of neurons using a multichannel laminar microelectrode while two rhesus macaques (*Macaca mulatta)* performed a delayed saccade task. This task temporally dissociates the stimulus presentation from the eye movement, making it a paradigm well-suited for examining population activity patterns throughout the sensorimotor transformation process. We characterized the activity pattern across the population offline during small sliding time bins through a dimensionality reduction algorithm (Gaussian Process Factor Analysis, GPFA). The latent subspaces formed by population activity during the time of the visual burst and the saccade were categorized as the visual and motor subspaces, respectively. The high separability of these subspaces was confirmed via linear discriminant analysis classification. We then quantified latent activity throughout individual trials as more visual-like or more motor-like using a "Visuomotor Proximity Index" (VMPI, based on metric in Dekleva et al., 2018). When plotting the VMPI versus time in the delay period, we did not see a smooth transition from visual- to motor-like. Surprisingly, however, when the VMPI was aligned on the onset time of a detected microsaccade, a consistent trend did emerge—population activity patterns shifted toward the visual subspace approximately 100ms after microsaccade onset and slowly relaxed back to the pre-microsaccade VMPI value. This lends evidence to the potential purpose of microsaccades in refreshing the visual stimulus on the retina. Despite the apparent lack of connection between delay period activity and sensorimotor processing, we found through methods similar to Afshar et al., 2011 that the pattern of population activity at the time of the movement cue was correlated to the animal's reaction time on that trial. Therefore, we conclude that SC delay period activity acts akin to a holding pattern, but one that is still correlated to the metrics of the eventual behavior.

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Poster

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Program #/Poster #: P499.11

Topic: D.08. Visual Sensory-motor Processing

Support: JSPS-JP16H06566

Title: Bayesian visuomotor-reflex modulation by remote state instabilities

Authors: *H. GOMI[1], N. ABEKAWA[2], K. DOYA[3];
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Abstract: Hand reaching movement is quickly adjusted if surrounding visual motion is suddenly applied during reaching (named manual following response, MFR). Two alternative accounts have been proposed to explain this behavior: one is that an illusory self-motion drives this adjustment, the other is that an illusory target shift induced by surrounding visual motion drives this adjustment. The latter was supported by perception studies of motion induced position shift (MIPS), but the counter evidence was recently shown by the behavioral study (Ueda et al. 2019 Sci Rep). To examine these two accounts from the computational viewpoint, we have tested models of estimating self-motion and of estimating external-motion as to whether they can explain experimental observations of the response modulation caused by contexts of postural and visual instabilities. If we assume that the MFR is driven by an illusory self-motion estimated from prior probability of self-motion and likelihood of self-motion given observation of visual motion, Bayesian optimal model predicts that contexts of the unstable posture and the unstable visual field respectively increase and decreases the MFR. On the other hand, if we assume that the MFR is driven by an illusory target shift induced by visual motion, Bayesian optimal model predicts the contextual modulations of MFR oppositely. In the experiment, participants (n=16) were asked to stand on the stable or unstable (moving) platform in the context phase (5 s) with watching the screen on which grating pattern was filled. The grating pattern was stable on the screen in the static visual session while it was randomly moved in the unstable visual session. After the context period, they were asked to make reaching movement toward a target flashed on the screen. During reaching in randomly selected trials, grating pattern started to move rightward or leftward to induce the reflexive manual response in the direction of visual motion. When comparing the MFR amplitudes for four contexts (stable/unstable postural x stable/unstable visual), we found that the MFR increased following the context of unstable posture, and decreased following the context of unstable visual pattern. Further, variance of likelihood, estimated from the mean and variance of posterior probability, in the Bayesian optimal model, increased following the unstable visual context, compared with the stable visual context. These observations support the self-motion account, and suggests that the implicit visuomotor control mechanism modulates reflexive adjustment during reaching by accessing body state prior (postural instability) reflecting environmental context.

Disclosures: H. Gomi: None. **N. Abekawa:** None. **K. Doya:** None.

Poster

P499. Visuomotor Processing: Physiology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P499.12

Topic: D.08. Visual Sensory-motor Processing

Support: Australian Research Council Discovery Project (DP170101500)

Title: Initial corticospinal responsiveness following visual target presentation during reaching reflects target direction rather than reach direction.

Authors: *R. DIVAKAR[1], G. E. LOEB[2], B. D. CORNEIL[3], G. WALLIS[1], T. J. CARROLL[1];
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Abstract: During visually guided reaching, proximal limb muscles can be activated within 80 ms of target appearance. Such "express" muscle responses are invariably tuned towards the direction of the visual target regardless of the reach direction, which prompts the hypothesis that they are driven by a subcortical tecto-reticulo-spinal pathway. Here we measured motor evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS) to probe the modulation of corticospinal excitability within 100ms after target presentation. Twenty participants were instructed to reach either towards (pro-reach) or away from (anti-reach) visual targets displayed randomly to right or left of the right hand. Electromyographic activity was recorded from the right Pectoralis Major (PEC), Posterior Deltoid (PD) and First Dorsal Interosseous (FDI). TMS was delivered over the left motor cortex 60, 70, 80, 90 or 100 ms after target presentation to induce MEPs in PEC. When the visual target and motor goal were congruent in the pro-reach condition, MEPs were enhanced when PEC was agonist and inhibited when PEC was antagonist, from 70ms onwards. In the anti-reach condition, corticospinal excitability at 70 and 80 ms initially reflected visual target location, but excitability reversed by 100 ms to reflect the reach direction. The PD muscle, which is antagonist to the PEC muscle in this task, showed a mirror opposite trend to the PEC results. By contrast, MEPs in a functionally irrelevant muscle, the FDI in the hand, were unchanged by target or reach direction, suggesting that the corticospinal excitability effects in proximal muscles are task-related. The observation that corticospinal excitability of proximal muscles invariably reflects the visual target rather than the reach direction at 70-80 ms after target presentation suggests that MEPs are modulated by processing associated with express muscle responses. The observation that corticospinal excitability reflects reach direction by 100 ms, irrespective of the physical location of the target, shows that motor output circuits are biased by "cognitive" rule-based processing surprisingly early. The early target and subsequent reach encoding in TMS evoked MEPs could arise at various levels in the neuraxis, including biasing of the: 1) motor cortex output neurons by incoming visual and reach signals through direct cortico-cortical or indirect tecto-cortical pathways; 2) spinal neurons by descending signals from the superior colliculus via the reticular formation followed by signals from cortical areas. Ongoing work will address whether these early target-directed changes in MEP size occur within the motor cortex or the spinal cord.

Disclosures: R. Divakar: None. **G.E. Loeb:** None. **B.D. Corneil:** None. **G. Wallis:** None. **T.J. Carroll:** None.

Poster

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Program #/Poster #: P499.13

Topic: D.08. Visual Sensory-motor Processing

Support: Vision: Science to Applications (VISTA)

Title: Effector-specific spatial codes in dorsolateral prefrontal cortex during a head-unrestrained reach task.

Authors: V. NACHER, P. ABEDI-KHOOZANI, V. BHARMAURIA, H. ARORA, X. YAN, S. SUN, H. WANG, D. CRAWFORD;
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Abstract: Dorsolateral prefrontal cortex (DLPFC) is associated with executive control and response selection, but the extent to which it is involved in effector-specific transformations is unclear. We addressed this question by recording single neurons from dorsolateral prefrontal cortex (DLPFC) while two trained monkeys performed a head-unrestrained reaching paradigm that allowed freely coordinated motion of gaze, head reaching in depth. Animals touched one of three central LEDs at waist level while maintaining gaze on a central fixation dot and were rewarded if they touched a target appearing at one of 15 locations in a 40° x 20° (visual angle) array. Preliminary analysis of 239 neurons in one monkey showed an assortment of target/stimulus, gaze, pre-reach and reach-timed responses in DLPFC. Most neurons could be described as falling into three main groups. ‘Early” neurons increased firing rate during the target presentation and gaze onset. “Early-late” neurons responded in a sustained way from target presentation until reach. Finally, “Late” neurons increased firing rate during the pre-reach and peak when the monkey reaches. We first tested for gaze, head and hand gain fields during the different neuronal responses and found that 47 % of the responses were gain modulated by initial hand position. A fraction (12 %) of the neurons showed gain fields for initial gaze position, and for both initial gaze and hand position (7 %). A small fraction of neurons showed gain fields for initial head position (3 %), and for both initial hand and head position (2 %). After removing the gain field effects, we fitted the residual data against various spatial models, and found that the visual response best encoded the target relative to the space (Ts), whereas responses at gaze and hand onset showed a tendency towards coding hand displacement (dA). In addition, some (20 %) neurons showed a preference for coding final head position or displacement. A more complete analysis will describe the complete coding and distribution of gaze, head and reach signals in this region.

Disclosures: V. Nacher: None. **P. Abedi-Khoozani:** None. **V. Bharmauria:** None. **H. Arora:** None. **X. Yan:** None. **S. Sun:** None. **H. Wang:** None. **D. Crawford:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.14

Topic: D.08. Visual Sensory-motor Processing

Support: BBSRC (BB/S006605/1)
Bial (A-29315)

Title: Population receptive fields in human visual cortex during active vision

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Abstract: To adequately localize sensory events, the brain must have an accurate representation of the receptor topography. In the visual system this is achieved with an organization that preserves the retinotopic topography of photoreceptors. However, because receptors can move with respect to other parts of the body, the mere topography of receptors is not sufficient for localization of external objects. In the case of vision, eye movements change the orientation of the entire retina with respect to the head and body. A computational solution to this problem is a modulation of response gain based on receptor orientation (e.g. based on eye position). In theory, gain fields allow for the transition from a purely retinotopic to an eye position invariant representation of visual space. Evidence for gain fields in the visual system comes primarily from neurophysiological studies with non-human primates. Still, it is not clear how and to what extent the gain field mechanism is implemented in the human visual hierarchy. Here, we measure high resolution functional MRI data while participants actively made guided eye movements. In our analysis, we first estimated population receptive fields (pRF) using data from a standard moving-bar paradigm. Next, we assessed to what extent these pRF estimates can account for the data from the eye movement paradigm. Finally, we estimate population gain fields on top of pRFs, testing whether eye-position based gain modulation increases the explained variance of the predicted contrast-based pRF response. Moreover, we assess how reliably eye-position can be decoded from different areas along the visual hierarchy. These results shed new light on how receptor position modulates sensory processing in the human brain, and our methods provide a new way of access to the computational code behind that modulation, accessing the large-scale organization of gain-field properties in human neocortex.

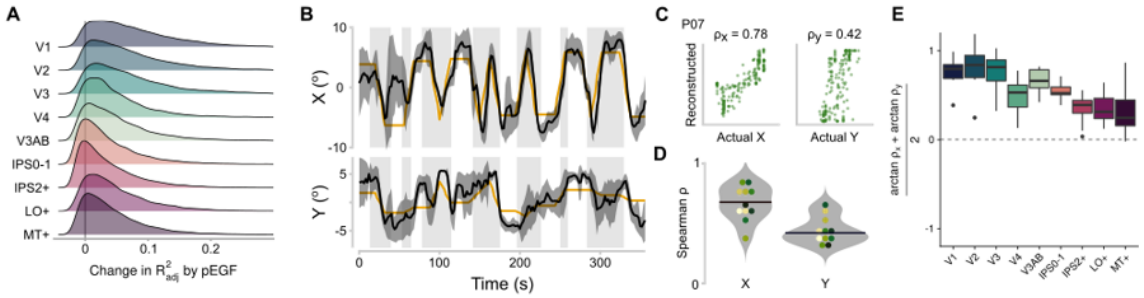


Figure 1. A. *Change in adjusted variance explained by adding population eye-position dependent gain fields (pEGF) to the contrast-driven pRF prediction of the BOLD responses in the eye movement task.* ***B.*** *Actual (yellow) and reconstructed (black) eye position in task B predicted from task A. Shaded area is the interquartile range across subjects.* ***C.*** *Example correlation between actual and reconstructed eye positions of participant 7.* ***D.*** *Distribution of Spearman correlation coefficients. Points represent different participants.* ***E.*** *Correlation between actual and reconstructed eye position across the visual areas.*

Disclosures: A. Fracasso: None. **K. Moravkova:** None. **J.H. Fabius:** None.

Poster

P499. Visuomotor Processing: Physiology

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Program #/Poster #: P499.15

Topic: D.08. Visual Sensory-motor Processing

Support: NIH EY014924

Title: Memory delay activity in visual cortex depends on movement preparation

Authors: *D. JONIKAITIS[1,2], T. MOORE[1,2];
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Abstract: Visuospatial working memory and gaze control are two behavioral functions that are known to be heavily interdependent and appear to involve interrelated neural circuits. Past neurophysiological studies have shown that neurons in many areas within primate visual cortex exhibit activity associated with spatial working memory. Specifically, the activity of neurons during the memory (delay) period depends on the location of the remembered stimulus. However, the extent to which that activity reflects working memory, or instead reflects the preparation of a behavioral response, remains unresolved. To address this question, we trained rhesus monkeys on a pair of tasks that dissociated spatial working memory from the behavioral response and measured neuronal responses in area V4. In one of the tasks (Look task), monkeys memorized a cue location, and after a delay period (1 - 1.5 seconds), were rewarded for making an eye movement to targets appearing at the cued location. In the other task (Avoid task), monkeys were instead rewarded for making an eye movement to a target appearing at a novel

location. Although the behavioral responses differed between the two tasks, looking at or avoiding the cued location, neither could be solved without memorizing that location. However, only in the Look task could monkeys prepare the behavioral response. We measured neuronal activity in area V4 of two monkeys using 16 - 32 channel, linear array electrodes (Plexon, Inc.) which were inserted largely perpendicular to the cortical surface. We compared neuronal activity during the memory delay period between the Look and Avoid tasks. During the Look task, V4 neurons exhibited elevated activity during the memory delay period when the remembered location corresponded to the visual RF. This modulation was individually significant in the V4 activity measured in both monkeys. In contrast, we observed no elevated activity at the remembered location during the Avoid task, a pattern that was consistent in data from both monkeys. These results indicate that the delay period activity in this visual area depends critically on the preparation of the behavioral response, in this case, eye movement preparation.

Disclosures: D. Jonikaitis: None. **T. Moore:** None.

Poster

P503. Cross-Modal Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P503.01

Topic: D.09. Multisensory Integration

Support: NRSA F31-EY031946 to SP
NIH R01-EY014882 to H-KL

Title: Visual deprivation-induced plasticity of higher order visual area inputs to the primary visual cortex

Authors: *S. PARKINS[1], X. CHEN[1], Y. JAOUI[2], H.-K. LEE[2,3,4,1];
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Abstract: Processing of sensory experience, which is essential for navigating and interacting with the world, relies heavily on feedback inputs from the higher-order cortical areas. This is further emphasized in the visual system where the connectivity between the higher-order visual areas and the primary visual cortex (V1) provides context to the information we see and allows us to pay attention to important aspects of the visual stimuli. It is well documented that V1 undergoes plastic changes in response to altered visual experience. For instance, in response to visual deprivation, V1 adapts by changing the strength of its connections in a layer specific manner. More specifically, we previously reported that after visual deprivation, lateral intracortical connections in V1 layer 2/3 increase in strength without changes in feedforward connections from layer 4. These changes were readily observed in adult mice, which suggests that visual deprivation is an effective means to produce plasticity in the adult brain. Feedback projections from higher-order cortical areas as well as other sensory cortical areas provide long-range intracortical inputs to V1 layer 2/3 neurons. Here we address the role of these long-range intracortical excitatory inputs in mediating visual deprivation-induced plasticity of V1. To do this, we first functionally identified different higher order visual areas (HVAs) surrounding V1 using the intrinsic signal imaging method developed by the Callaway's group. Using the anatomical landmarks, we then

performed stereotaxic injections to specific HVA to express channelrhodopsin-2. To assess the strength of these feedback inputs into V1, we recorded LED evoked Sr^{2+}-desynchronized miniature excitatory postsynaptic currents (mEPSCs) in V1 layer 2/3 neurons. Concurrently, we recorded mEPSCs in HVAs to determine whether the inputs to these regions also undergo experience-dependent plasticity as a result of visual deprivation. Our results will shed light on the cross-modal recruitment of V1 as well as the adaption of HVAs upon loss of vision.

Disclosures: S. Parkins: None. **X. Chen:** None. **Y. Jaoui:** None. **H. Lee:** None.

Poster

P503. Cross-Modal Processing IV

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Program #/Poster #: P503.02

Topic: D.09. Multisensory Integration

Support: Wellcome Trust, European Research Council (MECHIDENT)

Title: Optogenetic dissection of fronto-temporal neuronal circuits for audio-visual integration in primates

Authors: *B. AGAYBY[1], Y. KIKUCHI[1], R. S. MUERS[2], J. S. NACEF[1], M. C. SCHMID[3], C. I. PETKOV[1];
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Abstract: Although there can be multisensory interactions at nearly every stage of sensory processing, certain regions in the temporal and prefrontal cortex are often implicated in audio-visual integration. For instance, the upper bank of the Superior Temporal Sulcus (STS) and Ventro-Lateral Prefrontal Cortex (VLPFC, e.g., areas 44/45) have audio-visual bimodal neurons and clusters, interspersed within those that are primarily auditory or visual. Although there is evidence for monosynaptic input from auditory belt areas to VLPFC[1,2], it is not clear how this projection contributes to VLPFC function, including audiovisual integration. To address this, we tested whether optogenetic perturbation of auditory belt areas would influence VLPFC responses to voices, faces or both. We injected the optogenetic viral construct AAV9-CaMKII-ChR2-eYFP at multiple sites and depths (total volume = 36µl) in the anterior part of the auditory belt. Following expression, we confirmed strong spiking responses in auditory belt neurons in response to optogenetic stimulation modulated at 5Hz and 40Hz, using integrated optical fibres within Plexon S probes. Near the injected locations, there was an increase in multiunit activity (MUA) across the cortical layers in response to blue light (473nm) with the peak activity concentrated around the fibre location. Then, we investigated the effect of optogenetic stimulation of auditory belt neurons with or without simultaneous sensory stimulation with voices, faces or both on VLPFC area 44 neuronal and LFP responses across the cortical layers. Frontal Current Source Densities (CSDs) were markedly different to the sensory stimulation conditions and appeared to be modulated during auditory cortex optogenetic stimulation, in particular affecting deeper layer sinks/sources in the CSD. Work is underway in a second animal and we are also studying auditory optogenetic effects on STS neurons. Our preliminary results

demonstrate the feasibility of using macaque optogenetics to manipulate neuronal circuit activity during audio-visual integration, which aims to shed light on the role of rapid monosynaptic auditory input into fronto-temporal regions involved in sensory integration. 1. Romanski et al., Nat. Nsci 19992. Rocchi F, et al.. *Neuron*. 2021

Disclosures: B. Agayby: None. **Y. Kikuchi:** None. **R.S. Muers:** None. **J.S. Nacef:** None. **M.C. Schmid:** None. **C.I. Petkov:** None.

Poster

P503. Cross-Modal Processing IV

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Topic: D.09. Multisensory Integration

Support: Swedish Medical Research Council VR-M-K2013-62X-03026
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Xunta de Galicia ED431B 2021/04

Title: The fundamental network of gaze-stabilization - Ancient origins of subcortical visuovestibular integration

Authors: *T. WIBBLE[1], T. PANSELL[1], S. GRILLNER[2], J. PÉREZ-FERNÁNDEZ[3];
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Abstract: Eye movements originally evolved as a mean to allow gaze-stability during locomotion and other movements. The two principal mechanisms are the vestibulo-ocular reflex (VOR), which produces compensatory eye movements in the opposite direction of the head mediated by vestibular inputs, and the optokinetic reflex (OKR), that sees both eyes follow a continuous visual motion. In addition, some vertebrate species show a locomotion-related stabilization through reafferents or corollary discharges. Despite the importance of gaze-stabilization, our understanding of basic circuitry remains incomplete. The aim here is to investigate the visuo-vestibular control of gaze-stabilization using the lamprey representing the oldest group of vertebrates. To this end, we have designed an eye-brain-labyrinth preparation. By using a moving platform synchronized with two monitors, we could elicit visual and vestibular stimulations of varying intensities, while recording from extraocular muscles and vestibular nuclei. We show that lampreys possess a clear OKR, which added to the motor response when combined with the VOR during slower stimuli. At higher velocities, the VOR dominated. Lesion experiments and tracer injections allowed a characterization of the gaze-stabilizing network. Lesions of pretectum

abolished the OKR, whereas a tectal inactivation instead enhanced the visual contribution. Behavioural tests using video eye-tracking on intact lampreys rotated in three dimensions showed that the lamprey VOR features clear nystagmus. Experiments on a semi-intact preparation during locomotion resulted in clear, albeit weak, compensatory eye movements. The fact that the lamprey possesses both OKR and nystagmus, show that the building blocks for all subsequent eye movements were present already at the start of vertebrate evolution, implemented in the OKR, VOR and locomotion-supported gaze-stabilization. We also show that basic gaze-stabilization relies solely on subcortical structures, supporting the notion that pretectum acts as a first level integrator of visual motion and that neither cortex nor cerebellum is needed for the OKR to integrate with the VOR. Tectal downregulation of visual responses is likely due to its role in producing goal-oriented gaze-shifts. In conclusion, this study suggests that the basic circuitry underlying gaze-stabilization existed already at the point when lampreys diverged from the evolutionary lineage leading to mammals some 500 million years ago.

Disclosures: T. Wibble: None. **T. Pansell:** None. **S. Grillner:** None. **J. Pérez-Fernández:** None.

Poster

P503. Cross-Modal Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P503.04

Topic: D.09. Multisensory Integration

Support: NIH R01-DC017948

Title: Cross-modal plasticity of the higher order auditory thalamus

Authors: *G. EWALL[1], A. LIN[2], P. O. KANOLD[3], H.-K. LEE[4];
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Abstract: The phenomenon of cross-modal plasticity, or the process by which deprivation of one sensory modality induces alterations in processing of the spared modality, demonstrates that sensory processing in the brain is not siloed by modality is and more integrative than initially thought. We previously reported such cross-modal interactions by demonstrating visual deprivation-induced plasticity in the primary auditory cortex (A1) of adult mice. In particular, visual deprivation altered the A1 circuit to promote feedforward processing of auditory information, which may mediate heightened auditory function reported in blind individuals. Although the synaptic and circuit level alterations within A1 have been characterized, the mechanisms by which visual deprivation influences A1 is unknown. In addition, it is unknown whether cross-modal plasticity is a cortical phenomenon or manifests even in subcortical auditory circuits. To answer these questions, we examined the dorsal medial geniculate nucleus (MGd), a higher order auditory thalamic region known to receive inputs from multisensory areas and project broadly to auditory cortex. To test whether inputs to MGd undergo cross-modal plasticity, we performed whole-cell patch clamp recordings from MGd neurons in acute brain slices of adult mice deprived of vision by dark-exposure. We found a dramatic decrease in the strength of excitatory synaptic transmission

to MGd neurons with no change in the strength of inhibitory synaptic transmission following seven days of dark exposure. These results demonstrate that higher order thalamus exhibits cross-modal plasticity in adulthood and suggests a paraleminiscal route for multisensory influence on unimodal circuitry.
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Disclosures: G. Ewall: None. **A. Lin:** None. **P.O. Kanold:** None. **H. Lee:** None.

Poster

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Program #/Poster #: P503.05

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Support: Tartar fellowship
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Title: Appreciating the diversity: morphology and electrophysiology-based cell type classifications in the mouse insular cortex reveals projection-target and location-specific specializations

Authors: *B. C. JONGBLOETS[1,2], I. K. GINGERICH[2], Y. CHEN[2], T. J. LAMEYER[2], M. A. MUNIAK[2], T. MAO[2];
[1]Cell biology, Neurobio. and Biophysics; Biol. Department;Faculty of Science;Utrecht Univ., Utrecht, Netherlands; [2]Vollum Institute; Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: The insular cortex is an important multi-sensory integration site, and is pivotal for cognitive functions, motivational and homeostatic state processing, and interoceptive awareness. The insula relays these processed state signals to specific cortical, thalamic, and amygdalar subregions. Recent studies have identified that the activities of subpopulations of insular neurons correlate with specific behaviors, indicating that insular circuits are composed of different neuronal subtypes. Yet, a comprehensive understanding of the excitatory neuronal types in the insular cortex is currently lacking. Neuronal type classifications based on other cortical areas do not necessarily apply to the insula due to its unique cytoarchitectural structure, including subdivisions into granular (GI), dysgranular (DI), and agranular (AI) insula depending on the existence of the cortical layer 4.
In this study, we performed whole-cell patch-clamp recordings of the pyramidal neurons in the AI and DI of adult mice using acute brain slice preparations. Electric measurements of passive and active properties, including membrane resistance, action potential waveform, and spike behavior were obtained under current-clamp using biocytin-filled pipettes. Dendritic morphologies of the recorded neurons were revealed using *post-hoc* biocytin staining. Cell type classification analysis was performed based on a dataset of over 850 reconstructed dendritic morphologies and 300 electrical profiles. The anatomical locations of the cells were tracked. In addition, cortical, thalamic, and amygdalar projection targets of

over 230 recorded pyramidal neurons were identified using retrograde anatomical tracers. We identified up to 22 morphological, 12 electrical, and 18 cross-modality cell types. Interestingly, several cell types are located at specific insular subregions and project to distinct brain regions, indicating that local specializations of the neuronal circuits are in place to accommodate multi-modal information processing. Comparative analyses with previously published datasets indicate that functionally different cortical regions have specialized neuronal cell types that may constitute different local connectivity properties.

Disclosures: B.C. Jongbloets: None. **I.K. Gingerich:** None. **Y. Chen:** None. **T.J. Lameyer:** None. **M.A. Muniak:** None. **T. Mao:** None.

Poster

P503. Cross-Modal Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P503.06

Topic: D.09. Multisensory Integration

Support: NIMH (R00MH115082-04)
Whitehall Foundation (2019-05-44)
Georgia State University Brains & Behavior Fellowship

Title: Deviance detection to multisensory mismatch in posterior parietal cortex of mice

Authors: *A. B. VAN DERVEER[1], C. G. GALLIMORE[1], J. P. HAMM[1,2];
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Abstract: In a predictive coding framework, the brain is believed to generate predictive models which affect information processing at each stage in a hierarchically organized cortical network. Incoming sensory information is compared against these models, suppressing neural responses to expected stimuli and augmenting responses to unexpected stimuli. This modulation is evident in primary sensory cortices during a basic unisensory oddball paradigm; neural activity is reduced to repetitive stimuli (stimulus specific adaptation; SSA) and augmented to deviant stimuli (deviance detection; DD). It is unknown whether this occurs similarly in higher-order regions of cortex, such as posterior parietal cortex (PPC), a critical region for multisensory (MS) integration. Past work has shown that mouse PPC exhibits strong SSA, yet little DD to unisensory (US) stimuli. Here we test the hypothesis that PPC exhibits DD selectively to complex MS stimuli. We measured neuronal activity in PPC with two-photon calcium imaging in awake mice. All stimuli across paradigms were presented for 0.5s and had a 0.5-0.6s interstimulus interval. For the US visual "oddball" paradigm, we presented eight full square-wave gratings drifting in a random order (many standards control), then an oddball sequence with one redundant grating (88% "standards") and one deviant grating (12% "oddballs"). For the US auditory "oddball" paradigm, we presented mice with eight auditory frequencies in a random order, then an oddball sequence with one redundant tone (88% "standards") and one deviant tone (12% "oddballs"). Responses to the same stimulus were compared between oddball and many standards contexts to assess US DD (n=10, male and female). For the MS paradigm, visual (45º [Va] and 135º [Vb]) and auditory

stimuli (2.0kHz [Aa] and 4.0kHz [Ab]) were paired and presented semi-simultaneously (<10ms delay). Mice were trained with sequences of consistent AaVa and AbVb combinations, then presented MS "oddball" sequences, consisting of 87.5% trained pairs and 12.5% deviant pairs (AbVa (6.25%) ; AaVb (6.25%)). Responses to control and deviant MS pairs stimuli were compared (n=6, male and female) to assess MS DD. After averaging over all neurons, robust MS DD ($t(120)=4.29$, $p<.0001$), but not US DD (auditory: $t(318)=0.87$, $p=.385$; visual: $t(311)=0.56$, $p=.575$), was observed at the population level. These results suggest that while simple US prediction errors do not propagate through the cortical hierarchy to PPC, prediction errors to novel MS combinations generate genuine DD in PPC. This provides new evidence for the predictive coding framework.

Disclosures: A.B. Van Derveer: None. **C.G. Gallimore:** None. **J.P. Hamm:** None.

Poster

P503. Cross-Modal Processing IV

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Program #/Poster #: P503.07

Topic: D.09. Multisensory Integration

Support: Scientific Research 21120006
Scientific Research 19K12223

Title: Associative modulation in sensory cortices by second order fear conditioning

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Abstract: The sensory cortex was defined by responses to physical stimuli of specific modalities from the external world. Recently, it has been reported that the human and mammalian cerebral cortex induces associative additional responses to stimuli other than the main specific modality. In our previous study, we measured the plastic changes produced by fear conditioning combining pure tone and electrical foot shock (US) in the auditory and somatosensory cortices of guinea pigs, using optical recording with voltage-sensitive dyes. The results showed that auditory information could be retrieved by only electric shocks to the foot. This indicates that the somatosensory and auditory cortices are activated by a single sensory information in an associative manner. In this study, to investigate the expression of associative responses in the visual, auditory, and somatosensory cortices, cellular responses after first-order or second-order fear conditioning using foot shock, tone, and light, were measured using optical imaging. The results showed that (1) associative responses to sensory conditioning with tone and light was not seen in heart rate change as behavioral phenomena but was seen as changes in responses at the neuronal level. (2) Pre-fear conditioning (light and foot shock preceding tone and light) decreased (extinction) the associative response to foot shocks in the primary visual cortex compared with the response after the first-order fear conditioning with light and foot shock. In contrast, Post-fear conditioning (light and foot shock following tone and light) resulted in an increase (facilitation) in the associative responses.These results suggest that various bottom-up information is integrated into cortically induced associative responses, which are repeatedly or alternately traced by plastic changes in cortical network including facilitation and

extinction. Such an information-coupling process of cortical responses may play an important role in the dynamically linking of memory in the brain.

Disclosures: G. Tasaka: None. **Y. Ide:** None. **M. Tsukada:** None. **T. Aihara:** None.

Poster

P574. Motor Unit Recordings, Kinematics, and EMG II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P574.01

Topic: E.09. Motor Neurons and Muscle

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NIH R01 NS109237
NIH R01 NS099375

Title: Novel Flexible Multielectrode Arrays Record Multiple Single Motor Units and Reveal Organization of Behaviors Across Time Scales

Authors: *B. P. CHUNG[1], M. ZIA[3], M. J. WILLIAMS[1], K. A. THOMAS[1], J. LU[3], M. BAKIR[3], S. J. SOBER[2];
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Abstract: Recent advances in motor control research are leading to new insights about the structural organization of spinal sensorimotor circuits as well as functional dynamics of cortical and subcortical networks. Understanding how these systems produce complex motor behaviors also requires recordings from their output: coordinated activation of motor units that produce forces and drive movement. We have developed a novel approach to designing and fabricating flexible multielectrode arrays to record populations of single motor units and bulk electromyograms (EMG) during motor behaviors. Our fabrication process allows us to adapt a range of parameters including array shape/size, electrode size and spacing, and electrode surface treatment. By adjusting these parameters during our rapid design iterations, we are able to optimize the signal quality and array design for a variety of anatomical targets across species and muscle groups. In addition, our arrays are designed and developed through an integrated effort of neuroscientists and electrical engineers that facilitates straightforward implantation and use. Our flexible arrays provide a significant advantage over traditional EMG methods because we can record multiple single motor units or bulk EMG with high SNR and stability for acute experiments as well as chronic studies. In songbirds, for example, data collected with our electrode arrays show that breathing is organized by neural and behavioral timescales ranging from milliseconds to minutes and hours.

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Poster

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Topic: E.09. Motor Neurons and Muscle

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McKnight Foundation
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NIH R01NS099375

Title: High-resolution EMG recordings during skilled behavior in mice

Authors: *K. A. THOMAS[1], M. J. WILLIAMS[1], A. L. JACOB[1], B. CHUNG[1], M. ZIA[2], M. BAKIR[2], S. J. SOBER[1];
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Abstract: Understanding how the nervous system controls skilled movements has been limited by our lack of tools for recording muscle activity at high resolution. To overcome this, we have developed flexible electrode arrays for use in multiple species and muscle groups. Here, we present details of the design and usage of arrays specialized for recording from the muscles of the mouse forelimb. Forelimb-specific electrode arrays consist of multiple "threads," each bearing an array of electrode contacts, allowing us to record from multiple muscles simultaneously. The arrays presented here have been optimized for ease of surgical implantation, reducing procedure time and improving signal-to-noise ratio (SNR). These innovations also lessen tissue damage, and improve surgical outcomes. We also tested various methods for grounding the arrays and optimized this feature based on the SNR of single motor units. Low-impedance PEDOT-coated gold contacts allow each contact to record single motor unit impulses. Furthermore, these single units can be resolved with high SNR weeks after the original implantation, allowing for chronic studies. We are currently optimizing the parameters of electrode size, spacing, and number to maximize the number of individual motor units that can be simultaneously recorded from forelimb muscles. In preliminary experiments, we have implanted threads both superficially and intramuscularly in the triceps and trapezius. During free behavior, different channels recorded different sets of motor units, as assessed by the firing pattern and the shape and amplitude of spike waveforms. In ongoing studies we are using these arrays to investigate motor unit activity patterns during bimanual coordination and locomotion and to quantify how activity patterns change during sensorimotor learning. Furthermore, we plan to expand our current range of array designs to target the musculature of the distal forelimb and to improve long-term signal resolution and ease of surgical implantation.

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Poster

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Topic: E.09. Motor Neurons and Muscle

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Title: A low-latency behavioral feedback system for training, analyzing, and perturbing skilled forelimb rotation in rats

Authors: *M. RIGOTTI-THOMPSON[1], S. O'CONNELL[1], A. N. CORSTEN[1], F. ZHU[2], Y. H. ALI[1], K. LI[1], S. J. SOBER[3], C. PANDARINATH[1,4];
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Abstract: Among motor control tasks, skilled forelimb rotation is of particular interest due to its dependence on cortical input and involvement in naturalistic goal-oriented behavior (such as foraging and feeding). An unexplored aspect of this behavior which could provide insight on the closed-loop control mechanisms in the motor system is how subjects respond to perturbations during movement. To study the above, the rat model stands out as an appealing option due to its low-cost and potential for automated training, which enables scalability for large sample sizes. However, there is currently no highly configurable rat behavioral training system available for recording forelimb angular kinematics in response to torque perturbations, especially not one with low-latency (millisecond-timescale) feedback. In this work, we present a highly configurable behavioral feedback system that uses a rotary knob manipulandum for analyzing and sculpting skilled forelimb rotation behavior in freely moving rats. The system includes a variety of features which distinguish it from current alternatives in the literature. For example, it provides customizable torque feedback during motion, while simultaneously recording the kinematics, torques, and Cartesian forces applied by the subject. Using this system, we have trained several female Long-Evans rats to perform forelimb supination under varying torque conditions. The system's low-latency capabilities allows us to sculpt their behavior to execute knob supination to over 75 degrees, and to study how the timing of their behavior varies when torque perturbations are introduced at different stages of the task. Thus, our system provides an effective tool for probing rat motor control while collecting a range of behavioral variables. When paired with electrophysiological data such as neural recordings and electromyography (EMG), this setup will allow us to deconstruct motor command signals that drive forelimb rotation and investigate closed-loop control in a motor cortex-driven behavior.

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Poster

P574. Motor Unit Recordings, Kinematics, and EMG II

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Topic: E.09. Motor Neurons and Muscle

Support: EFRE GE-2-2-023A (REXO)
EFRE IT- 2-2-023 (VAFES)

Title: Generation of human-like reaching movements using the attractor dynamics approach

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Abstract: Our research aims for a systematic understanding of the generation of human arm movements. The activation of a population of directionally tuned motor cortical neurons determines the direction of motion, which was particularly confirmed for reaching tasks (Georgopoulos et al., 1986). Motion parameters are continuously updated during movement when direction is changed. Such insights can be interpreted as the combination of a nominal trajectory with real-time optimal feedback control (Osu et al., 2015).
In accordance with these findings, direction-coded movement generation has been proposed for robotics: Based on behavioural attractor dynamics, motion is modelled by means of differential equations with behavioural variables in target approaching angles and velocity characteristics as dynamical system attractors (Rano and Iossifidis, 2013). Usually, a spherical representation of these variables and their time derivatives is employed in modelling.
The present work incorporates attractor dynamics to model natural human arm reaching behaviour by applying methods of parameter fitting in dynamical systems. The corresponding movement trajectories can be decomposed into a transport and a lift/descend component (Grimme et al., 2012). Assuming simple reaching tasks to consist of initiation, travel, and approach phase, the travel phase is defined as the time between the extrema of the lift/descend component. Based on human subject data from reaching experiments, we show that the hand trajectory in terms of position and velocity course can be successfully modelled for the travel phase.
The results of curve fitting by minimizing the mean square error can be remarkably improved when utilizing an ellipsoid-based representation of the attractor dynamics behavioural variables. Hereby, approaching of the angle-based attractor is conducted by means of an ellipsoidal coordinate transformation instead of the usually applied spherical one. Furthermore, we analyze and compare the fitted parameters for different tasks of individual subjects. Evaluation of human-likeness reveals that the generated movements exhibit typical human properties and that the applied model is well suited to describe the observations.
As a next step, we will evaluate different measures to quantify the variance of experimentally obtained trajectories. Further work will target at adapting varying movement tasks in order to explain and imitate natural biological behaviour as well as deviations in it. By that, we aim to obtain knowledge for pathological analysis, in particular the modelling and early detection of specific movement disorders by focussing on the hand trajectory.

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Poster

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Program #/Poster #: P574.05

Topic: E.09. Motor Neurons and Muscle

Support: GE-2-2-023A (REXO)
IT- 2-2-023 (VAFES)

Title: From motion to muscle

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Abstract: Muscle activity plays an important role in understanding human motion execution and detecting neuromuscular diseases as well as being used to control prosthetic devices. The availability of experimental data is always a restricting factor, especially when large data sets are needed to train machine learning algorithms. Therefore, models which generate artificial muscle signals are currently under research. Most approaches are based on analytical models using muscle and signal characteristics to reveal the composition of muscle activity. We present the artificial muscle activity generator (AMAG) as a new approach to artificially generate muscle signals for the upper limb based on deep neural networks with the support of motion-related parameters. The EMG data were recorded from eight upper limb muscles (*deltoid anterior, lateral and posterior, biceps short head, triceps brachii lateral head, pronator teres, flexor carpi ulnaris, and extensor carpi radialis longus*) with the *Delsys Trigno System*. The motion data were obtained using the *Xsens Motion Capture System* with its sensors placed on each arm segment and the upper body. Each subject was asked to execute over 30 simple and complex motions with 19 repetitions in a single session. A total of 10 healthy subjects (3 female, 7 male in the age of 25 +4 years) participated in the experiment.We investigate different motion data as input of the deep learning algorithm and their impact on the artificial muscle signal. In particular, we compare using angular information of the associated body segments, with inputting the changes in muscle length computed using *OpenSim*. The latter corresponds to the neural signal sent from the brain to the muscle, whereas the angular information is the result of change in the muscle length and is needed for movement planning.Several different neural network architectures are considered starting from a basic feedforward neural network (FNN) to more advanced long short-term memory (LSTM) utilizing the time dependency of muscle activity. Besides these recurrent models, we tested a convolutional neural network (CNN) and generative adversarial networks (GAN).The LSTM and CNN show promising results with a mean absolute difference of 1.06% (SD=1.91) and 1.10% (SD=2.19) respectively to the original EMG data set for untrained motion-related data with the former needing much more computation time. The AMAG helps to gain insight into motion processing by varying the input data for example by considering motion data of different movements and comparing the resulting artificially generated muscle signals.

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Poster

P574. Motor Unit Recordings, Kinematics, and EMG II

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Program #/Poster #: P574.06

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant NS098509

Title: Quantifying errors in the estimation of human motoneuron excitability through the use of hybrid motor unit spike trains

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Abstract: Spinal motoneurons possess active channels which serve to alter their intrinsic excitability. Remarkably, the discharge of spinal motoneurons can be assessed in humans by recording and decomposing the discharge of the group of muscle fibers that individual motoneuron innervate. From these spike times, analyses can be performed to estimate the intrinsic excitability of spinal motoneurons (e.g. delta-f). In the past decade there have been substantial improvements in our ability to decompose human motor units. However, issues remain regarding the accuracy of these approaches. Here, we assessed the impact of motor unit decomposition errors and motor unit yield on the assessment of human motoneuron excitability. An average of 19 motor units were gathered from 10 participants during performance of linear time varying contractions. Each spike from all signals was corrected for accuracy. Using these highly accurate spike time data, we created millions of hybrid spike trains by imposing six forms of errors on these signals. From these hybrid signals, we found that errors in specific locations of the signals cause specific changes to delta-f values. For example, removing spikes at the onset of discharge and adding spikes randomly throughout the spike train caused delta-f values to increase, whereas removing spikes at the end of the contraction or randomly throughout the contraction caused delta-f values to decrease. Interestingly, small shifts in spike times had a negligible effect on any parameter calculated. Such data are consistent across multiple muscles. This work suggests that errors located at the onset and offset of motor unit discharge are critical to accurate assessments of motoneuron excitability. However, outside of these edges, the precise timing of any given spike is relatively insignificant for accurate estimates of human spinal motoneuron excitability. These results provide new insights into the impact of decomposition errors on our interpretation of these data and will guide future efforts for further automation of this cleaning. Further work will be focused on using these hybrid signals to provide an index of confidence in the original signal.

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Poster

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Topic: E.09. Motor Neurons and Muscle

Title: Inhibitory muscle components in muscle synergies extracted by the rectified latent variable model from electromyographic data

Authors: *X. GUO[1], C. LAN[1], B. HE[2], T. TAKEI[4], K. SEKI[5], V. C. CHEUNG[3,6], R. H. CHAN[1]; [1]Electrical Engin., City Univ. of Hong Kong, Hong Kong, China; [3]Sch. of Biomed. Sciences, and The Gerald Choa Neurosci. Ctr., [2]The Chinese Univ. of Hong Kong, Hong Kong, China; [4]Grad Sch. of Med., Kyoto Univ., Kyoto, Japan; [5]Natl.inst.Neurosci., Tokyo, Japan; [6]Joint Lab. of Bioresources and Mol. Res. of Common Dieases, The Chinese Univ. of Hong Kong and Kunming Inst. of Zoology of The Chinese Acad. of Sci., Hong Kong, China

Abstract: The non-negative matrix factorization (NMF), widely used in motor neuroscience for the identification of muscle synergies from electromyographic data (EMG), extracts non-negative synergies and is unable to identify potential negative components in synergies underpinned by inhibitory spinal interneurons. To overcome this constraint, we propose to utilize the rectified latent variable model (RLVM) to extract muscle synergies. RLVM uses an autoencoder neural network for parameter initialization. The weight matrix of its neural network could be negative while the latent variables must remain non-negative. If the input to the model is EMG, the weight matrix and latent variables are the muscle synergies and the temporal activation coefficients, respectively. Here, we compare the performances of NMF and RLVM in the identification of muscle synergies in simulated and experimental datasets. Our simulated datasets included one consisting of only non-negative values and another with both positive and negative values. On average, RLVM performed better in identifying the muscle-synergy subspace, but NMF outputs had a higher correlation with ground truth even when the simulated data were corrupted with signal-dependent or Gaussian noise. Finally, we applied RLVM to a previously published experimental dataset comprising EMG from upper-limb muscles and spike recordings of spinal premotor interneurons during voluntary grasping of two monkeys. The RLVM and NMF synergies were highly similar, but a few small negative muscle components were observed in the RLVM synergies. The muscles with negative components identified by RLVM were close to 0 in their corresponding synergies identified by NMF. Also, the negative components of the RLVM synergies agreed with the muscle connectivity of the premotor interneurons with inhibitory muscle fields, as identified by spike-triggered averaging of EMG. Our results demonstrate the usefulness of RLVM in extracting potential inhibitory muscle-synergy components from EMG.

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Poster

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Title: Estimating neural drive from EMG using deep learning-based dynamical systems modeling

Authors: *L. N. WIMALASENA[1], J. F. BRAUN[2,3], M. R. KESHTKARAN[1], D. HOFMANN[4,5], J. GALLEGO[7], C. ALESSANDRO[8,11], M. C. TRESCH[8,9,12], L. E. MILLER[8,9,10,12], C. PANDARINATH[1,6]; [1]Coulter Dept. of Biomed. Engin., Emory Univ. / Georgia Tech., Atlanta, GA; [2]Dept. of Electrical and Computer Engin., Tech. Univ. of Munich, Munich, Germany; [3]Sch. of Life Sci., École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [4]Dept. of Physics, [5]Initiative in Theory and Modeling of Living Systems, [6]Dept. of Neurosurg., Emory Univ., Atlanta, GA; [7]Dept. of Bioengineering, Imperial Col. London, London, United Kingdom; [8]Dept. of Physiol., [9]Dept. of Physical Med. and Rehabil., Northwestern Univ., Chicago, IL; [10]Dept. of Biomed. Engin., Northwestern Univ., Evanston, IL; [11]Dept. of Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [12]Shirley Ryan Ability Lab., Chicago, IL

Abstract: To study the neural strategies that underlie behavior, it is often necessary to estimate how muscles are activated across a variety of behavioral conditions. However, estimating the latent command signal that underlies muscle activation - often termed “neural drive” - is challenging due to the complexity of recorded electromyographic (EMG) signals. For example, differences in the timing of action potentials generated from separate motor units surrounding an EMG electrode may result in partial overlap of the recorded waveforms and cancellation of EMG signal on the channel. Common practices often estimate neural drive independently for each muscle channel (e.g., low-pass filtering), and require manual tuning of model hyperparameters (e.g., filter cut-off frequency) to capture estimates of neural drive that preserve behavioral-relevant features. Here, we adapted AutoLFADS, a large-scale, unsupervised deep learning approach, to estimate neural drive from multi-muscle EMG signals. As muscles are typically activated in coordination over time, we hypothesized that accurately modeling the spatial and temporal regularities that underlie multi-muscle activation using recurrent neural network (RNN) models like AutoLFADS can produce better estimates of neural drive for a given muscle. We tested AutoLFADS using two model systems: (1) rat hindlimb during locomotion and (2) monkey forearm during an isometric wrist task. When applied to the rat data, the model produced single-trial estimates of neural drive that improved decoding of joint kinematics over standard approaches to EMG processing like smoothing and Bayesian filtering. We found that AutoLFADS functions adaptively to adjust its frequency response characteristics according to the time course of different phases of behavior, removing the need to define a single fixed cut-off frequency for the entire behavior. Similarly, when applied to the monkey data, AutoLFADS enabled more accurate prediction of measured forces, including unexpected high-frequency oscillations that were obscured by traditional EMG processing. The AutoLFADS-inferred estimates of neural drive were also closely correlated with simultaneously-recorded motor cortical activity, suggesting that signatures of descending cortical commands are preserved when modeling dynamics governing muscles. Ultimately, this method leverages both dynamical systems modeling and artificial neural networks to provide precise estimates of neural drive for multiple muscles that can be used for further studies of multi-muscle coordination and their control by upstream brain areas.

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Poster

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Program #/Poster #: P574.09

Topic: E.09. Motor Neurons and Muscle

Title: Investigation of evaluating method for neuromuscular function from the decomposed motor unit using delsys neuromap system

Authors: *H. FUNAKOSHI[1], Y. USAMI[3], M. YOSHIDA[1], T. ITO[1], T. MASUDA[4], T. KOKUBUN[2]; [2]Physical Therapy, [1]Grad. school of Saitama Prefectural Univ., Saitama, Japan; [3]Grad. school of Saitama Prefectural Univ., Saitama, Japan; [4]Fukushima Univ., Fukushima, Japan

Abstract: Motor unit action potential (MUAP) brings us important information about the neuromuscular function than compound action potential. In previous studies, the needle EMG or High-density surface EMG (HD-sEMG) are used for MUAP analysis. These studies reported that the change of inter-pulse interval (IPI), firing rate (FR), muscle fiber conduction velocity (MFCV) occurs according to fatigue. However, because the arrays of Delsys wireless 4 channel surface EMG (4ch-sEMG) are fewer than HD-sEMG, it's not clear whether 4ch-sEMG can evaluate neuro muscle function from MUAP. 4ch-sEMG has the possibility that enables us to evaluate muscle fatigue more easily and in detail. The purpose of this study is to investigate the evaluating methods from the MUAPs estimated by 4ch-sEMG and NeuroMap system. The subject was a healthy young man, and a 4ch-sEMG was put on dominant biceps brachii. The task was repeating isometric contraction holding a 3.5kg dumbbell with the elbow bent 90 degrees for 30 seconds 15 times. The intervals between repeated trials were 10 seconds. Then, we investigated the fluctuation of IPI, FR, MFCV referencing correlation coefficients. MFCV was calculated as the ratio between the electrode separation and the conduction delay between decomposed template MUAP of 2 of 4 channels lined vertically. The standard deviation and average of IPI were not changed according to repeated contraction. In FR, only peak FR of the total MU average showed a slight correlation ($r = 0.519$). Additionally, the mean and peak FR of the first 5 MUs recruited showed a negative correlation($r = -0.58$, -0.74) with the last 5 MUs. The first trial of MFCV was 3.89m/sec, the Final trial was 1.99m/sec, and it showed a slight negative correlation ($r = -0.68$). These results indicate adaptation to reduce fatigue as much as possible. Considering that the fast type of muscle fiber is fatigable, the slow type should be dominant for continuing tasks efficiently. We thought that correlation of peak FR could indicate increase activity of small MU because basically, big MU is low frequency. Additionally, negative correlation in the first and last 5MUs also indicates adaptation to fatigue because in constant torque MU combination fluctuated for each trial. In other words, the big MU is ready for the next contraction during small MU works and vice versa. Regarding MFCV, this result shows a similar result to a previous study about MFCV of fatigable biceps brachii. However, it is not clear whether this correlation of MFCV indicates fatigue or adaptation, Because the load is low. Further study is needed to elucidate if the results of 4ch-sEMG matchs HD-sEMG and, defference of neuromuscular function between low and high load.

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Poster

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Topic: E.09. Motor Neurons and Muscle

Support: NSF Grant 1954587

Title: Common neural input within and between lower limb muscles at different motor coordination tasks

Authors: *N. RUBIN[1], X. HU[2], H. HUANG[3];
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Abstract: Motor units are the fundamental unit of motor control. Motor unit synchronization can be calculated to identify common synaptic inputs in neural circuitry during muscle coordination. This study compared common inputs to lower limb muscles across tasks requiring different muscle coordination patterns. Multichannel surface electromyogram (EMG) signals were recorded on the right and left tibiales anterior (dorsiflexors) and medial gastrocnemii (plantarflexors) muscles, while able-bodied human subjects conducted dynamic tasks involving either dorsiflexion (squats), plantarflexion (heel-raises), or both motions (anterior-posterior postural sway). After decomposing EMG into motor unit firings, we conducted coherence analyses of composite motor unit firing event trains in the beta (13-30 Hz) and low-gamma (30-60 Hz) frequency bands. Our results indicated similar levels of common input occurring between tasks involving activation of either dorsi/plantar-flexors or both antagonistic muscle pairs. Additionally, motor units within the same muscle consistently received the highest levels of common inputs, while decreased levels of common input occurred between bilateral homologous and antagonistic muscle pairs, respectively. The outcomes could help understand mechanisms of lower limb neuromuscular coordination and may provide a benchmark for individuals with neuromuscular conditions.

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Poster

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Title: Spatial coding of conspecific electrosensory signals by a heterogeneous pyramidal cell population

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Abstract: A ubiquitous feature of neural systems is to encode spatial information to help localize the source of sensory signals of ethological importance. Spatial processing varies across systems and many studies revealed sophisticated mechanisms in place to support the localization process but we are still unravelling the subtleties of how spatial and temporal information is processed. The electrosense of weakly electric ghost knifefish serves as an excellent model system for quantifying the neural coding efficiency of sensory signals. Behavioral studies on conspecific interaction suggest that the sensory system is extremely sensitive and supports the detection and localization of conspecifics tens of centimeters away. The localization of spatially localized objects in this system has been previously investigated but the signal of conspecific is spatially diffuse and the mechanisms that support their accurate localization are unknown. Here, we investigate the spatial representation of conspecific signals in the hindbrain to determine how the spatiotemporal properties of the heterogenous population of pyramidal cells affect the neural coding of conspecific signals in different spatial contexts. We hypothesize that specific subset of cells provide more accurate spatial information about conspecifics. We use extracellular electrophysiological techniques to record from pyramidal cells across multiple maps in the electrosensory lateral line lobe (ELL). We stimulated the fish with an artificial signal that replicates both the spatial and temporal structure of conspecific signals. The stimulus was emitted from various locations around the fish and consisted of a sinusoidal “beat” amplitude modulation experienced during social encounters. We recorded from cells with various receptive field positions covering the whole body and analyzed the spike train with spike-train distance metrics and neural network classifiers to determine how accurately the location of the stimulus is encoded. We found that some pyramidal cells encode the spatial information accurately while others contribute little to spatial coding of these signals. Our results help us understand how the heterogeneity of a population of cells allow the efficient processing of signals.

Disclosures: O.E. Milam: None. **G. Marsat:** None.

Poster

P578. Sensory Systems II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P578.02

Topic: F.01. Neuroethology

Support: NSF-IOS Grant 1942960

Title: Identifying stereotyped movement patterns during social interactions in weakly electric fish

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Abstract: Sensory systems are typically adapted to encode behaviorally signals efficiently and so quantifying the characteristics of relevant sensory signals is key to understand the sensory task that must be performed by the nervous system. Localizing the source of a signal is crucial to guiding the behavior of the animal successfully. Studies on spatial processing have revealed intricate mechanisms allowing the animal to be extremely accurate in their motor output despite the localization cues being weak or small. The electrosensory system of gymnotid fish has the hallmark of such extreme sensitivity including, for example, when a fish localizes a conspecific to interact socially. Here we aim to better understand spatial processing in these fish by characterizing the signals they experience during social interaction and that allows them to navigate relative to one-another. To reach this goal we recorded fish interacting in infrared lighting to build a database of the swimming kinematic of fish interacting in a wide range of situations. To elicit a range of scenarios and obtain a wide range of swimming behaviors, we varied the social and environmental context. Complex behaviors such as social interactions are typically composed of stereotype bouts of movements. Ethograms can be used to identify these stereotyped patterns and their sequence; modern computational tools permit a more rigorous quantitative approach to identifying stereotyped behaviors and their sequence. We established an algorithm to identify stereotyped patterns of movements during a variety of social interactions. Knowing the relative position and movement of the two individuals while interacting allowed us to define the behaviorally relevant spatio-temporal structure of the electrosensory input mediating the behavior. We expect this information to be crucial in future studies of spatial processing in these fish aimed at revealing neural mechanisms enhancing localization accuracy.

Disclosures: K.L. Ramachandra: None. **G. Marsat:** None.

Poster

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Topic: F.01. Neuroethology

Support: NIH grant R01NS086859
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Pew Scholars Program in the Biomedical Sciences
McKnight Technological Innovations in Neuroscience Awards

Title: Reverse engineering Drosophila thermotaxis

Authors: *J. SIMÕES, J. LEVY, P. ZHAO, W. KATH, A. PARA, M. GALLIO;
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Abstract: Simple innate behavior is often described as hard-wired and largely inflexible. Here, we study the avoidance of unfavorable hot temperature in the fruit fly *Drosophila melanogaster*, a fundamental behavior and an ideal system to probe the extent to which simple innate behavior may be largely hard-wired. First, we produce the first high-resolution characterization of heat avoidance and thermotaxis in adult *Drosophila*. Our first goal is to define the basic functional organization of thesensory system that

guides these innate behaviors in adult fruit flies. Our next objective is to compare fly heat avoidance with the behavior of an *in silico* vehicle model (a "Braitenberg vehicle"), explicitly probing the notion that the fly's innate avoidance of hot temperature can be understood as a combination of hard-wired responses. Our results demonstrate that hot receptor neurons of the antenna and its molecular heat sensor, Gr28B.d, are essential for flies both to navigate shallow temperature gradients ("thermotaxis"), as well as to produce escape turns away from heat when the flies encounter steep thermal boundaries. High-resolution fly tracking combined with a 3D simulation of the thermal environment shows that, in steep thermal gradients, the direction of escape turns is determined by minute temperature differences between the antennae (0.1°-1 °C). In parallel, live calcium imagingconfirms that such small stimuli reliably activate both peripheral thermosensory neurons andcentral circuits. Based on our measurements, we evolve a fly/vehicle model with two symmetrical sensors and motors (a "Braitenberg vehicle") which closely approximates basic fly thermotaxis in steep thermal gradients. Critical differences between real flies and the hard-wired vehicle reveal that fly heat avoidance involves decision-making, relies on rapid learning, and is robust to new conditions, features generally associated with more complex behavior.

Disclosures: J. Simões: None. **J. Levy:** None. **P. Zhao:** None. **W. Kath:** None. **A. Para:** None. **M. Gallio:** None.

Poster

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Program #/Poster #: P578.04

Topic: F.01. Neuroethology

Support: NSF-IOS Grant 1942960

Title: Modeling the spatial dynamic of sensory image and receptors activation during social interaction in weakly electric fish.

Authors: *G. MARSAT[1], K. L. RAMACHANDRA[2], O. E. MILAM[2];
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Abstract: Extracting spatial information from sensory signals can be computationally intensive when the signal activates most of the receptors and differences in activation must be compared to extract localization cues. Efficiency in this process relies in part on the spatio-temporal response properties of the receptors being adapted to the characteristics of behaviorally relevant signals. Heterogeneity in neural responses has been shown to be an important determinant of coding efficiency by populations of neurons but most of the work on this topic has focused on coding of the temporal aspects of the signal. Here, we investigate the effect of neural heterogeneity on the coding of spatial information by a population of neurons. We used the electrosensory system of gymnotid fish as a model system because we understand in detail how temporal information is encoded in sensory neurons. However, little is known regarding how spatial information about conspecific signals is encoded. When two fish interact socially, they are exposed to each other's constant electric organ discharged which enables them to localize other

individuals. These signals are spatially diffuse and often weak so localization relies on comparing minute differences across the array of receptors. We hypothesize that efficient localization relies on the heterogeneity of receptors' properties being adjusted to the properties of behaviorally relevant signals. By modeling 2 aspects of the sensory process. We first use a model of the electric fields generated by interacting fish to quantify the strength of the signal at each receptor location during social interactions. Second, we simulate a population of electroreceptors (tuberous p-units) with leaky-integrate-and-fire models calibrated to replicate the known response properties of these cells. The stimuli applied to these model neurons are based on the signal strength calculated from the electric field model. By changing the degree of heterogeneity present in the population we show that the accuracy of spatial coding is influenced by the degree of heterogeneity present in the population. Our study thus extends the generality of the role of heterogeneity in shaping coding accuracy to include spatial coding.

Disclosures: G. Marsat: None. **K.L. Ramachandra:** None. **O.E. Milam:** None.

Poster

P578. Sensory Systems II

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Program #/Poster #: P578.05

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant number 16H06544
Grant-in-Aid for JSPS Research Fellow 19J10862

Title: Roles of neural signals descending from and ascending to the brain in the cricket escape behavior

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Abstract: To survive a predator's attack, prey animals including insects must exhibit escape responses that are appropriately regulated in terms of their moving speed, distance, and direction. Insect locomotion is considered to be controlled by an interaction between the brain, which is involved in behavioral decision-making, and the thoracic ganglia (TG), which are primary motor centers. However, it remains unknown which descending and ascending signals from/to the brain are involved in the regulation of insects' escape behavior. In other words, it is still unclear what aspects in the escape locomotion of insects depend on the neural communication between the brain and TG. We addressed the distinct roles of the brain and TG in the wind-elicited escape behavior of crickets, which is mediated by abdominal mechanosensory organs called 'cerci'. We unilaterally cut the ventral nerve cord (VNC) at different locations, between the brain and TG, or between the TG and terminal abdominal ganglion (TAG), which is a primary sensory center of the airflow sensing system, to assess the effects of partial ablation of these intersegmental communications on escape responses. The half lesion of ascending signals to the brain greatly reduced the jumping response rather than running, indicating that sensory information processing in the brain is essential for the choice of escape responses. The half lesion of descending signals from the brain to the TG impaired locomotor performance and directional control of the escape responses,

suggesting that locomotion in the escape behavior largely depends on the descending signals from the brain. Finally, by an extracellular recording from the cervical VNC, we found the differences in the temporal profile of the descending spiking activities prior to the escape running or jumping. Our results demonstrated that the brain sends the descending signals encoding the behavioral choice and locomotor regulation to the TG, while the TG seems to have other specific roles, such as in the preparation of escape movement.

Disclosures: H. Ogawa: None. **N. Sato:** None. **H. Shidara:** None.

Poster

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Program #/Poster #: P578.06

Topic: F.01. Neuroethology

Support: AU Grant 201160

Title: Evaluating variability of phonotaxis and selective processing of its underlying neural elements in an insect model

Authors: *B. NAVIA, J. AN, J. RIM, G. ATKINS;
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Abstract: The phonotactic behavior of female cricket *Acheta domesticus* as observed in the lab, has been shown to vary among individuals. In response to computer-generated auditory stimuli, some females are finely tuned and attracted to calls with syllable periods which match those of the natural calls of the males (for *A. domesticus* 50 - 70 ms). Other females respond phonotactically to calls with a wider range of syllable periods (30 - 90 ms) including or not the most attractive range. Therefore, lacking the ability to discriminate between attractive and unattractive calls. Factors that contribute to this variability include age, temperature and levels of JHIII. We show the presence of neurochemicals such as histamine to influence phonotaxis. Prothoracic nanoinjection of histamine, resulted in females responding phonotactically to calls with a wider range of syllable periods, compared to the same females' preferences before injections and therefore acting as a neuromodulator. Additionally, when females are exposed to males, but not allowed to mate, their ability to discriminate attractive calls is reduced. This implies factors other than mating, alter the females' phonotactic behavior in a way that parallels the results reported for injection of histamine as well as lower levels of JHIII as seen in older females. The effect of said factors in identified underlying neural elements such as the auditory neuron L3/AN2, continues to be evaluated. The response of the L3/AN2 in females with the ability to discriminate attractive calls also varies in ways that parallel the phonotactic variability mentioned above. Evaluation of L3/AN2's response, provides insight to a proposed mechanism, involved in call recognition and phonotaxis. Implications of results of the study and proposed mechanism are discussed.

Disclosures: B. Navia: None. **J. An:** None. **J. Rim:** None. **G. Atkins:** None.

Poster

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Program #/Poster #: P578.07

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant number 16H06544

Title: Mechanosensory antennal inputs modulate cercal-mediated escape behavior in crickets

Authors: *O. N. IFERE[1], H. SHIDARA[2,3], N. SATO[1], H. OGAWA[2];
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Abstract: Animals avoid obstacles along their path successfully by acquiring and integrating information of surrounding objects such as shape and location using multiple sensory organs. Crickets detect air currents in nearfield by their abdominal mechanosensory organ, cerci, respond to it as a sensory cue of predator's approach, and exhibit escape movement in opposite direction to the stimulus. Antennae are another crucial mechanosensory organ of insects to detect surrounding objects. Crickets, which are nocturnal insects, rely mostly on tactile information of surrounding objects sensed by antennae to guide their locomotion in the environment. However, it remains unclear if crickets modulate their escape behavior mediated by the cercal system depending on the spatial information of surroundings acquired by the antennal system. Using an open looped treadmill system, we examined wind-elicited escape behavior in darkness when an object such as rod and wall were placed at different locations to be detected by the antenna. Our results indicated that crickets modulated the movement direction in the escape behavior depending on object shape, distance, and orientation. Crickets usually move forward in response to the air puff from behind. When a wall was placed on the side of crickets close to their antenna, the escape movement was biased to the object-free side. Whereas the lateral movement elicited by the air-puff from the side was biased backwards by that wall. These results imply that the crickets modulate their movements to avoid collision with obstacles on the escape path. These modulations of the movement direction were observed for the near wall positioned anteriorly but not posteriorly, suggesting that the crickets modulated their behavior adapting to the object location. We also tested the effects of the wall positioned in front of cricket on the escape behavior. The forward movement triggered by the airflow from behind was suppressed and curved bilaterally by the front center wall accessible to both antennae. In contrast, the one-sided frontal plate to be accessed by only one antenna biased the movement to the plate-free side. The escape trajectory was also biased by the one-sided wall even though the antenna on the wall side was unilaterally ablated, suggesting that a single antenna is sufficient to detect location of front objects. Probably, edge detection even by a single antenna would be more crucial for object localization than bilateral comparison of antennal inputs indicating 'presence or absence' of objects. We concluded that crickets modulated their escape behavior depending on spatial information of surrounding objects by using antennal inputs.

Disclosures: O.N. Ifere: None. **H. Shidara:** None. **N. Sato:** None. **H. Ogawa:** None.

Poster

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Program #/Poster #: P578.08

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant number 16H06544

Title: Cricket changes their wind-elicited escape behavior depending on locomotion states

Authors: *K. KIUCHI[1], H. SHIDARA[2,3], Y. IWATANI[4], H. OGAWA[2];
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Abstract: Animals change their behavior depending on situation and context such as environmental and internal factors and their interaction. Since the adaptive behavioral changes are important in their survival strategy, many neuroscience studies address the issue about influence of internal and external factors on behavioral changes so far. Locomotion state of animals is one of the internal factors that have the greatest impacts on sensory perception and stimulus-triggered behavior. However, due to technical difficulty to apply high reproducible stimuli to moving animals repeatedly, the behavior changes depending on locomotion state have been investigated only on semi-restraint animals. To tackle this issue, we investigated wind-elicited escape behavior in the freely moving crickets, which exhibit jumping and running in response to airflow. We adopted the servosphere treadmill system with a markerless visual tracking technique, which allow us to keep small animals such as insects in the same position and orientation without restraint (Iwatani et. al., 2019). A short airflow was applied to spontaneously-walking crickets from a specific direction out of eight, and the airflow-elicited escape behavior was recorded with high-speed video camera. In most trials, when the walking crickets was stimulated, they quickly pause their movement and then started escape behavior. We compared the escape behavior between the moving and standing still crickets in various locomotion parameters, including response probability, jumping selection ratio, reaction time, velocity, distance, and directional accuracy of the movement. The probability of escape movement for moving crickets was higher than that for standing still ones. In addition, nearly 100% of moving cricket showed the pause response to even the slowest stimulus while less than 10% of crickets standing still showed the escape response. These results indicated that the threshold for pausing in moving crickets was much lower than that for escaping in standing still ones. There was no difference in the selection ratio of jumping between moving and standing still crickets. The locomotion state also affected other parameters. The moving crickets exhibited running escape with delayed reaction time, lower velocity, shorter distance. In addition, its movement direction was less accurately controlled than those in standing still crickets. Taken together, it is suggested that the high sensitivity to the airflow stimulus in moving crickets likely compensates poor performance in their escape response.

Disclosures: K. Kiuchi: None. **H. Shidara:** None. **Y. Iwatani:** None. **H. Ogawa:** None.

Poster

P639. Sleep: Systems: Computational Models and Analytical Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P639.01

Topic: F.08. Biological Rhythms and Sleep

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NINDS Grant 5R01NS104368
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NIH Grant S10OD028632-01
Sloan Research Fellowship
Jenny and Jeff Kelter Fellowship from the CSHL School of Biological Sciences

Title: Heterogeneity of vigilance states across cortical areas described by a low-dimensional manifold

Authors: *J. WANG[1], R. KWAPICH[2], S. CHAUVETTE[3], I. V. TIMOFEEV[4], T. A. ENGEL[2];
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Abstract: Brain states across sleep and wakefulness are conventionally divided into wake, Slow-Wave Sleep (SWS) and Rapid-Eye Movement (REM) sleep, which differ by a variety of psychological, physiological, and neurophysiological signatures. These states are usually classified by application of hand-crafted criteria to spectral power of Local Field Potential (LFP) or electroencephalogram (EEG) in specific frequency bands combined with differences in muscle tone measured with electromyography (EMG). Recent evidence indicates that the classical wake, SWS and REM are insufficient to capture the complexity of vigilance state dynamics on the brain-wide scale, which exhibit microstates and co-existence of heterogeneous electrophysiological signatures across different cortical areas. To account for the complexity and heterogeneity of vigilance states across the cortex, we developed an approach to uncover a low-dimensional manifold on which these states may be represented. To discover this manifold, we apply an unsupervised dimensionality reduction based on Variational Autoencoders (VAEs) to EMG and multi-site LFP activity recorded continuously from 14 different cortical areas in mice during the natural variation of sleep and wake cycles. First, we apply our model to activity on each of the 14 channels separately. For single channels, the inferred manifold reveals three clusters corresponding to the basic states of wake, SWS, and REM, as well as uncovers differences between cortical areas in the prevalence and characteristics of these states. Next, we apply our model to simultaneous activity on 14 electrodes to uncover the relationships between these cortical areas, such as when the entire brain is in one state, or split between multiple states. Our model discovers a continuous manifold that reveals the co-existence of states across cortical areas which occurs in the transitional region connecting the uniform cortex-wide states. Lastly, we fit the low-dimensional latent representations obtained from all cortical areas with a Hidden Markov Model (HMM) to segment and characterize the dynamics governing vigilance states. Our model provides a framework for understanding the propagation of heterogeneous states across the cortex, as well as for studying how these states are affected by factors such as sensory experience or disease. In conclusion, our work elucidates the regional co-existence of wake and sleep states as a common feature of laboratory mice brain activity.

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Poster

P639. Sleep: Systems: Computational Models and Analytical Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P639.02

Topic:

Title: Cortical wide-field imaging reveals the dominant role of hippocampal Gamma-events in orchestrating modular activation

Authors: *R. PEDROSA, F. STELLA, F. P. BATTAGLIA;
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Abstract: Recent advancements in anatomical and functional imaging techniques have led to a profound reappraisal of the principles of cortical mapping, emphasizing whole-brain networks organization around few functional and connectivity gradients. Yet, how spontaneous activity propagates, its relationship with sub-cortical regions like the hippocampus and its involvement in memory processes, remain largely unknown. Here, we investigate the fine-grained spatiotemporal dynamics of spontaneous activity in the entire dorsal cortex together with its time-resolved interaction with the hippocampus. For this, we analyzed two different datasets: (1) mice under urethane anesthesia with simultaneous recordings of wide-field voltage sensitive dye transients (VSD), cortical ECoG, and hippocampal CA1 LFP. And, (2) transgenic mice expressing voltage sensitive indicator (VSI) during natural sleep with simultaneous recordings of wide-field voltage imaging and high density silicon probe in the hippocampus. When measuring transients from the VSD, ECoG and VSI signal, we find event size distribution to be well approximated by a power law-like distribution, with condition-dependent parameters. Nevertheless, separately analyzing groups of transients of different magnitude reveals a major modulation in the transient activity structure. In fact, while small transients consist of a limited number of co-activation modes involving a sub-set of cortical networks (related to the Default Mode Network), larger transients extend to a substantial portion of the cortical surface and can be clustered depending on where they originate: one family is preceded by Retrosplenial cortex (RS) activation, the other is instead triggered by Somatosensory Cortex. Such classification also allows to identify hippocampal gamma oscillations as the principal signature of cortico-hippocampal interactions: hippocampal gamma power is proportional to the size of the cortical transients and shows a preferential association with RS-led transients. Accordingly, we also find a significant causal interaction pointing from RS activation to hippocampal gamma amplitude. On the contrary, ripple events appear to have a much looser association with cortical activity evolution. Taken together, our results provide a concrete description of the complex hierarchical structure shaping activity propagation between cortical areas and within the cortico-hippocampal loop, and points to RS and hippocampal gamma oscillations as the main organizational elements of the network.

Disclosures: R. Pedrosa: None. **F. Stella:** None. **F.P. Battaglia:** None.

Poster

P639. Sleep: Systems: Computational Models and Analytical Tools II

Location: Virtual Only

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Program #/Poster #: P639.03

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01 NS118440
NSF 1757574

Title: Ach regulates differential role of sleep stages in sleep dependent memory consolidation

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Abstract: ACh regulates differential role of sleep stages in sleep dependent memory consolidation
Michael Satchell[1], Alexis Simmons[2], Sara Aton[3], Michal Zochowski[4]
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Across vertebrate species, behavioral states transition consistently from wake to non-rapid eye movement (NREM) sleep to REM. The functional significance of this state ordering (with NREM preceding REM during sleep cycles) is unknown. Critically, NREM and REM sleep states are associated with dramatically different physiological features – including characteristic differences in neuronal firing patterns and rates, network oscillations, neuromodulation, and even gene expression. We have built a reduced computational model of interacting excitatory and inhibitory networks to probe how state-specific changes in ACh alter network dynamics and consequently engram consolidation via synaptic, spike timing dependent plasticity (STDP). We show that the sequential, bidirectional changes in ACh neuromodulation during NREM and REM sleep may play a vital role in consolidation, particularly when more than one memory trace is being stored simultaneously in a neural network. In the low-ACh (NREM-like) state, synapses from neurons activated by learning (i.e., engram neurons) to other neurons in the network are primarily strengthened through spike timing-dependent plasticity. In the subsequent high-ACh (REM-like) state, recruitment of GABAergic neurotransmission in the network suppresses activity among neurons not actively recruited into expanded memory traces by engram neurons during prior NREM. In scenarios where two separate memory traces (i.e., two groups of engram neurons) are introduced to the network, this sequence of changes to ACh signaling is vital to the generation of two completely segregated, but expanded, memory traces.
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Disclosures: M. Satchell: None. **A. Simmons:** None. **S.J. Aton:** None. **M.R. Zochowski:** None.

Poster

P639. Sleep: Systems: Computational Models and Analytical Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P639.04

Topic: F.08. Biological Rhythms and Sleep

Title: Creating an Entirely Automatic Sleep Scoring Algorithm Using EEG and EMG power

Authors: *K. M. KEUS[1], K. K. M. WRIGHT[1], J. HOLLOWAY[1], V. MATHUR[2], Y. CABRERA[1], G. R. POE[3];
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Abstract: Sleep scoring is a process by which states of sleep are characterized for later analysis. This process is traditionally accomplished manually by an "expert scorer" using the frequency makeup of either electroencephalography (EEG) or local field potential (LFP) recordings in the mammalian brain. In 2018, Bagur et al. discovered that an automatic sleep scoring algorithm could be constructed using LFP-derived gamma (50-70 Hz) power in the olfactory bulb (OB) and the ratio between theta (5-10 Hz) and delta (2-5 Hz) power in the hippocampus in mice. Gamma power was used to delineate sleep and wake states, and theta/delta power ratio to delineate NREM/REM, bypassing the need for manual scoring. In this study, we replicated these results in rats rather than mice and using EEG rather than LFP; furthermore, we improved on the existing method by recording from the frontal cortex (LfEEG) and the parietal cortex (LpEEG) rather than the OB and the hippocampus, respectively, resulting in easier surgical implantation without sacrificing efficacy. A scoring method based on electromyography (EMG) power was also constructed to demarcate wake from sleep. This method was then used as a check on gamma power-derived sleep classification, where output from the LfEEG thresholding was run through EMG scoring to remove erroneously classified stages of wake. We used a thresholding method to assign sleep states based on the distribution shape of power values of the gamma range, theta/delta ratio, and EMG range (30-245 Hz, excluding points around 60 Hz to reduce noise). To build this program, we used novel in-house MATLAB code in combination with pre-existing MATLAB sleep scoring and power analysis code (Brooks et al., 2009). We then compared our state classification output to manual scoring of the same recordings. Preliminary average percent agreement between wake/sleep distinction was 91.03% and average Cohen's Kappa was 0.8158. Average values calculated from a confusion matrix, including accuracy, precision, F1, and recall values, were 0.9131, 0.9257, 0.9741, and 0.8822, respectively. For EMG thresholding, average percent agreement was 89.99% and average Cohen’s Kappa was 0.7919. For NREM/REM distinction, average percent agreement was 94.50% and average Cohen’s Kappa was 0.8255. To date, we have successfully shown that gamma power from LfEEG and EMG power from the nuchal muscle in rats can be utilized to delineate wake and sleep, and theta/delta power from LpEEG can be used to delineate NREM and REM. Ultimately, we have created a simple program that can be used to score sleep entirely from electrical recordings, bypassing the need for training data and traditional manual scoring entirely.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: KIST Intramural grant 2E30962
NRF of Korea 2017R1A2B3012659

Title: Efficient mouse sleep-stage scoring by transfer learning of human EEG pre-trained model

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Abstract: Classification of neurobiological signals has immense potential for various applications such as anomalous brain signal detection, individual identification, and BCI (brain-computer interface). Moreover, it can also benefit neurobiological studies on animal models by helping to classify brain states from recorded brain signals. However, the classification of neural signals has traditionally been a laborious task requiring manual labeling by experts. Recent studies have proposed ways to alleviate the necessity of large labeled datasets by applying self-supervised learning in tandem with transfer learning. Meanwhile, neural oscillations are known to be largely preserved across mammalian species. Therefore, this study tested the possibility of applying transfer learning to a human EEG pre-trained model in the task of classifying sleep stages within mouse neurobiological recordings. A previously reported transformer-based pre-trained model (BENDR), trained on a large human EEG dataset with contrastive predictive coding, was adapted and fine-tuned with mouse LFP signals from sleep experiments. This approach dramatically reduced the amount of required labeled data in the fine-tuning step while retaining competitive performance in the mouse sleep-stage scoring task. Furthermore, the transformer-based nature of the model allowed raw neural data to be used as the input while intuitively visualizing neural signatures attended by the network during classification. This study opens up the possibility of utilizing a general-purpose classifier, pre-trained with abundant unlabeled data acquired from the same or different species, in performing downstream classification of neural time series data, especially under circumstances of data scarcity.

Disclosures: G. Lee: None. **B. Kim:** None. **J. Choi:** None.

Poster

P639. Sleep: Systems: Computational Models and Analytical Tools II

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Program #/Poster #: P639.06

Topic: F.08. Biological Rhythms and Sleep

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Helmholtz Association Initiative and Networking Fund ZT-I-0003

Title: An adaptable analysis pipeline makes cortical wave phenomena comparable across heterogeneous datasets

Authors: *R. GUTZEN[1,2,3,4], G. DE BONIS[5], E. PASTORELLI[5,6], C. CAPONE[5], C. DE LUCA[5,6], A. ALLEGRA MASCARO[7,8], F. RESTA[7], F. PAVONE[7], M. V. SANCHEZ-VIVES[9,10], M. MATTIA[11], S. GRÜN[1,2,3,4], A. DAVISON[12], P. PAOLUCCI[5], M. DENKER[1,2,3];
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Abstract: In the past decades, neuroscience excelled at accumulating a rich, heterogeneous landscape of datasets and methodologies. However, it is a challenge to effectively leverage the benefits of such diversity by combining the insights from across experiments, species, and measurement techniques. Integration of this heterogeneity requires rigorous analysis workflows that offer to distill consistent, reproducible, comparable, and reusable conclusions. Aligning data from various sources enables not only "big-data" analysis approaches, but also allows to produce a broader experimental basis for validating models and theories across the experimental and computational scales of description.
Here, we explore such an approach in the context of slow cortical waves (up to 5 Hz). Slow waves are persistently observed in sleep and anesthesia across various species and various measurement techniques [Alkire et al. (2008) Science 322.5903]. Furthermore, such activity is expressed by various models [Sanchez-Vives et al. (2017) Neuron 94.5; Pastorelli et al. (2019) Front Syst Neurosci 13:33]. First, we address the issue of providing a comparable quantitative description of the wave dynamics to compare such heterogeneous data on a conceptual level by designing a general and modular analysis pipeline approach that is adaptable to a variety of applications. Here, the key objective is to interface existing methods, standards, and tools in a flexible manner in order to serve the requirements of a wide range of datasets and research questions using a common set of analysis components. Moreover, by building on and co-developing other specialized open-source tools, we further emphasize the reusability and extendability of each of the pipeline components.
Based on this design, we present the Slow Wave Analysis Pipeline (SWAP) as a concrete, reusable implementation to perform broad, detailed, and rigorous comparisons of slow wave characteristics, such as velocities or directions. We apply SWAP to a range of openly available ECoG [De Bonis et al. (2019) Front Syst Neursci 13:70] and calcium imaging [Celotto et al. (2020) M&Ps 3.1:14] datasets and investigate the influences of experimental parameters such as the mice's genetic strain, the type and dosage of anesthetics, the measurement technique and the spatial resolution. We also demonstrate the pipeline's capabilities to benchmark specific methods within the analysis by exchanging them with another method and by analyzing the same pool of data.
Finally, we discuss how the premise of reusability and modularity helps to derive other analysis pipelines for similar research endeavors to amplify collaborative research.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P647.01

Topic: F.09. Food and Water Intake and Energy Balance

Support: F32DK120298

Title: Diet and Parent-of-Origin Dependent Effects on Body Composition, Locomotor Activity, and AgRP Neuronal Activity are Sex Specific in PWK/PhJ x C57BL/6J F_1 Mice

Authors: A. C. KORGAN, S. L. A. MARTIN, Z. J. D. BRIDGES, K. M. S. O'CONNELL;
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Abstract: Interactions between genetics and environment (GxE) impact brain development, behavior, and risk for disease, such as obesity and type II diabetes. Additionally, food intake and body composition are regulated by parent-of-origin effects throughout development and into adulthood via differential allele-specific gene expression in various brain regions. The arcuate nucleus of the hypothalamus (ARH) is a hot-spot for allele-specific expression in these studies. A primary neuronal subtype in the ARH, agouti-related peptide (AgRP) neurons, are essential for driving food intake. These neurons play a key role in integrating peripheral and central signals to modulate food intake, body weight (fat mass), and locomotor (food seeking) behavior. Consistent with their role in energy balance, AgRP neuronal activity is tightly correlated with nutritional status. We have previously demonstrated that AgRP neuronal activity is sensitive to diet, thus diet-dependent plasticity may be a causal factor in obesity. Previous research has primarily used inbred mouse models and single parent-of-origin designs that lack genetic and epigenetic diversity, and do not capture the considerable influence that genetic factors play in controlling obesity and bodyweight. Therefore, we utilized an F_1 panel of mice that are resilient and susceptible to diet-induced obesity (DIO): DIO resilient wild-derived PWK/PhJ mice were bred with DIO susceptible C57BL/6J mice (expressing a NPY^{GFP} reporter) to generate both paternal PWK (PWKxB6) and paternal B6 (B6xPWK) mice. We found that fat-content, locomotor activity, feeding, and AgRP neuronal activity were influenced by parent-of-origin in a sex-specific manner. B6xPWK males had increased body fat, an effect attenuated by HFD feeding, and were less active in the elevated plus maze (EPM), compared to PWKxB6 males. Further, only PWKxB6 males were susceptible to diet-induced increases in AgRP neuronal activity, because chow fed B6xPWK males had an increased firing rate. HFD fed B6xPWK females had increased body fat, compared to B6xPWK chow and both chow and HFD PWKxB6 mice. Chow and HFD fed B6xPWK females were less active in the open field and EPM. B6xPWK females had decreased AgRP neuronal activity but we did not identify diet-induced changes in AgRP neuronal activity in female mice, which aligns with previous research. Ongoing work will explore parent-of-origin dependent changes in food preference, hypothalamic gene expression, and explore the impact of maternal care on offspring development. These studies will identify genetic traits linked to weight gain and obesity, providing insights into the diversity of the human response to DIO.

Disclosures: A.C. Korgan: None. **S.L.A. Martin:** None. **Z.J.D. Bridges:** None. **K.M.S. O'Connell:** None.

Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Topic: F.09. Food and Water Intake and Energy Balance

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FAPESP 2015/23467-7
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CNPq

Title: Hypothalamic angiotensinergic AT1 receptor mRNA expression and angiotensin II responses in female SHR treated with estradiol

Authors: E. D. PEREIRA, Jr, L. M. OLIVEIRA, G. C. NUNES, P. P. C. SOUZA, L. A. DE LUCA, Jr, E. COLOMBARI, D. S. A. COLOMBARI, ***J. MENANI**, C. A. F. ANDRADE;
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Abstract: Hypertension is one of the most prevalent non-communicable diseases in the world. The spontaneously hypertensive rat (SHR), an animal model of primary hypertension, ingests more NaCl than normotensive strains. Estrogens have significant influence on cardiovascular regulation and hydromineral balance. We have shown that estrogens reduce NaCl intake and palatability in female SHRs, but we do not know whether such an effect involves the brain renin-angiotensin system (RAS). Here we investigated: 1) the expression of hypothalamic RAS components, 2) central angiotensin II-induced pressor and drinking responses in female SHRs treated with estradiol. Adult ovariectomized (OVX) female SHRs with a guide cannula implanted in the lateral ventricle and a femoral artery catheter were used. Rats were treated with β estradiol (E2, 10 μg/kg of body weight - b.w.) or vehicle (VEH, sunflower oil, 0.1 ml) for 8 days. Angiotensin II (ANG II, 50 ng/1 μl) was administered intracerebroventricularly (icv). E2 treatment reduced icv ANG II-induced water intake (3.7 ± 0.5, vs. VEH: 6 ± 0.5 ml/100 g b.w.) and pressor response (22 ± 7, vs. VEH: 37 ± 4 mmHg). Quantitative real-time PCR analysis (qPCR) showed that the relative hypothalamic mRNA expression of angiotensinergic AT1 receptor (Agtr1a) was reduced in E2-treated OVX female SHRs (0.82 ± 0.16, vs. VEH: 1 ± 0.11). There was no effect on relative mRNA expression of hypothalamic Agtr2, ACE and ACE2. The results suggest that the reduction of hypothalamic Agtr1a mRNA expression might be a reason for the reduction in ANG II-induced pressor and dipsogenic responses in female SHRs treated with E2.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Title: Evaluation of the function of hindbrain ependymal cells in glucose sensing by analyzing the counterregulatory responses to glucoprivation in female rats with ependymal denudation.

Authors: *M. SATO[1], F. MAGATA[1], H. TSUKAMURA[2], F. MATSUDA[1];
[1]The Univ. of Tokyo, Tokyo, Japan; [2]Nagoya Univ., Nagoya, Japan

Abstract: The hindbrain has been suggested to play a pivotal role in maintaining reproductive function, gluconeogenesis, and feeding during malnutrition. Our previous studies showed that ependymal cells lining of the 4th ventricle (4V) express glucokinase and glucose transporter 2, which are important molecules for glucose sensing, and that ependymal cells are activated by hindbrain glucoprivation. These findings suggest that the 4V ependymal cells function as a glucose sensor. The present study aimed to determine whether the 4V ependymal cells mediate the counterregulatory responses against hindbrain glucoprivation. We generated rats, whose 4V ependymal cells were denuded, and analyzed the effect of hindbrain glucoprivation on their luteinizing hormone (LH) secretion, blood glucose level, and food intake. Estrogen-implanted ovariectomized female rats (n = 6-8 in each group) were used. Neuraminidase dissolved in UPW (100 mU), which reportedly causes ependymal denudation, or UPW was infused into the 4V of female rats for 10 min. Consecutively, 2-deoxy-D-glucose (2DG), a glucose utilization inhibitor, or xylose, as an isosmotic control, was infused into the 4V for 100 min (40 mg/kg body weight). For the analysis of the pulsatile luteinizing hormone (LH) secretion, blood samples were collected every 6 min for 3 h started from 1 h before the 4V neuraminidase infusion and blood glucose levels were also measured every 30 min from just before the 4V neuraminidase infusion. After the last blood sampling, food intake was measured for 3 h. Immediately after the food intake measurement, rats were transcardially perfused with 4% paraformaldehyde and the brain was obtained to make paraffin-embedded sections. Histological analysis of the brain sections with HE staining revealed that 4V ependymocytes were denuded in the rats treated with 4V neuraminidase administration. 4V 2DG infusion enhanced food intake in control rats but failed to increase the food intake of rats with ependymal denudation. On the other hand, rats with 4V 2DG infusion showed lower LH pulse amplitude and higher blood glucose levels in both control rats and rats with ependymal denudation. Taken together, the present study suggests that the 4V ependymal cells, at least in part, function as a key glucose sensor to mainly regulate feeding during malnutrition.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P647.04

Topic: F.09. Food and Water Intake and Energy Balance

Title: The role of uric acid in the development of hyperalgesia in overweight ovariectomized rats

Authors: *O. A. JARAMILLO-MORALES[1], J. V. ESPINOSA-JUÁREZ[2], M. FERNÁNDEZ-MOYA[1], L. A. VERGARA-HERNÁNDEZ[1], M. E. BARRETO-ARIAS[1], F. J. LÓPEZ-MUÑOZ[3];
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Abstract: Menopause is a condition associated with a greater perception of painful stimuli and an increase in adipose tissue. In addition weight gain is known to be related to changes in pain perception; however, its mechanism is unclear. Objective. The aims of this study were to analyze the behavioral responses of hypoestrogenic overweight Wistar rats to thermal stimuli and to analyze the glucose and uric acid levels in this population. Methods. Animals with hypoestrogenism induced by bilateral ovariectomy were used. Animals received a hypercaloric diet (30% sucrose) or normal water with standard laboratory food *ad libitum* for 4 weeks; thermal nociception and body weight were measured during this period. Four weeks after treatment, glucose and uric acid levels and abdominal fat weight were measured in both groups. Nociception was assessed using the "Plantar test". Results. Overweight ovariectomized Wistar rats showed significantly higher body weight and abdominal fat weight than the control group. A hyperalgesic response was observed in sucrose-fed animals. Thermal latency was also significantly decreased during the 4th week in these animals compared to that of the controls. There were no differences in glucose levels, but uric acid levels were altered between groups. Conclusions. Our data indicate that increased body weight, abdominal fat and increased uric acid levels are associated with the hyperalgesic responses observed in ovariectomized overweight female rats.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Program #/Poster #: P647.05

Topic: F.09. Food and Water Intake and Energy Balance

Support: T32DK112751-01

Title: Loss of ciliary adenylyl cyclase 3 in the ventromedial hypothalamus resulted in a sex-dependent obese phenotype

Authors: *G. DENG, K. SAITO, U. SINGH, Y. DENG, J. DICKEY, J. JIANG, H. CUI;
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Abstract: Obesity, a metabolic disorder characterized by an excessive accumulation of body fat, continues to be a major economic and health burden to the global populace, as it is the most significant risk factor for heart disease, diabetes, and hypertension. Genome-wide association studies have identified several genes involved in obesity development, including *ADCY3*, a gene encoding for the enzyme adenylyl cyclase 3 (AC3). AC3 is a critical mediator of the cyclic adenosine monophosphate (cAMP) signaling pathway and is enriched in the primary cilium, a solitary immotile organelle protruding from most mammalian cells, including neurons. The primary cilia act as the cellular antenna to sense and relay changes in the extracellular microenvironment and mounting evidence support a role for the primary cilia as a critical regulator of the energy homeostasis. Patients carrying loss-of-function *ADCY3* variants are obese and are at increased risk of developing type II diabetes mellitus (T2DM). Consistently, whole-body *Adcy3* knockout mice also develop obesity; however, the underlying mechanisms by which AC3 affects metabolic homeostasis remain unclear. Here, we examined the impact of AC3 loss within the ventromedial nucleus of hypothalamus (VMH), a brain region critical for coordinated control of energy and glucose homeostasis, on energy metabolism. We generated mice with VMH-specific *Adcy3* loss (Adcy3$^{SF\text{-}1KO}$ mice) by crossing SF-1^{Cre+} mice with Adcy3$^{F/F}$ mice and subjected them to metabolic phenotyping to assess energy balance and glucose homeostasis. We observed a sexually dimorphic effect on body weight under standard chow diet; male Adcy3$^{SF\text{-}1KO}$ mice displayed normal body weight gain comparable to control littermates, whereas female Adcy3$^{SF\text{-}1KO}$ mice gained a significant more weight compared to control littermates (Con 24.34g v KO 30.61g, $p < 0.0001$). Strikingly, however, both sexes of Adcy3$^{SF\text{-}1KO}$ mice exhibited improved glucose tolerance (AUC: M Con 17,826 v KO 15,165, $p = 0.02$; F Con 15,263 v KO 13,238, $p = 0.03$) without affecting fed and overnight fasting blood glucose levels. Taken together, these results underscore the importance of AC3-mediated ciliary cAMP signaling in VMH neurons for the regulation of energy balance and glucose homeostasis in a sex-dependent manner.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Topic: F.09. Food and Water Intake and Energy Balance

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Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (2019/01306-2)

Title: Effects of chronic central leptin infusion on food intake of offspring of dams with mild hyperglycemia associated with snack intake

Authors: *G. P. OLIVEIRA[1,2], A. G. CRUZ[1,2], G. V. SILVA[2], L. P. RODRIGUES[2], M. G. MARTINS[1,2], B. WOODSIDE[3], A. C. I. KISS[1,2];
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Abstract: There is evidence that offspring from diabetic dams show differences on energy balance and leptin levels. Besides maternal metabolism, it is known that maternal nutrition can also compromise those parameters in the offspring. However, the effects of their association on offspring food intake have not been explored yet. Therefore, the aim of this study was to evaluate the effects of chronic central leptin infusion on food intake of offspring of dams with mild hyperglycemia associated with snack intake. Sprague-Dawley rats were used. Female rats were mated and on pregnancy day (PD) 0 were randomly divided into 2 experimental groups: standard diet (n=28) or standard diet + snacks (n=27). Snacks compromised of potato chips and a red fruit-flavored sucrose syrup solution 1.5%). On pregnancy day 7, both experimental groups were then subdivided into normoglycemic dams and dams that were rendered hyperglycemic by streptozotocin administration (STZ, 35mg/kg, i.p.). Thus 4 experimental groups: Control (n=15), Control-Snack (n=14), STZ (n=13), and STZ-Snack (n=13). On PD 21, rats gave birth naturally and litters were culled to 4 males and 4 females. On postnatal day 75 (PND 75), 2 male and 2 female offspring from each litter were used and each received a different central treatment (saline or leptin). Thus, the offspring experimental groups were formed according to maternal metabolism (normoglycemic or hyperglycemic), maternal diet (standard chow or standard chow plus snacks), sex (male or female) and treatment (saline or leptin). On PND 82 animals underwent surgery for implantation of a cannula in the cerebral lateral ventricle (Alzet® model 2001) which released saline 0,9% or leptin (1 µg of leptin per day at a rate of 1 µl/hour for 7 consecutive days). Body weight and food intake were daily monitored for 7 days before and 7 days after surgery. On PND 89, rats were killed and cannula placement was evaluated. All experimental procedures were approved by the local ethics committee (Protocol 1134). Offspring of hyperglycemic dams were hyperphagic, presenting an increased food intake even before surgery. As expected, leptin treatment reduced food intake and body weight in all treated animals. Response to leptin was modified by sex and also by maternal snack intake, with offspring from dams fed with snacks showing an increased response to central leptin, regardless of maternal metabolism. In conclusion, maternal hyperglycemia changed offspring food intake pattern. Maternal snack intake increased offspring response to central leptin in a sex dependent manner. However, the association of both maternal factors did not lead to further effects for the offspring food intake.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P647.07

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH Grant P20GM103430, PI: Bongsup Cho, University of Rhode Island
Rhode Island Foundation (RIF) Grant 5213_20200592, PI: Anika Toorie

Title: Elucidation of sex-specific hedonic and homeostatic disturbances caused by an obesogenic diet in Sprague Dawley (Rattus norvegicus) rats

Authors: *J. GAULIN, K. SALHANY, Jr., J. MELO, Z. DJABAKATIE, F. DEJU-CALIXTO, A. TOORIE;
Biol., Rhode Island Col., Providence, RI

Abstract: Chronic overconsumption of hyperpalatable, hypercaloric foods is a growing concern in modern society, despite increased awareness and mitigation efforts to reduce its prevalence. It is a significant contributing factor to metabolic syndrome, a cluster of symptoms that includes hypertension, hyperglycemia, abdominal obesity, and abnormal cholesterol levels. Unresolved metabolic syndrome can paradoxically result from or lead to insulin resistance and the development of type 2 diabetes, among other diseases. Dysregulation in both central (brain) and peripheral tissue (i.e., liver and adipose tissues) contributes to the development of metabolic syndrome. In this study, male and female subjects were fed a high-fat diet (HFD) or a standard control diet for 12 weeks. Findings revealed that males are prone to development of metabolic dyshomeostasis while females are resilient to the effects of chronic HFD exposure. While no differences in anhedonia were discerned, HFD males displayed behaviors suggestive of enhanced anxiety. We posit that glucoregulatory and anxiety-related effects are likely due to changes in stress hormone physiology in both central and peripheral tissues, in tandem with dysregulated hepatic glucose metabolism.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Program #/Poster #: P647.08

Topic: F.09. Food and Water Intake and Energy Balance

Support: R01 AA028218.

Title: Sex Differences in Binge Eating of Palatable Food and Expression of Pituitary Adenylate Cyclase-Activating Polypeptide in the Thalamic Paraventricular Nucleus in Rodents

Authors: *G. CURTIS, A. T. GARGIULO, B. PIRINO, J. R. BARSON;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Binge eating disorder, characterized by the overconsumption of food in a discrete time period, is the most common eating disorder in the United States and affects women more than men. Both the

neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), and the limbic brain region, the paraventricular nucleus of the thalamus (PVT), have been implicated in feeding behavior. We have recently identified high levels of the peptide isoform, PACAP-27 (more than PACAP-38), in cells of the PVT. To investigate possible mechanisms behind sex differences in the rate of binge eating disorder, we used limited home-cage access (2 hours/day, 4 days/week) to Milk Chocolate Ensure Plus® to induce binge-type eating in male and female mice. Control groups of male and female mice were given access to chow and water but not Ensure. Chow, water, and Ensure were measured before and after the two-hour "binge" period. Under this 6-week paradigm, and with chow available ad libitum, female compared to male mice demonstrated greater binge-type eating of Ensure, consuming more calories per body weight during the two-hour binge period. While these male and female mice did not differ in 24-hour caloric intake per body weight, female mice in the binge-type eating group consumed significantly more calories from sugar than male mice during this period, indicating that they are preferentially consuming this carbohydrate as a calorie source. In the control groups, male and female mice did not differ in their chow intake during the two-hour binge period. Using quantitative real-time PCR (qRT-PCR) to examine PVT PACAP mRNA in adult male and female mice with no history of binge eating, we found that females had higher gene expression of PVT PACAP than males. Similarly, in rats, females also had higher levels of PACAP mRNA, in both the anterior PVT and posterior PVT. Finally, using immunohistochemistry in rats, we found that females had higher PACAP peptide levels, of both PACAP-27 and PACAP-38, across the entire PVT. Our results indicate that females demonstrate greater binge-type eating and higher levels of PVT PACAP than males. Given the known associations of PACAP and the PVT with feeding, this suggests that PACAP in the PVT could drive binge eating behavior.

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Poster

P647. Ingestive Behaviors: Contribution of Sex and Sex Comparisons

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Topic: F.09. Food and Water Intake and Energy Balance

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Title: Interactions of sex and physical activity levels on hedonic feeding

Authors: *C. L. GANN[1], Y. CAM[1], D. A. SHAY[2], A. DAY[1], V. J. VIEIRA-POTTER[2], T. R. SCHACHTMAN[1], M. J. WILL[1];
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Abstract: Considering the obesity epidemic is largely attributed to an energy imbalance, it is crucial to understand the behavioral and biological mechanistic interactions between intake of energy dense food and level of physical activity. Previous research has shown sex dependent influences of physical activity on diet preferences, specifically differences in palatable high fat diet intake. We hypothesize that this sex difference involves principles of reward substitution. Female rats have been shown to demonstrate higher

levels for the self-administration of drugs of abuse, palatable food intake, and voluntary wheel running, when compared to males. Considering this sex difference across multiple rewarding events, the present study explored how palatable diet intake and physical activity may be influenced by reward substitution in male and female Wistar outbred rats. Following a 1-week acclimation to voluntary wheel running access (RUN) with ad libitum standard chow diet, rats were given access to both ab libitum high fat diet (60% fat) along with standard chow diet for the next 4-week testing period (Weeks 2-5). Food consumption, body weight, and running duration and distance were recorded daily. All groups were given 1 week in the RUN condition (week 2) followed by 1 week of a locked wheel condition (SED) (week 3), to determine diet preference change between the RUN and SED conditions. During weeks 4 and 5, one half of the males and females were placed back in the RUN condition, while the other half remained in the SED condition. At the end of week 5, striatal and hypothalamic brain regions and plasma were collected, and multiple gene and protein profiles were assessed. Results showed that there was a sex dependent effect of RUN treatment on decreasing palatable food intake in males, which was reversible by returning rats to SED conditions.

Disclosures: C.L. Gann: None. **Y. Cam:** None. **D.A. Shay:** None. **A. Day:** None. **V.J. Vieira-Potter:** None. **T.R. Schachtman:** None. **M.J. Will:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P673.01

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Guiding the future by linking the past: Adolescent development of value-based generalization

Authors: *A. QUACH[1], D. SHOHAMY[2,3], G. WIMMER[4], A. GALVAN[5], B. CASEY[6], J. Y. DAVIDOW[1];
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Abstract: Generalizing from past experience is important for guiding adaptive decision-making in new situations. Adolescence is a life-stage full of new experiences during which individuals face increasing opportunities for self-guided decision-making. Research has shown that adolescents can make adaptive value-guided decisions, however, protracted neural coordination of subcortical learning systems with cortical systems may constrain their ability to flexibly generalize value across related experiences to guide novel decision-making. To test this hypothesis, participants (N=111, ages 8-30) completed a motivated learning and generalization task with three stages. First, participants learned stimulus-stimulus associations in the absence of feedback, then a subset of stimuli from these pairs underwent probabilistic reward conditioning (i.e., learned stimulus-outcome associations), and finally, a critical decision-making test evaluated the extent to which value generalized across overlapping experiences. We found that stimulus-stimulus and stimulus-outcome learning did not vary by age, suggesting that all participants learned the contingencies similarly, and allowing us to ask about age-related differences in how these

associative relationships are used to guide novel decision-making. While participants of all ages were similarly able to make optimal choices based on previously conditioned options, in contrast, optimal choices requiring the integration of value across overlapping learning experiences increased with age. This pattern of results suggests protracted development of the ability to generalize value across related experiences. Ongoing examination of resting-state functional connectivity will relate these differences in value-based generalization to age-related changes in intrinsic neural networks. These findings will shed light on mechanisms underlying how adolescents make decisions as they navigate new experiences throughout development.

Disclosures: A. Quach: None. **D. Shohamy:** None. **G. Wimmer:** None. **A. Galvan:** None. **B. Casey:** None. **J.Y. Davidow:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P673.02

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Shiseido Co., Ltd.

Title: Investigation of decision-making process during cosmetics purchasing

Authors: *K. HIRABAYASHI[1], Y. SAHEKI[1], K. IIJIMA[2,3], K. MATSUMORI[2,4,5], K. MATSUMOTO[2], K. TAGAI[1];
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Abstract: Decision making behaviors, including the selection and purchase of products by consumers, can be explained by the "*decision utility*" in conventional economics. Meanwhile experiences that occur around the decision (*experienced utility*) also affect the actual decision making. In our previous research, we developed a new monetary task to measure the neural correlates of decision utility as well as 2 important aspects of the experienced utility i.e. *instant utility* and *remembered utility*. We identified the brain regions involved in each utility calculation and constructed a mathematical model by using this task. However, it is unclear how generalizable the findings from the abstract fractal images are to actual consumer purchasing behavior. Here we sought to investigate the neural mechanisms of purchasing behavior by using a modified version of the previous task. The experiment comprised 4 sessions, with each session comprising 3 parts: A Selection part and Evaluation part (repeated 10 times) and a Remember part (at the end of the session). In the Selection part, the participants were shown 2 lipsticks, the combination of which was selected at random without replacement from a total of 5 lipsticks. The participants were asked to select the lipstick which more preferred. In the Evaluation part, they saw a photo of their own face made-up virtually with the chosen lipstick, superimposed on a scene. The virtually made-up face was presented four times in total in the Evaluation part, superimposed on four

different scenes (e.g. party, mountain, or funeral). In the Remember part, the participants were asked to evaluate the remembered value of each lipstick. During this task, fMRI was used to investigate the neural responses. We found no statistically significant response at the decision to choose a lipstick during the Selection. During experiencing whether the lipstick suits them during the Evaluation part, right fusiform (rFG) was significantly activated. When they remember the value of the lipsticks, significant activation was shown in the Angular Gyrus (AG) and in part of the Midbrain. We suggest that during the Evaluation part, the processing of the face activates the rFG. Meanwhile, in the Remembering part, the significant activation in the AG and midbrain was consistent with our previous study and likely reflects memory retrieval and reward process, respectively. We speculate that remembering the simulated cosmetics experiences triggers reward processes, such that future choice of cosmetics can be based on this remembered utility. Although future studies are necessary, the neuronal process underlying purchasing behavior can support product development.

Disclosures: K. Hirabayashi: A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **Y. Saheki:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd.. **K. Iijima:** None. **K. Matsumori:** None. **K. Matsumoto:** None. **K. Tagai:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd..

Poster

P673. Human Reward and Appetitive Learning and Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P673.03

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH NICHD R01HD097619

Title: Neural mechanisms underlying expectations of reward-based task performance

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[1]Biomed. Engin., Johns Hopkins Sch. of Med., Baltimore, MD; [2]Kennedy Krieger Inst., Baltimore, MD

Abstract: When performing a motor task, it is essential for us to generate expectations of the outcomes of our actions. Both our actions and external environmental factors contribute to the realization of our outcomes, and it is important for us to understand how these different factors give rise to our eventual expectations. There is a limited understanding of how the brain integrates information about motor performance and environmental factors when generating our expectations of performance. To dissociate these factors, we had subjects perform a skilled button-pressing task in which they controlled a cursor into a variable size target for reward. Participants were also presented with cues associated with probabilistic outcomes that were not contingent on performance. This meant that even if a participant successfully performed the task, there would be a chance of not receiving a reward. The probabilistic outcome was independent of the participants' performance. The difficulty of the game (target size) as well as the probabilistic outcome cue were presented to participants prior to starting a trial, and at separate time points. In addition to performing the skilled task for reward, subjects also made choices to either perform the tasks of varying difficulty, or accept potential probabilistic outcomes (i.e., monetary gamble) that was not associated with task performance. Using the choice data, we computed the preference of each subject

to perform the task over the probabilistic outcome. Participants' choices showed that they were accurate in assessing their performance during easy trials, but significantly over-estimated their performance for the difficult trials. We plan on doing further analysis of our imaging data to examine how BOLD activations in reward regions differentially encode task performance and probabilistic outcomes.

Disclosures: J. Lee: None. **V.S. Chib:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P673.04

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Shiseido Co., Ltd.

Title: Trends in instant utilities determine decision through remembered utility

Authors: *K. IIJIMA[1,2], K. MATSUMORI[1,3,4], Y. SAHEKI[5], K. HIRABAYASHI[5], K. TAGAI[5], K. MATSUMOTO[1];
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Abstract: There has long been tension between two different usages of the term "utility". *Decision utility*, adopted in current economics and decision theory, refers to the weight of an outcome in a decision and is inferred from observed choice behavior. However, in classical utilitarianism, utility refers to pleasure and pain, and such *experienced utility* can be reported in real time (*instant utility*), or in retrospective evaluations of past episodes (*remembered utility*). To bridge these two core meanings of utility in the human brain, we developed a novel task for measuring neural correlates of decision, instant and remembered utility. By choosing between two fractal images, participants received a series of monetary rewards depending on the chosen image in 10 discrete steps repeated. Occasionally, participants were asked to report their current pleasantness (instant utility) or retrospective pleasantness (remembered utility) for the fractal image. We assigned six different patterns of reward series (descending (D), constant (C), and ascending (A) patterns of large rewards and those patterns of small rewards) to six fractal images, respectively. Participants gradually learned the value of fractals and showed rational choice behavior (large vs. small). Interestingly, even among the same reward category (large or small), they showed particular preference for reward series (i.e., D > C > A). The remembered utility for each reward series gradually dissociated from the others, reflecting the learning of value. Reported instant utility roughly reflected the trends of monetary reward series. However, the sums of instant utilities over the whole steps were dramatically dissociated from objective reward amounts. The instant utility of later steps seemed to be less affected by reward amounts. The sum of instant utilities over the whole steps also seems to reflect the preference for reward series in choice behavior. Moreover, a multiple regression analysis to instant utility indicated that presenting particular series itself affected instant utility regardless

of current amounts of monetary reward. Furthermore, we developed computational models to examine the dependency among utilities and reward. Model selection confirmed that instant utility, in addition to the objective reward, had a role in determining remembered and decision utility. The selected model suggests that trends in instant utility determine decision utility through remembered utility. As the next step, we will analyze the neural responses with the newly developed decision-making model to differentiate the three utilities in the brain.

Disclosures: K. Iijima: None. **K. Matsumori:** None. **Y. Saheki:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **K. Hirabayashi:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **K. Tagai:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd.. **K. Matsumoto:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

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Program #/Poster #: P673.05

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Marie Sklodowska-Curie Action H2020-MSCA-IF-2018-#845176
ANR PRC : ANR-19-CE37-0014-01

Title: The intrinsic value of choice of free versus forced choice in human subjects

Authors: *J. MUNUERA[1], M. R. AGOST[2], V. CHAMBON[2], B. LAU[1];
[1]Paris Brain Inst., Paris, France; [2]Inst. Jean-Nicod, Ecole Normale Supérieure, Paris, France

Abstract: When deciding between opportunities leading to further choices and those that do not, humans and other animals frequently choose to choose, even when doing so does not immediately lead to reward. We sought to understand the mechanisms involved in choice preference by asking human subjects to perform a two-stage task separating decisions to choose from actions that lead directly to reward. In each trial, subjects made a 1st stage choice (meta-choice) between two options defining the 2nd stage: the opportunity to choose between two fractal targets (free condition) or performing an obligatory selection of another fractal target (forced condition). Rewards were delivered probabilistically for 2nd stage actions, and in different blocks we varied either overall expected value (keeping maximal reward probabilities equal between free and forced actions) or relative expected value (increasing the reward probability of forced actions). We found that subjects prefer free to forced actions when they yielded similar expected reward (65%). Increasing the expected value of forced actions progressively reduced preference for free actions (39% when p(reward|forced) = 0.95 and p(reward|free) = 0.75). However, we observed substantial inter-subject variability, with ~13% of subjects exhibiting near-exclusive preference for free actions. We fit temporal-difference reinforcement learning (TDRL) models to investigate inter-subject differences and test whether trial-by-trial data could be explained by distortion of rewards obtained from free actions (overvaluation) and/or the use of greedy targets in calculating reward prediction errors (Q-learning variants compared to SARSA). Model comparisons indicated that it was necessary to incorporate overvaluation of rewards obtained from free actions to account for choice-seeking behavior, and that

using greedy targets alone was insufficient to explain observed choice preference. Our results advance our understanding of one facet of "intrinsic motivation" related to why people value choice

Disclosures: J. Munuera: None. **M.R. Agost:** None. **V. Chambon:** None. **B. Lau:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

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Program #/Poster #: P673.06

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01DA040965
P30GM103398-05

Title: Exercise attenuates incubation of craving for food high in fat

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Abstract: Exercise attenuates incubation of craving for food high in fat
Kirkpatrick GE[1,3], Dingess PM[2], Brown TE[1,2,3]
[1]Biomedical Program, University of Wyoming, Laramie, WY 82071[2]School of Pharmacy, University of Wyoming, Laramie, WY 82071[3] Neuroscience Program, Washington State University, Pullman WA 91163
We have previously shown that cue-induced craving for food high in fat increases over time (incubation of craving); however, whether this time dependent increase can be attenuated is unknown. To address this question, 60d male Sprague Dawley rats underwent self-administration training for a 60% high-fat (HF) pellet, which was associated with the presentation of a compound stimulus (light+tone) for 10 d. Rats were tested for lever responding in the absence of the HF pellet but in the presence of the cues one day after training. Rats did not undergo any subsequent operant training for 30d. During the 30d abstinence period, a subset of rats were exposed to high intensity interval exercise. Both groups were tested again on day 30, identically to the 1d test. Consistent with our previous work, we found that rats without exercise demonstrated significant incubation of craving (1d: 28.23±3.26; 30d: 58.62±7.31; data are mean ± SEM). However, rats exposed to exercise during the abstinence period did not show an incubation of craving effect at 30 d (1d: 26.67±3.41; 30d: 30.25±3.66). These results indicate that exercise could reduce increased craving during abstinence, which may reduce overeating and the development of obesity.

Disclosures: G.E. Kirkpatrick: None. **T.E. Brown:** None. **P.M. Dingess:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

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Program #/Poster #: P673.07

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Fondation Recherche Médicale FDM201906008526
Agence Nationale de la Recherche ANR-19-CE37-0014

Title: Subthalamic nucleus modulation and dopaminergic treatment influence free choice preference on Parkinson's disease patients

Authors: *D. BENDETOWICZ[1,2], B. LAU[1], E. HAINQUE[1,2], C. KARACHI[1,3], J. MUNUERA[1]; [1]Sorbonne Université, Inst. du Cerveau - Paris Brain Inst. - ICM, Inserm, CNRS, Paris, France; [2]Neurol., [3]Neurosurg., AP-HP, Hôpital de la Pitié Salpêtrière, Paris, France

Abstract: Dopamine neuron activity is closely related to the reinforcement of newly experienced appetitive stimuli or rewards. According to the common currency theory, the dopaminergic system acts as a stimulus reinforcer regardless of the reward type which can be basic like food or reproduction or more complex (or cognitive), like getting advanced information or having the ability to choose between several options in uncertain situations. Cognitive rewards can be regarded as rewarding by increasing knowledge or influence of the agent on its environment. Animals and humans express a natural preference for situations when choices are available compared to the absence of choice. However, the neural mechanisms underlying such behavior are poorly understood. We hypothesize that cognitive rewards are encoded by the dopaminergic system. We tested cognitive rewards (choice preference) using a task on patients with Parkinson's disease as a model of dopamine depletion. We designed a two-step task where subjects had to select between two rewarding images, either by choosing themselves (choice trials) or forced by the computer (forced trials). Before testing, subjects were extensively trained on paired-images with imbalanced probability of reward, one being more rewarding than the other. Reward contingencies were equivalent between forced and choice conditions and the most rewarding image was always selected by the computer in the forced condition. By doing so, forced and choice conditions were economically equivalent in terms of maximizing the total amount of reward.
We tested 37 patients and compared their performance with (ON) and without (OFF) surgical or dopaminergic treatment. 13 patients were treated with Deep Brain Stimulation (DBS group) of the subthalamic nucleus (STN) and 24 patients were treated with levodopa medication only (MED group). Preliminary results show that DBS patients have a higher preference for choice when DBS was ON (Mean=76%) compared to OFF (Mean=46%). No difference was observed in MED patients, with a high preference for choice trials both ON (Mean=76%) and OFF treatment (Mean=74%). Notably, we observed a positive and negative association respectively between L-DOPA daily dose and duration of disease with preference for choice.
We observed that free choice opportunity is influenced by neuromodulation of the STN activity. In line with the idea that DBS of the STN enhances incentive stimulus selection, this result suggests that free choice acts as a cognitive reward. Furthermore, higher choice preference on MED patients could be related to long-term effects of chronic L-DOPA intake.

Disclosures: D. Bendetowicz: Other; Travel grant from Boston Scientific. **B. Lau:** None. **E. Hainque:** None. **C. Karachi:** Other; Lecture fees and research funding from Boston Scientific and Medtronic. **J. Munuera:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P673.08

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Grand Challenge Award to Dr. James Cavanagh

Title: The reward positivity is enhanced in individuals with alcohol use disorder

Authors: *G. SINGH[1], E. CAMPBELL[1], J. HOGEVEEN[1], E. CLAUS[2], K. WITKIEWITZ[1], J. CAVANAGH[1,2];
[1]Dept. of Psychology, Univ. of New Mexico, Albuquerque, NM; [2]Mind Res. Network, Albuquerque, NM

Abstract: The Reward Positivity (RewP) is a positive deflection in the EEG following reward receipt. Recent evidence suggests that the RewP is modulated by both reward probability as well as subjective rating of liking. Here we examined the sensitivity of the RewP to positive affective and alcohol images in individuals with alcohol use disorder (AUD). We recruited 49 participants (AUD =27, Control= 22). Participants completed both a standard 2-doors task with point feedback (green +1 or red -1) as well as a reinforcement learning task with picture feedback (puppy or alcohol images over a green or red screen). The AUD group had an enhanced RewP to point feedback in the 2-doors task ($F(1,48) = 21.78$, $p<0.001$), as well as a main effect of larger RewP to all valanced picture feedback ($F(1,48) = 29.2$, $p<0.005$), yet there was no difference between puppy or alcohol images ($F(1,48) =3.88$, $p=0.88$). Across all participants, there was a positive correlation between image "liking" ratings and RewP amplitudes ($\rho= 0.321$, $p=0.05$), replicating prior findings of an affective influence on the size of the RewP. These findings indicate that individuals with AUD have a larger RewP at baseline and suggests a domain-general enhancement of reward responsiveness in the AUD group while any modulation of this signal by alcohol-specific cues is in line with general "liking" related trends observed in control samples. Keywords: Reward Positivity, AUD, Affective Imagery

Disclosures: G. Singh: None. **E. Campbell:** None. **J. Hogeveen:** None. **E. Claus:** None. **K. Witkiewitz:** None. **J. Cavanagh:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

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Program #/Poster #: P673.09

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R01DC015426
BBRF 27969

Title: Disentangling the content of sensory prediction errors in the human midbrain

Authors: *J. D. HOWARD[1,2], D. S. EDMONDS[2], T. KAHNT[2];
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Abstract: Prediction errors encoded in the dopaminergic midbrain represent a fundamental mechanism by which reward predictions are updated during learning. Recent studies in rats and humans have demonstrated that, in addition to signaling violations in value expectations, these responses also signal violations in the sensory properties of expected outcomes. Moreover, such sensory prediction errors have been shown to carry information about the specific identity of the reward that is delivered at the time of the outcome. However, whether this ensemble information reflects what was unexpectedly not received (i.e., the omitted reward) or what was unexpectedly received (i.e., the experienced reward) has not been tested. To answer this question, we designed a novel transreinforcer reversal learning task in which hungry human participants (N=30) intermittently experienced violations in three value-matched food odors while undergoing function magnetic resonance imaging (fMRI). Preliminary analysis of the fMRI data revealed that activity in the midbrain was significantly higher on error trials (i.e., when an unexpected odor was delivered) compared to non-error trials ($F_{2,58}$ = 6.92, p = 0.003), replicating previous studies showing that value-matched rewards evoked sensory prediction errors in this region. Critically, by incorporating 3 distinct food odor rewards in this experiment, we are able to create comparisons between conditions in which the expected odor reward is different but the received odor reward is identical, and conversely in which expected odor reward is identical but the received odor reward is different. By conducting pattern-based analysis of the fMRI activity ensembles evoked in these conditions, we aim to test whether information represented in sensory prediction error responses reflects omitted or received reward identity. Such findings would have implications for understanding how error signals originating in the dopaminergic midbrain support model-based learning of associative information.

Disclosures: J.D. Howard: None. **D.S. Edmonds:** None. **T. Kahnt:** None.

Poster

P673. Human Reward and Appetitive Learning and Memory

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: IITP Grant (No. 2020 0 01450, Artificial Intelligence Convergence Research Center [Pusan National University]
BK21 Four, Korean Southeast Center for the 4th Industrial Revolution Leader Education

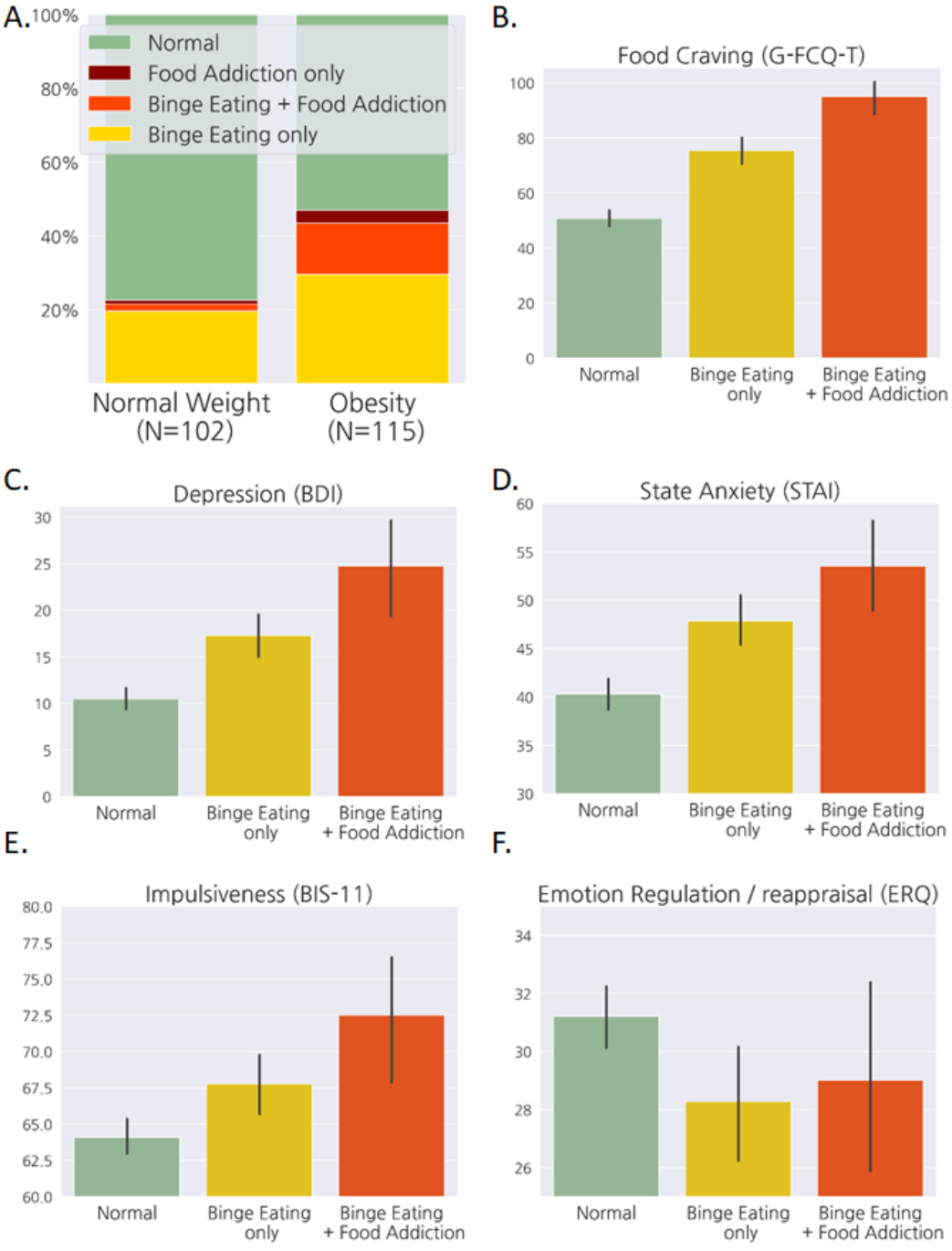
Title: Obesity, binge-eating and food addiction: Mental health and cognitive risk factors

Authors: *J. JEONG, Y. JEON, K. BAEK;
Pusan Natl. Univ., Pusan, Korea, Republic of

Abstract: Obesity is a serious health issue, and compulsive eating problem such as binge-eating and food addiction has been implicated as potential causes. However, the comorbidity of obesity, binge-eating and food addiction is still not much clear, and the psychological and cognitive factors underlying these eating problems. Here we recruited 102 normal-weighted subjects and 115 obese subjects in the outpatient clinic

and local community to investigate the relationship between obesity, binge-eating and food addiction. We used the following clinical questionnaires: Binge Eating Scale (BES), Yale Food Addiction Scale 2.0 (YFAS), Eating Disorder Diagnostic Scale, General Food Craving Questionnaire-Trait (G-FCQ-T), Beck Depression Inventory (BDI), State/Trait Anxiety Inventory (STAI), Barratt Impulsiveness Scale-11 (BIS-11), The Behavioral Inhibition and Behavioral Approach Systems (BIS/BAS), and Emotion Regulation Questionnaire (ERQ). As shown in Fig. 1A, the prevalence of binge-eating was double in the obese population. However, clinical questionnaire scores were not affected by obesity itself ($p > 0.05$ in 3-way ANOVA on obesity, binge-eating and food addiction) except BIS/BAS. Thus, we collapsed these two body weight groups and divided into 3 groups for later analysis: Normal vs. Binge-eating only vs. Binge-eating + Food addiction as shown in Fig.1B~F. Interestingly, both binge-eating and food addiction increased not only food craving but also depression and anxiety measured with BDI, STAI and Impulsiveness (Normal < Binge-eating only < Binge-eating + Food addiction, all $p < 0.001$, Tukey's test). Reappraisal strategy in ERQ was much less observed in the binge-eating group compared to the normal population as shown in Fig.1F. The present study suggests that binge-eating disorder is not only affecting on body weight but also mental health (e.g. depression and anxiety). Food addiction often manifested as a more severe form of compulsive eating problem. In conclusion, cognitive risk factors for binge-eating/food addiction such as impulsiveness should be further investigated.

Fig 1. (A) The prevalence rate of binge-eating and food addiction in the normal weight and the obesity populations. (B) ~ (F) Comparison of questionnaire scores across 3 groups: Normal vs. Binge-eating only vs. Binge Eating + Food addiction (Here both normal weight and obesity populations are collapsed together).



Disclosures: J. Jeong: None. **Y. Jeon:** None. **K. Baek:** None.

Poster

P677. Motivation: Subcortical Neurocircuitry IV

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P677.01

Topic: G.03. Motivation

Support: NIH Grant T32DA07268
NIH Grant MH063649
NIH Grant DA015188

Title: Nucleus accumbens and central amygdala D1-type and D2-type neurons promote reward motivation

Authors: *D. NGUYEN, K. C. BERRIDGE;
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Both the nucleus accumbens (NAc) and the central nucleus of the amygdala (CeA) are striatal-type structures that contain two populations of medium spiny neurons (MSNs): one population expresses primarily D1-type (D1R) dopamine receptors, whereas the other expresses D2-type (D2R) dopamine receptors. Much evidence indicates that D1R and D2R are involved in reward and anti-reward processes, respectively; however, emerging evidence suggests that D2R neurons can also promote reward motivation depending on the situation and behavioral task. The potentially bi-valent properties of D2R neurons raises the question of whether the selectivity of neuron activation is important, given that D2R is also expressed on cholinergic interneurons and elsewhere in addition to MSNs in both NAc and CeA. To explore this question, the present study uses a novel line of transgenic rats that express Cre in neurons containing adenosine 2a receptors (A2aR), which are expressed solely on D2R MSNs in both the NAc and CeA. A2aR-Cre and D1R-Cre rats were tested for positive optogenetic self-stimulation in NAc and CeA in a place-based self-administration task (RTPP) and in active-response instrumental tasks (spout touch, lever press, nose poke). We found that in both regions, D1R neurons produced robust laser self-stimulation in both place-based and active-response tasks. By contrast, A2aR neurons produced self-stimulation only in the place-based and not in the active-response tasks. Furthermore, the degree of self-stimulation varied depending on the length of laser activation (1 sec vs 8 sec bins) as well as on the parameters used for laser activation (10-40 Hz frequencies and 1-10 mW intensities). Our results are consistent with strong D1R involvement in reward motivation. Our results also suggest that A2aR (D2R MSNs) can also contribute to lesser reward motivation, but only in situation-dependent ways, promoting reward when self-stimulation is administered passively but not when an active instrumental response is required to earn laser illuminations.

Disclosures: D. Nguyen: None. **K.C. Berridge:** None.

Poster

P677. Motivation: Subcortical Neurocircuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P677.02

Topic: G.03. Motivation

Support: R01-DK106188
R01-DK115526
R01-DA044204
R21-DA045277
T32-DK101357

Title: Intra-nucleus accumbens insulin reduces food intake and motivation for food

Authors: *J. E. FINNELL[1], C. R. FERRARIO[1,2];
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Abstract: Insulin receptors are expressed throughout the brain, including within mesocorticolimbic circuits. For example, insulin from the periphery is rapidly distributed into the striatum, which has a high proportion of insulin binding (Havrankova et al., 1978). In humans and rodents, insulin alters neural function to decrease food intake, but mechanisms are unknown. Recent studies showed that insulin alters dopamine transmission within the NAc and VTA, and that insulin receptor activation enhances presynaptic glutamate release within the NAc. This region plays critical roles in food-seeking and feeding behaviors. Furthermore, diet-induced obesity reduces NA insulin receptor expression and the ability of insulin to enhance NAc glutamate transmission. However, how insulin within the NAc may influence food-seeking and feeding behavior is unclear. Therefore, here we determined how intra-NAc insulin affects cue-triggered food-seeking, food intake, and motivation to obtain food in adult male rats. Food intake, break point using a progressive ratio schedule, and Pavlovian conditioned approach were measured in healthy weight rats. Direct infusion of insulin into the NAc did not affect conditioned approach compared to vehicle infusion. However, home cage food intake immediately following this test was significantly reduced. Furthermore, intra-NAc insulin reduced break point compared to vehicle, and this effect was partially reversed by insulin receptor blockade. Additional studies examining effects of insulin on conditioned aversion are currently under way and will inform interpretation of key results. Results to date show that insulin within the NAc does not alter the incentive-motivational properties of a food cue, but instead reduces the motivation to consume food. This not only has implications for the regulation of food-seeking and eating, but may also be important in the dysregulation of feeding that accompanies obesity.

Disclosures: J.E. Finnell: None. **C.R. Ferrario:** None.

Poster

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Topic: G.03. Motivation

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NIH DA015188
NIH MH063649
NIH MH125613

Title: Optogenetic identification of hedonic hotspots in orbitofrontal cortex, insula, ventral pallidum, and anterior cingulate cortex that control liking and wanting for sweet reward

Authors: *I. MORALES[1], M. AYOUB[1], J. OLNEY[1], K. C. BERRIDGE[2];
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Abstract: Reward consists of learning, 'liking', and 'wanting' components, but 'liking' remains the least understood. Hedonic function is causally amplified by brain hedonic hotspots in nucleus accumbens, ventral pallidum, orbitofrontal cortex (OFC), and insula when neurochemically stimulated during the taste reactivity test. This test categorizes affective reactions to positive 'liking' and aversive 'disgust' components. Here we present novel data showing that optogenetic manipulations to control neuronal activity in the hedonic hotspots of cortical OFC and insula, as well as in subcortical ventral pallidum doubles the number of hedonic 'liking' reactions elicited by the sweet taste of sucrose. Hedonic enhancement was anatomically restricted to the hedonic hotspots as the same manipulations inside the same brain structures but outside the hedonic hotspots fails to increase 'liking' and even may oppositely suppress hedonic 'liking' despite still generating robust increases in incentive motivation to food. Furthermore, we identify a novel hedonic hotspot in caudal anterior cingulate cortex (pACC) never previously described and find that ChR2 stimulation of neurons within this new pACC hotspot doubles hedonic 'liking' as well as incentive motivation or 'wanting' for sucrose. Subcortically, we also show that VP neurons bidirectionally control hedonic impact, as optogenetic inhibitions of the VP hotspot suppresses hedonic 'liking' reactions to sucrose and replaces them with aversive 'disgust'. VP control of 'wanting' and 'liking' was further explored by selectively targeting VP^{GABA} neurons within the VP hotspot, using transgenic GAD1 Cre rats, finding that GABA neurons particularly promote hedonic 'liking' reactions to sucrose. Overall, our findings suggest that hedonic hotspots in the brain are robust hedonic entities in brain corticolimbic sites, whether stimulated pharmacologically or optogenetically, that form a functional hedonic circuit to enhance 'liking'.

Disclosures: I. Morales: None. **M. Ayoub:** None. **J. Olney:** None. **K.C. Berridge:** None.

Poster

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Topic: G.03. Motivation

Support: NIDA Grant 5R01DA015188-15
NIMH Grant R01MH063649-16A

Title: The role of CRF neurons in cocaine pursuit and addiction

Authors: *K. EMERY[1], L. TITTLE[2], K. C. BERRIDGE[3];
[1]Univ. of Michigan Neurosci. Grad. Program, Ann Arbor, MI; [3]Psychology, [2]Univ. of Michigan, Ann Arbor, MI

Abstract: The role of CRF neurons in cocaine pursuit and addiction Katie Emery, Lucas Tittle, Kent Berridge
Neurons that express corticotropin releasing factor (CRF) are typically regarded by opponent-process and allostasis theories of addiction as an "anti-reward" mechanism of aversive states in drug withdrawal, which causes addictive relapse and drug consumption to alleviate the distress (George et al., 2012). However, our lab has shown that optogenetic stimulation of CRF neurons in either central amygdala (CeA) or nucleus accumbens (NAc) instead activates incentive motivation, with positive motivational valence (e.g., laser self-stimulation), to increase pursuit of laser-paired intravenous cocaine or sucrose rewards (Baumgartner et al. 2021; submitted). Conversely, optogenetic stimulation of CRF neurons in bed nucleus of the stria terminalis (BNST), while plausibly aversive, failed to increase pursuit of cocaine or sucrose. However, it is possible that drug experience with extended cocaine access, to induce greater dependence, might switch the role of CRF neurons to better fit the traditional opponent-process view of distress-induction to drive hedonic self-medication. For example, stress experience has been shown to flip the valence of NAc CRF-induced motivation from positive to negative (Lemos et al. 2012). To test this hypothesis, we gave *crh*-Cre rats experience with two weeks of a long-access schedule of cocaine self-administration (6 hrs per session) to induce DA-receptor downregulation and dependence. We then assess whether optogenetic activation of CRF neurons in CeA or BNST causes an aversive state that promotes cocaine consumption, as posited by allostasis theory. Alternatively, we test whether CRF neurons instead promote cocaine pursuit primarily via incentive motivation even after extended drug self-administration, as it does in relatively drug-naïve rats. In a separate line of studies, we assess whether CRF neurotransmitter itself specifically mediates motivation produced by optogenetic stimulation of CRF neurons, versus whether other co-released neurotransmitters are primarily responsible. To assess this, we intraventricularly deliver a CRF antagonist (D-Phe-CRF) together with optogenetic stimulation of CRF neurons prior to motivational tests.

Disclosures: K. Emery: None. **L. Tittle:** None. **K.C. Berridge:** None.

Poster

P677. Motivation: Subcortical Neurocircuitry IV

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Program #/Poster #: P677.05

Topic: G.03. Motivation

Support: NIH R01 MH065974

Title: Afferent control of cholinergic interneurons in the nucleus accumbens medial shell

Authors: *C. BAIMEL, E. JANG, S. L. SCUDDER, P. G. ANASTASIADES, K. MANOOCHERI, A. G. CARTER;
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Abstract: Despite representing less than 1% of neurons in the nucleus accumbens (NAc), cholinergic interneurons (ChIs) exert dominant modulatory influence over the region and play a central role in guiding motivated behaviour. ChIs provide dense local innervation and are tonically active, but alter their activity patterns in response to salient stimuli and during reward learning. While the regulation of ChIs is well studied in the dorsal striatum, little is known about how they are engaged in the NAc. Multiple excitatory inputs project to the NAc, but how they target and regulate the activity of ChIs is largely unknown. We have identified the circuit and synaptic mechanisms through which long range inputs alter ChI firing in the NAc medial shell. We find that the paraventricular nucleus of the thalamus (PVT) and the ventral hippocampus (vHPC) are the main excitatory inputs to ChIs in the NAc medial shell. While the PVT activates ChIs, the vHPC strongly pauses firing, due to pronounced recruitment of feed-forward inhibition. In contrast to the dorsal striatum, this inhibition reflects strong connections from local parvalbumin interneurons onto ChIs. Our results highlight how different afferent streams operate through the local circuit to engage ChIs in the NAc medial shell, revealing fundamental differences in local connectivity.

Disclosures: C. Baimel: None. **E. Jang:** None. **S.L. Scudder:** None. **P.G. Anastasiades:** None. **K. Manoocheri:** None. **A.G. Carter:** None.

Poster

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MEXT KAKENHI 21K07259

Title: Pathway-selective silencing of ventral striatum neurons projecting to the ventral pallidum elevates motivational states under approach-avoidance conflict in nonhuman primates

Authors: *J. OH[1,2], S. AMEMORI[2], K.-I. INOUE[1], K. KIMURA[1], M. TAKADA[1], K. AMEMORI[2]; [1]Systems Neurosci. Section, Primate Res. Institute, Kyoto Univ., Inuyama, Japan; [2]Inst. for the Advanced Study of Human Biol. (ASHBi), Kyoto Univ., Kyoto, Japan

Abstract: Studies have suggested that both the ventral striatum (vStr) and the ventral pallidum (VP) are involved in regulating approach motivation in reward-seeking behaviors and avoidance motivation in challenging situations where animals are required to escape from aversive events. Because the vStr sends a massive projection to the VP, the vStr-VP pathway could play a causal role in regulating motivation depending on the approach or avoidance behavioral contexts. To address this issue, we trained a macaque

monkey to perform Approach-Avoidance (Ap-Av) conflict and Approach-Approach (Ap-Ap) tasks. Unlike the Ap-Ap task, where the monkey chose between two rewarding options, the Ap-Av conflict task required the monkey to decide whether to accept or reject offers composed of rewarding and aversive outcomes (an air-puff delivered to the face). By comparing the behaviors in these two tasks, we could investigate how an aversive context influences behaviors, including Ap-Av decision-making. During the performance of the tasks, we manipulated the vStr activity by using the DREADDs technique. We injected a viral vector carrying the gene of inhibitory hM4Di receptor (AAV2.1-CaMKII-hM4Di) bilaterally into the vStr. Then we locally infused DCZ (deschloro-clozapine), a novel ligand for DREADDs, into the VP to suppress synaptic input from the vStr. The selective suppression of activity of the vSTr-VP pathway exhibited notable effects in the Ap-Av conflict task. First, we observed a significant elevation of the monkey's motivation to perform the Ap-Av conflict task. The suppressed activity significantly reduced the frequency of omission errors (Kolmogorov-Smirnov test, $P<0.001$) and the reaction time of the target selection (two sampled t-test, $P<0.001$), as compared to the control sessions. Second, we found a significant elevation in arousal level, characterized by an evoked pupil dilation (t-test, $P<0.001$). Moreover, such manipulation induced a significant change in the Ap-Av decision-making, characterized by the increases in Ap choice for the rewarding offers (t-test, $P<0.05$) and in Av choice for the aversive offers (t-test, $P<0.01$). The change in the choice pattern could be interpreted as reduced fluctuations in the Ap-Av decision-making. Importantly, the silencing of the vSTr-VP pathway did not cause the increase in either the motivational state or the arousal level in the Ap-Ap task. The induced behavioral change is in favor of the hypothesis that the vStr-VP pathway regulates motivation, specifically in challenging situations with approach-avoidance conflict.

Disclosures: J. Oh: None. **S. Amemori:** None. **K. Inoue:** None. **K. Kimura:** None. **M. Takada:** None. **K. Amemori:** None.

Poster

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Topic: G.03. Motivation

Support: R00 DA042895
T32 DA007234

Title: Progressive recruitment of dorsolateral striatum dopamine signaling underlies cue-evoked movement invigoration

Authors: *L. ENGEL[1], A. WOLFF[1], S. SINHA[2], M. BLAKE[1], V. COLLINS[1], B. SAUNDERS[1]; [1]Univ. of Minnesota, Minneapolis, MN; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Environmental cues, through Pavlovian learning, become conditioned stimuli that guide animals toward the acquisition of rewards (for example, food) by invigorating and directing seeking behavior. We have previously shown that brief optogenetic excitation of dopamine neurons, in temporal association with visual sensory cues, can instantiate those cues as conditioned stimuli that evoke

conditioned movements. It remains unclear 1) how dopamine-neuron mediated, cue-evoked behavior is signaled by dopamine release downstream in striatal subregions and 2) how subregional signals evolve across stages of learning. Here, we made use of a genetically encoded dopamine biosensor (dLight) to monitor dopamine signaling simultaneously in multiple striatal regions with fiber photometry, while tracking detailed movement features, during optogenetic Pavlovian cue conditioning of VTA or SNc dopamine neurons. Our results demonstrate a serial, progressive pattern of cue-evoked dopamine signaling across ventral to dorsal striatal subregions that correlates with different features of cue-evoked behavior. Cues paired with optogenetic activation of VTA dopamine neurons evoked dopamine release in the nucleus accumbens core relatively early in training, when behavioral responses were slower and directed toward the cue. This pattern evolved as conditioning progressed. Late in training, cue-evoked signals emerged in the dorsolateral striatum, as movement patterns became more vigorous and not directed at the cue. Cues paired with optogenetic activation of SNc dopamine neurons did not reliably evoke dopamine release in the dorsolateral striatum, even though those cues spurred vigorous movements. Further, optogenetic inhibition of DLS dopamine terminals during the first 2 seconds of cue presentations late, but not early, in training decreased the probability of cue-evoked locomotion and increased the latency of movement initiation in VTA conditioned animals. Together our studies show dissociable, parallel functions for ventral and dorsal striatal dopamine signaling in guiding versus invigorating behaviors. Further, they suggest that large-scale plasticity across ventral-to-dorsal striatal dopamine networks emerges during Pavlovian learning to coordinate behavioral diversity.

Disclosures: L. Engel: None. **A. Wolff:** None. **S. Sinha:** None. **V. Collins:** None. **B. Saunders:** None.

Poster

P684. Animal Models of Social Behavior and Cognition

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Topic: H.06. Social Cognition

Support: Canadian Foundation for Innovation
Natural Sciences and Engineering Research Council of Canada
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Title: Neural basis of empathy for pain in mice

Authors: *S. J. POULSON[1,2], I. ARAIN[1], A. MANDATORI[1], A. NAIR[4], L. J. MARTIN[1,2,3];
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Abstract: Social animals, including humans and rodents, can detect signals from group members that indicate changes in the environment, such as threats or potential for injury. Signals from group members indicating potential for pain or injury likely range across modalities of perception, e.g. visual cues like paw licking, vocalizations, and olfactory cues. Interestingly, social context plays a large role in enhancing pain behavior. Research in mice has shown that familiar mice express more pain when together than when alone, and bystander mice develop sensitivity to painful stimuli after interacting with cagemates in pain.

Yet the neural mechanisms that drive the enhancement of pain due to social stimuli are unknown. Our aim was to develop a short paradigm where mice express overt cues of pain, then use modern tools to explore neural mechanisms underlying enhanced pain in the uninjured partner. We paired same-sex cagemate adult mice (C57Bl/6, 8-10 weeks, male or female) in a 14.6 cm x 14.6 cm cubicle and deemed one mouse the observer and the other mouse the demonstrator. After a 1-h habituation, pain (2.5% formalin, 20 µL, intraplantar to the left hind paw) or control (0.9% saline pH 7.2, 20 µL) was applied to the demonstrator mouse and returned to the cubicle with the uninjected observer mouse. We video-recorded 30-min of interaction between the observer and demonstrator and scored social interactions, location and movement in the cubicle, and anxiety behaviors. The demonstrator mouse was then removed from the cubicle. Next, enhanced behavioral responses in the observer mouse were measured following evoked stimuli on the hind paw including a chemical pain stimulus that does not normally evoke significant pain behaviors (0.5% formalin, 20 µL, intraplantar, 1-h) or increasing mechanical pressure (Ugo Basile, Dynamic Plantar Aesthesiometer). We found that mice that observed cagemates in pain expressed more pain behavior in the post-test than mice that observed saline controls. After the 1-h formalin post-test, we collected brain tissue of the observer mice and used immunohistochemistry to detect cells with increased expression of c-fos protein, a marker for neuronal cell activation, and compared number of activated neurons in brain regions of interest. We show exploratory behavioral pharmacology and whole tissue immunohistochemistry data between groups. Our findings promote continued investigation of the neurobiology underlying contextual pain modulation, including how others influence our pain experiences, building a greater understanding of the social-communicative elements of the biopsychosocial model of pain.

Disclosures: S.J. Poulson: None. **I. Arain:** None. **A. Mandatori:** None. **L.J. Martin:** None.

Poster

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Topic: H.06. Social Cognition

Support: NRF of Korea 2017R1A2B3012659
KIST Intramural grant 2E30962

Title: Distinct oscillatory patterns of the basolateral amygdala-medial prefrontal cortex circuitry of winning and losing during the tube test

Authors: *Y. LEE[1], J. CHOI[2];
[1]Dept. of Animal Sci. & Biotech., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Brain Sci. Inst., KIST, Seoul, Korea, Republic of

Abstract: During conflict situations, neural activities of relatively dominant and submissive subjects are noticeably distinguishable. Since not only just information the two subjects accept but also how that information is processed differ, this will be outwardly expressed into various behaviors. In addition, how confidently the outcome is determined also affects neural activity of both subjects. The medial prefrontal

cortex (mPFC) plays an important role in determination of dominance. The mPFC is known to regulate social behaviors and decision-making, with numerous projections to subcortical regions. Among those regions, the basolateral amygdala (BLA) is stimulated by the mPFC during social cognition and emotion processing. Number of studies have shown different brain activity depending on the dominance of each individual, but dominance dependent neural activities have rarely identified, especially with real-time data. In this study, we would like to present neural dynamics in the mPFC-BLA circuit during the tube test, one of the robust behavioral experiments of measuring dominance states in laboratory rodents. The trial starts as two mice are located at the middle of the tube and ends when one mouse pushes out the opponent to the outside of the tube. With the position data extracted from video during the test, speed of each mouse is calculated. As we inspect the data with regard to the speed of the mice, the power of the 24~32 Hz beta oscillations in the mPFC and the BLA increased as the winner pushes the loser mouse more confidently, with faster proceeding speed. Moreover, fear- and stress-related BLA gamma oscillations (low gamma, 40~60 Hz, high gamma, 70~100 Hz) appeared stronger as the mouse is pushed back roughly. As the BLA is known to receive top-down modulation from the mPFC, mPFC-BLA connectivity will show difference depending on different situations and relative dominance of the mouse. Thus in this study, we would like to present dynamical directionality in the mPFC-BLA circuit during the tube test and build up a classifier that can predict the behavior of the mouse with the neural activity.

Disclosures: Y. Lee: None. **J. Choi:** None.

Poster

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Topic: H.06. Social Cognition

Support: NSERC

Title: The effect of estrogens in the paraventricular nucleus on rapid social recognition in male mice

Authors: *P. PALETTA, S. MCGUINNESS, E. CHOLERIS;
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Abstract: Both estrogens and oxytocin have previously been shown to be necessary in order for social recognition (SR) to occur, as knocking out the genes for the estrogen receptors, oxytocin (OT), or the OT receptor (OTR) resulted in impaired SR. Similarly, administrations of 17β-estradiol (E2), estrogen receptor agonists, or oxytocin facilitated SR. Since both estrogens and OT are needed it had been hypothesized that they may interact in some way to facilitate SR. A proposed model of this interaction suggested that estrogens binding to their receptors in the paraventricular nucleus of the hypothalamus (PVN), where the majority of OT is produced, would facilitate the production and release of OT. The OT would then bind to the OTR in the medial amygdala (MeA), a region important for OT mediated SR, so that olfactory information about encountered individuals can be used to recognize a familiar individual, since the MeA also receives direct projections from the olfactory bulbs. We have previously tested this model in female mice, to determine if it is accurate and if it occurs through estrogens' rapid mechanisms.

We first infused E2 into the PVN of ovariectomized mice and found that it rapidly facilitated SR. We next infused a subeffective dose of an OTR antagonist (OTRA), a dose that by itself cannot block SR, into the MeA and the most effective dose of E2 into the PVN, and found that the OTRA was able to block the rapid facilitating effect of E2 on SR. These results showed support for the interaction between estrogens and OT on SR, as well as this effect occurring through estrogens' rapid mechanisms. However, this has only been tested in females so far and the current experiment aims to replicate these tests in males. Castrated male mice receive E2 infused into the PVN and are tested in a SR paradigm. In this paradigm, two same-sex stimulus mice are presented to the experimental mouse for 2 five-minute sample phases. This is followed by a five-minute test phase, where 2 stimulus mice are presented again, however one is replaced with a novel mouse. Since, mice prefer novelty, if the novel stimulus mouse is investigated more, it suggests they recognize the familiar mouse. The paradigm takes place within 40 minutes to test the rapid mechanisms of estrogens and was designed to be "difficult" so that the vehicle group will not show SR, and therefore any facilitating effects of the treatment can be observed. If it is found that SR is facilitated, it would suggest that estrogens in the PVN of both males and females can rapidly facilitate SR. If, however, we find that E2 in the PVN does not facilitate SR, it will show a sex difference in how SR is mediated.

Disclosures: P. Paletta: None. **S. McGuinness:** None. **E. Choleris:** None.

Poster

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Topic: H.06. Social Cognition

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KBRI Grant 21-BR-03-04
National Research Foundation of Korea Grant NRF-2021R1F1A1064658

Title: Increase of the excitability of neurons projecting to medial prefrontal cortex in basolateral amygdala in social fear-conditioned mice

Authors: J. YEO[1], *S. LEE[2];
[1]Dept. of Brain and Cognitive Sci., Daegu Gyeongbuk Inst. of Sci. and Technol. (DGIST), Daegu, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: The basolateral amygdala (BLA) to the medial prefrontal cortex (mPFC) pathway plays a role in fear and social behaviors. However, the changes in this pathway upon social fear formation are not exclusively examined. We adopted a social fear conditioning paradigm and evoked a high level of social fear in mice without changing general anxiety and learning ability. We used a retrograde tracer to identify neurons projecting to the mPFC in BLA. The frequency of action potential evoked by intracellular current injection increased upon social fear conditioning. In addition, the resting membrane potentials and rheobase currents are changed in social fear-conditioned mice. These results indicate the increase in

excitability of neurons projecting to the mPFC in BLA upon social fear conditioning and suggest a reciprocal modulation of activity between the BLA and mPFC in social fear behavior.

Disclosures: J. Yeo: A. Employment/Salary (full or part-time):; Korea Brain Research Institute (KBRI). **S. Lee:** None.

Poster

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Topic: H.06. Social Cognition

Support: NSERC Grant

Title: Androgens and estrogens in the Bed Nucleus of the Stria Terminalis of male mice rapidly modulate social recognition and aggression, possibly interacting with vasopressin

Authors: *D. ASPESI, Z. R. BRILL, G. GUILLAUME, E. CHOLERIS;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Social recognition (SR) allows to identify previously investigated conspecifics and to emit appropriate pro-social or -aggressive behaviours. Androgens are involved in both SR and aggression, with effects possibly mediated by estrogenic action, including those regulated by rapid mechanisms. Testosterone (T) can rapidly interact with other neuroendocrine systems such as vasopressin (AVP) to modulate SR and aggression. The AVP system includes highly sexually differentiated brain regions, such as the bed nucleus of the stria terminalis (BNST) and the lateral septum (LS), which show more AVP neurons and fibers in males than in females. The androgens/AVP interplay impacts social and aggressive behaviours, even if the mechanisms involved are currently poorly understood. To elucidate the rapid, non-genomic, effects of androgens and estrogens on SR and AVP in the BNST, adult castrated (CX) male mice were intracerebrally infused with one of 4 doses of T (0.25, 0.5, 0.75, 1µg of T in 0.5µl of DMSO/side), one of 3 doses of 17β-estradiol (E2; 25, 50, 100nM of E2 in 0.5µl of aCSF/alcohol) or one of 4 doses of dihydrotestosterone (DHT; 0.0625, 0.125, 0.25, 0.5µg of T in 0.5µl of DMSO/side). Mice were then exposed to a 'difficult' SR paradigm, in which CX mice showed an impairment, consisting of two 5-min sample phases with 2 familiar conspecifics, and one test phase with the choice between a familiar or a novel mouse. To evaluate the specificity of the effects on SR, other groups of CX mice were tested in a 'difficult' object recognition (OR) paradigm, in which gonadally intact animals showed an impairment, consisting of one 5-min sample phase with 2 different objects, and one test phase with a new and a familiar object. To assess aggression, mice were tested in a resident-intruder (RI) paradigm at either 35- or 120-min post-infusion to evaluate rapid and long-lasting effects. Results revealed that infusing T, E2, or DHT in the BNST facilitated SR, with CX mice spending more time investigating a novel over a familiar CX mouse, with an inverted U-shaped dose-response. An opposite effect was found in the OR test, in which T, E2, or DHT impaired OR with a U-shaped dose-response. In addition, none of the steroids elicited overt aggression towards the intruders, but they all increased the dominance score in CX mice at 35-min and 120-min. Immunohistochemical analysis revealed a transient increase of AVP fiber

density in the LS 35-, but not 120-min, after the infusion of T, suggesting a rapid interaction of T with AVP, probably affecting its trafficking. Elucidating the AVP-sex hormones interplay may lead to new therapeutic approaches for psychopathologies of social behavior with marked sex differences.

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Poster

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Program #/Poster #: P684.06

Topic: H.06. Social Cognition

Support: NIH R01 MH118237
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Title: Dopamine 1 receptor activity modulates social behavior and cortical influence on amygdala activity in an age-dependent manner.

Authors: N. C. FERRARA[1], W. MCMICHAEL[2], M. PADIVAL[1], J. A. ROSENKRANZ[1];
[1]Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]The Col. of Wooster, Wooster, OH

Abstract: Adolescence is characterized by transitions in social engagement and ongoing cortical maturation, which likely contribute to the age-dependent changes in the regulation of emotions. Engagement in social behavior and brain maturation influence each other and are critical for appropriate social responding later in life. The basolateral amygdala (BLA) is critical for social behavior and receives extensive inputs from the prefrontal cortex (PFC). During adolescence, PFC inputs to BLA increase in strength and more readily activate intra-BLA inhibitory circuits. Understanding the way in which PFC-BLA circuits are regulated to alter social behavior, particularly in an immature circuit, is essential for a clear understanding of neuropsychiatric disorders characterized by abnormal social behavior. One way in which PFC-BLA circuits are regulated is through dopamine 1 receptors (D1R), but much less is known about D1R regulation of social behavior and what this does in the still maturing PFC-BLA circuit. Here, we investigated the relationship between D1R modulation of PFC driven changes in BLA activity and social behavior in adults and adolescents. We found that D1R activation resulted in elevated zif268 expression, used as a proxy for cellular activity, as well as increased glutamate sensitivity in the BLA. D1R agonism reduced PFC-driven inhibition of BLA activity in adults but facilitated this process in adolescents, suggesting that while D1R agonism can increase BLA neuronal activity, it has a distinct impact on the maturing PFC-BLA circuit. Further, we found that D1R agonism had opposing effects on social interaction, where age-specific social behaviors were increased in adolescents but were modestly reduced in adults, but D1R agonism uniformly increased BLA activity in both adults and adolescents during social engagement. These results begin to provide insight to the changes in D1R modulation of cortico-amygdala circuitry from adolescence to adulthood that contribute to the refinement of social behaviors.

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Poster

P684. Animal Models of Social Behavior and Cognition

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P684.07

Topic: H.06. Social Cognition

Support: SOURCE grant
NSF grant IOS1754869

Title: Social effect of learning that food is inedible in Aplysia californica

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Abstract: In previous studies, it has been shown that Aplysia can learn that food is inedible after repeated exposure to netted food. Aplysia retain this knowledge for 24 hours. Aplysia are social animals, and the presence of other animals affects their ability to learn (Schwarz, M., Blumberg, S., & Susswein, A. J., Behavioral Neuroscience, 1998). We have now shown a more advanced form of social signaling in which one animal's training affects another animal.We studied this question in 7 pairs of animals. The training procedure was performed with inedible food—dulse wrapped in plankton netting. This allowed animals to taste the seaweed without allowing ingestion. Animals were trained and tested in pairs, with one individual receiving training earlier than the other. To acclimate animals to the scent of food, 0.2 grams of inaccessible food was added to the water one hour prior to the first training session. During training, animals could not make physical contact due to a perforated barrier between them. Netted food was given to the first animal to induce it to feed, and the animal attempted to swallow the food until it ceased responding to the inedible food. The training time—the time between food first entering the mouth and the animal giving up on food—was recorded. One hour later, the training time for the second animal was then recorded in the same manner. We found that when two Aplysia were trained on netted food sequentially, the second animal consistently stopped responding to inedible food more quickly than the first animal. Of the 7 pairs of animals, 6 showed this reduction in response to inedible food. Furthermore, this study tested the animals for memory retention 24 hours after training, with the order of testing blinded. In animals that had been trained first, 5 out of 7 showed a reduced time to stop responding to inedible food, suggesting that they had retained memory of the training. Of the remaining two animals, one was not tested and the other did not show a reduction in testing time. In animals trained second, we found that 3 out of 7 showed a reduced time to stop responding after 24 hours. In this group, 2 animals did not show a reduction in testing time, whereas the remaining animal was not tested. These results suggest that memory retention is not affected in animals that were trained first, but may be reduced in the animals that were trained second. It is possible that this may be due to the reduced time they spent responding to inedible food on the first day. We will test the hypothesis that the interaction between the animals is due to pheromone release by the first animal as it learns that food is inedible.

Disclosures: Y. Zhang: None. **R. Wilcox:** None. **J.P. Gill:** None. **A.J. Susswein:** None. **H.J. Chiel:** None.

Poster

P684. Animal Models of Social Behavior and Cognition

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Topic: H.05. Working Memory

Support: University of Miami, Academic Enhancement Research Fellowship
Grant # PAR3152016-003 Pioneer Academics, LLC

Title: A machine-learning approach to choreographic analysis of pose and motifs in rhythmic movements of Snowball, the dancing cockatoo

Authors: T. HU[1], B. SANGHERA[1,2], *J. S. KANWAL[1];
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Abstract: Rhythms constitute a fundamental organizing feature of processes and activities in the natural world. Humans have a special ability to entrain rhythmic movements in the form of dancing to the beat and other acoustic patterns in music. Only a few nonhuman species have the capability of entraining their bodily movements and dancing to human-created music. Here, using a deep-learning neural network, DeepLabCut (DLC), we tracked movements of multiple body parts in a cockatoo, Snowball, that was previously shown to dance to the sound of music (Keehn et al., 2019). To test for a modular organization of movement patterns in response to music, we conducted pose analysis using normal-mixtures clustering and the recently developed Variational Animal Motion Embedding (VAME) software for multivariate time-series analysis. DLC tracked well (> 90% probability) 11 of the 14 hand-scored dance movements using markers placed on 8 key body parts (neck, foot, head, wingtip, etc.). Our machine-learning approach to dance movements yielded a discretization of continuous body movements into behavioral syllables or “dynamic poses” and the presence of several elementary modules or "motifs" hidden within the previously classified dance movements. The clustering algorithm yielded a best fit for 14 dynamic poses, some of which wholly or partially overlapped with the hand-scored dance movements, such as Down-Shake, Downward, Foot-Lift, etc. Other poses were distributed among 2 to 4 of the hand-scored dance movements. VAME analysis, specified for 11 motif clusters matching the qualitatively described 11 dance movements, revealed a mismatch between hand-scored and machine-learning assessment of movement modules. On average, each previously described dance pattern contained 3.72 motifs. “Foot-Lift” and “Head-Foot Sync” shared 3 of the 5 VAME-specified motifs present within each dance pattern. “Down-Shake” and “Downward”, however, had no overlap in motifs despite both dance movements appearing similar. A somewhat similar result was obtained for a second VAME-specified clustering of 22 motifs. For this, on average, each hand-scored dance movements contained 5.36 motifs. Both, the “Head-Foot Sync” and the “Foot-Lift Down-Swing”, dances involved the rhythmic movement of the head and foot. These two dance movements shared 4/5 VAME-specified motifs, suggesting that directionality of motion of a body part was over-ruled by synchronous patterns of movement of multiple body parts by a VAME-specified classifier. We speculate that movements entrained by a predictive music rhythm allow automated dopamine-mediated selection of action patterns that are intrinsically rewarding.

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Poster

P692. Human Emotion III

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Program #/Poster #: P692.01

Topic: G.04. Emotion

Support: UCSD Office of Research Affairs Center Launch Program

Title: Affect modeling of stereoencephalographic signals during naturalistic acoustic stimuli

Authors: *A. PATEL[1,2], G. CHAU[1], J. HUANG[1], S. BEN-HAIM[3], J. SHIH[4], T.-P. JUNG[2], V. GILJA[1]; [1]Electrical and Computer Engin., [2]Inst. for Neural Computation, [3]Neurolog. Surgery, [4]Neurosciences, UCSD, La Jolla, CA

Abstract: Human affect is a complex signal composed of changes in behavioral response, physiological response, and perceived experience. The mapping of these behavioral and physiological responses to reported experiences can vary greatly across individuals and be influenced by a multitude of factors at both short and long timescales. Existing decoders utilizing non-invasive electroencephalography (EEG) and heart-rate variability have demonstrated an ability to classify affect across a range of auditory and visual stimuli. These recordings capture heavily processed features and provide a glimpse at the underlying subcortical networks. Looking to better understand the underlying mechanisms driving affect, recent invasive stereoEEG studies have demonstrated discriminability among affect measures across long, unstructured recordings (Kirkby et. al., Cell 2018). Exploring the temporal sensitivity of affect modeling techniques in relevant subcortical structures, we apply similar techniques to selected sounds maximizing evoked responses in two primary axes of affect – valence and arousal – from the International Affective Digitized Sound (IADS) database (Bradley & Lang, 2007). The study was administered to four male subjects being treated for intractable epilepsy and implanted with stereoEEG probes in limbic regions including the amygdala, hippocampus, insula, and cingulate. The task involved presenting a series of 6 second auditory stimuli and subsequent survey (self-assessment manikin or simple engagement-oriented) pairs. As an initial strategy, physiological power bands of the neural data including alpha (8-13 Hz) and beta (13-30 Hz) corresponding to active stimuli presentation periods are decomposed into independent components. These features are used to construct statistical models and are evaluated against results from existing IADS-EEG studies (Bos, 2006) with comparable decoder performance (> 60%) in a subset of subjects. Examining neural responses across subjects, we attempt to identify coherence networks as outlined in Kirkby et. al. and apply dynamical systems modeling approaches to better understand the mapping from neural activity in limbic networks to perceived affect. Such a direct measurement and understanding of the neural circuits that give rise to affect could enable objective evaluation of affect and mood through machine learning based inference.

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currently consults for Paradromics, Inc. They had no role in study design, data collection and analysis, decision to publish, or preparation of the abstract..

Poster

P692. Human Emotion III

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Program #/Poster #: P692.02

Topic: G.04. Emotion

Support: NIDA U01DA043098
Office of Naval Research (ONR) 00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
The Pritzker Neuropsychiatric Research Consortium

Title: Anatomical Mapping and Gene Expression Patterns of the Human Thalamus Midline Nuclei.

Authors: *A. MEDINA[1], R. CALZAVARA[1], W. E. BUNNEY[2], B. BUNNEY[3], R. M. MYERS[4], A. SCHATZBERG[5], J. D. BARCHAS[6], F. LEE[7], H. AKIL[1], S. J. WATSON, Jr[1];
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Abstract: The thalamus is generally considered as a relay center, a hub of sorts where information is collected and processed, then transmitted to specific areas of the cerebral cortex. In fact, the thalamic areas dedicated to sifting motor and sensory information constitute the majority of the structure's mass. However, small, specific subnuclei within the thalami appear to be involved in operations pertinent to the limbic system and connect to subcortical limbic structures. The most recognizable of them is the Paraventricular Nucleus (PVT). In humans, the PVT is a thin cellular cluster located along the edge of the third ventricle. Embryologically, this nucleus develops as part of the epithalamus, along with the pineal gland and the habenular nuclei. Therefore, it can be expected that its connectivity and function differ from the majority of thalamic structures. And yet, the human PVT is hardly distinguishable histologically from the neighboring nuclei. In this study, we aim to gain some insight into the functionality of the human PVT and the similarities or differences it may have with surrounding structures by comparing their gene expression patterns. Materials and Methods: Human brain blocks containing the thalamus were obtained from the Brain Donor Program at the University of California, Irvine by agreement with the Pritzker Neuropsychiatric Consortium. Five subjects with no history of psychiatric or neurological disease were used for this study. Variables that could alter gene expression patterns were controlled for, so all samples used had a tissue pH above 6.5 and agonal factor scores (AFS) of zero. The fresh-frozen blocks were sectioned at 10um and serial sections were processed for acetylcholinesterase stain, Kluver/Luxol Fast Blue stain, and different *in situ* hybridization probes including calcium-binding proteins, transcription factors, and neurotransmitter-related enzymes. Results: the combined use of histological stains and *in situ* hybridization allowed us to discern the distribution of midline thalamic nuclei while also providing insights into the possible functional relationships between them, i.e. areas that appear histologically

indistinguishable from one another show divergent gene expression patterns that hint at discreet functional differences.

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Poster

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Topic: G.04. Emotion

Support: NIH Intramural Program - 1ZICMH002889
NIH Intramural Program - 1ZIAMH002889

Title: Determining frequency bands to observe amygdala for a neurofeedback task using MEG beamformers

Authors: *A. WANG, F. W. CARVER, J. STOUT, T. HOLROYD, A. NAMYST, J. Y. CHUNG, A. C. NUGENT;
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Abstract: Neurofeedback is a process in which auditory and/or visual feedback is used to guide a participant to gradually alter the amount of activity produced in part of the brain. While highly researched in EEG and fMRI, there are relatively fewer studies employing neurofeedback in MEG (magnetoencephalography). In addition, most MEG neurofeedback studies involve data directly from channels, rather than utilizing source localization. Subcortical regions such as the amygdala are also considered more difficult to observe with MEG. Prior to executing a neurofeedback experiment designed to alter activity levels in the amygdala, we must determine what frequency bands to target. We used a CTF MEG System with 275 channels and collected data from twenty-two healthy controls. Subjects completed a Hariri Hammer task, an emotion matching task that produces strong amygdalar activation, and were instructed to match either emotional faces or shapes (control) in a blocked trial format. MEG adaptive beamforming was used to analyze the one second interval after presentation of the target faces and shapes in theta (4-7 Hz), alpha (7-13 Hz), beta (13-35 Hz), low gamma (35-65 Hz), and high gamma (65-115 Hz) frequency bands. Furthermore, a time frequency analysis was conducted to narrow down specific time windows within the one second interval where amygdala activity is most prominent. One sample statistic t-tests of the contrast between faces and shapes revealed that within the alpha frequency band from 0.2 to 1 seconds, there was significantly more activity present in response to faces vs. shapes in the left amygdala with a cluster peak effect size of 1.133 ($q < 0.005$, $p < 0.001$). In addition, within the beta frequency band from 0.2 to 1 seconds, the right amygdala showed significantly more activity to faces vs. shapes with a cluster peak effect size of 0.799 ($q < 0.005$, $p < 0.005$). However, in the theta, low gamma, and high gamma frequency bands, no significant differences between faces vs. shapes was found in the amygdala. Our findings provide evidence that both the alpha and beta frequency bands can be

considered candidates to target the amygdala in the future neurofeedback task and other experiments. Additionally, theta, low gamma, and high gamma frequency bands would not be optimal to use in the neurofeedback task. These exploratory results will be confirmed with future research that will be able to verify whether amygdalar activity can be observed within the alpha and beta frequency bands in the context of real-time neurofeedback. Nonetheless, successful observation of the amygdala using MEG adaptive beamforming suggests that real-time neurofeedback MEG studies are feasible.

Disclosures: A. Wang: None. **F.W. Carver:** None. **J. Stout:** None. **T. Holroyd:** None. **A. Namyst:** None. **J.Y. Chung:** None. **A.C. Nugent:** None.

Poster

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Program #/Poster #: P692.04

Topic: G.04. Emotion

Support: R01 MH116026

Title: Overlapping and distinct neural mechanisms for emotion generation and reappraisal

Authors: *K. BO[1], T. KRAYNAK[2], M. SUN[1], P. J. GIANAROS[2], T. D. WAGER[1];
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Abstract: Reappraisal is an emotion regulation strategy that involves reinterpreting the meaning of a stimulus such that the resultant emotion is changed, and early studies suggested that reappraisal is represented in the prefrontal cortex (PFC). Emotion generation is thought by some theorists to be mediated by non-meaning related subcortical limbic areas. Recent electrophysiological data, however, suggests that reappraisal begins in the meaning construction period of emotion generation, suggesting the possibility of share (co-localized) neural representations. In this study, participants (n=182) viewed or reappraised aversive pictures from the International Affective Picture System (IAPS) while undergoing fMRI. On 'reappraise negative' trials, participants generated thoughts to reduce the negative feelings evoked by aversive images. On 'look negative' and 'look neutral' trials, participants viewed matched aversive or neutral images without reappraising. We computed Bayes Factors to evaluate relative evidence that brain regions encode or do not encode several psychological hypotheses -- (1) emotion generation and reappraisal share overlapping neural mechanisms, (2) reappraisal involves specific neural mechanisms that do not involve emotion generation, and (3) there might exist emotion generation regions that are not affected by reappraisal. Emotion generation was modeled by the contrast between 'look negative' vs. 'look neutral', while reappraisal was modeled by the contrast between 'reappraisal negative vs. look negative'. We found that emotion reappraisal and generation shared overlapping features across multiple regions, including anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), supplementary motor area and inferior parietal lobe, featuring high Bayes factors for both contrasts. We also found distributed brain regions activated specific to reappraisal, including the temporal pole, ACC, and DLPFC. Finally, we found generation-specific regions including amygdala, primary visual cortex,

orbital frontal cortex, putamen, as well as the posterior portion of the DLPFC, and putamen. The present findings suggest that there are both shared and dissociable neural representations of emotion generation and reappraisal processes. The unique neural activity involved in reappraisal play roles in goal maintenance and cognitive control.

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Poster

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Topic: G.04. Emotion

Support: Isaac Newton Trust / Wellcome Trust ISSF / University of Cambridge Joint Research Grants Scheme

Title: Using ERP measures of attention during encoding to constrain tests of the emotional Context Maintenance and Retrieval model of free recall.

Authors: R. HELLERSTEDT[1], V. K. ZARUBIN[2], K. R. MICKLEY STEINMETZ[3], N. D. DAW[4], ***D. TALMI**[1];
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Abstract: Supported by vast behavioural and neural data, retrieved-context theory is the state-of-the-art in describing the rules which govern the chances that a present experience will come to mind later (Howard & Kahana, 2002). It determines the likelihood of recalling an experience through the similarity between its encoding and retrieval "contexts" - abstract constructs implemented in brain states. In addition to similarity between temporally-contiguous brain states, retrieved-context theory recognises that semantic and experiential similarity also influence which experience would come to mind. Our variant of retrieved-context theory, eCMR (emotional Context-Maintenance and Retrieval), focuses on the emotional sub-dimension of experiential similarity as a way of explaining emotional memory enhancement in terms of more general memory processes.
eCMR simulates increased attention towards emotional items during encoding with the parameter Φ_{emot}. In simulations, increased values of Φ_{emot} predict increases in emotionally-enhanced recall. The Late Positive Potential (LPP) is a widely used electrophysiological index of increased attention towards emotional stimuli. Increased LPP amplitudes provide sensitive, specific measure of the impact of emotion at the individual subject level (Schupp & Kirmse, 2021). Thus, if Φ_{emot} controls differential LPP amplitudes, then variations in emotion-enhanced LPP amplitudes during encoding will correlate with subsequent emotion-enhanced recall. LPP amplitude differences may then be used to constrain empirical tests of eCMR - a joint neurocognitive modelling approach.
To test this hypothesis, we reanalysed data from the mixed list condition in Zarubin et al., 2020. We replicated their observation of subsequent memory effects in LPP which were greater for negative than

neutral pictures. However, analysis of Bayesian Pearson correlations between LPP and memory enhancements (emotion vs. neutral) across participants provided moderate evidence favouring the null hypothesis. Similarly, although LPP amplitudes were consistent across experimental blocks, Bayesian one-sample *t*-tests showed that the average within-subject Spearman correlations between LPP and memory enhancements (emotion vs. neutral) across experiment blocks again moderately favoured the null hypothesis.
Taken together, our findings suggest the relationship between emotion-dependent increases in LPP amplitudes and free recall are not consistent at any level of analysis. This result suggests that the LPP component may not be useful for the purpose of model constraint.

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Poster

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Support: BBRF Independent Investigator Grant 22249
NIH/NIDCD R01 DC006287
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Title: Distinct inter-subject synchronized responses to movie clip in emotion and language brain networks

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Abstract: Background: Watching a movie dialogue closely mimics the receptive aspects of participating in a real-life conversation, and was shown to engage the distributed multimodal neural networks that support spoken language communication. We previously demonstrated the feasibility of using movie-fMRI for mapping the language network on an individual basis. Here, we tested whether a movie clip with an emotionally evocative narrative and social interactions would elicit highly synchronized responses across individuals, and could be used to reliably map emotion and language brain networks.
Methods: A 7-min clip from the movie "The Parent Trap" was shown to 22 right-handed healthy subjects (11 women, mean age 26.3 yrs, range 19-39 yrs, all English speakers) during an fMRI scanning session. The clip consisted of a sequence of scenes with spoken emotional dialogue and an evolving narrative interleaved with scenes of background music and no dialogue. Voxel-wise inter-subject correlation (ISC) was applied to reveal brain regions with similar responses across subjects. Independent component analysis (ICA) was applied to identify emotion and language components from the movie-fMRI, based on spatial correlation with functionally-defined canonical templates of the networks derived from Neurosynth. Emotion and language regions of interest (ROIs) were defined as the intersection of the ISC

map and the corresponding ICA map, and the mean time-course was extracted from each ROI in each subject.
Results: ISC indicated that movie watching induced synchronized responses in extensive brain areas, including auditory, visual, temporoparietal language, and fronto-limbic emotion, networks. ICA identified two emotion components comprising the bilateral amygdala and bilateral anterior insula, respectively, and one language component comprising left lateralized inferior and middle frontal, and middle temporal, cortices. There were strong positive correlations between the time courses of the left and right amygdala ($r=0.63\pm0.20$), and left and right insula ($r=0.59\pm0.12$), and weak correlations between the time courses of the amygdala and language ROIs ($r=0.27\pm0.24$), and the insula and language ROIs ($r=0.32\pm0.19$). The activation peaks in the language ROI corresponded to scenes with spoken dialogues, whereas the activation peaks in the emotion ROIs corresponded to emotional scenes with and without dialogue.
Conclusions: These findings suggest that different movie features induce spatiotemporally distinct responses in different functional networks, and that emotion and language networks can be mapped reliably from movie-fMRI using strictly data-driven approaches.

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Poster

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Program #/Poster #: P692.07

Topic: G.04. Emotion

Support: ERC-2017-STG Grant 757583

Title: Effects of the D2 antagonist haloperidol on emotion perception from point light walkers depend on working memory span

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Abstract: Evidence from studies involving patients with Parkinson's disease, Huntington's disease and schizophrenia proposes a role for the neurotransmitter dopamine (DA) in emotion recognition. However, to date studies in which DA is pharmacologically manipulated in healthy volunteers have failed to provide behavioral evidence in support of this thesis. The lack of behavioral effects of dopaminergic manipulation on emotion recognition, as well as contradictory findings of effects of DA agents on blood oxygenation level dependent (BOLD) responses in areas crucial for emotion recognition, may be attributable to interindividual differences in susceptibility to pharmacological interventions. Whilst it has been well established in cognitive studies that responses to dopaminergic drugs can depend on individual baseline DA function, the emotion recognition literature so far has failed to statistically account for these possible interindividual differences. Using an approach that accounts for individual differences in baseline DA function, the present study tested whether the DA D2 receptor antagonist haloperidol

modulated emotion recognition from dynamic, whole-body motion cues.
We used a double-blind, placebo-controlled cross-over design to test effects of the D2 antagonist haloperidol on participants' emotion recognition from gait, using dynamic point-light-walker (PLW) stimuli. On two separate days, once after receiving 2.5mg Haloperidol and once after receiving placebo, 32 healthy participants (16 males; mean age = 26.36) first completed a visual working memory (WM) task (WM span has been shown to be a reliable indicator for striatal DA synthesis capacity and hence was used as a proxy for individual baseline DA function). Subsequently, participants viewed angry, happy and sad PLWs and rated how intensely they felt each emotion was expressed in each stimulus.
Using Bayesian mixed effects models, we observed that drug effects on emotion perception depended on WM span, such that under the drug, participants with low WM span gave increased emotion intensity ratings (ß = 0.47, CrI = [0.16, 0.78]), whereas high WM individuals gave decreased intensity ratings (ß = -0.47, CrI = [-0.78, -0.15]). Whilst the involvement of dopaminergic processes in facial emotion recognition has been previously established, this study is the first to show that DA modulates emotion recognition from whole-body motion. Furthermore, the present study confirms that dopaminergic drug effects on emotion recognition depend on individual baseline DA function and highlights the need to model interindividual differences in drug responsivity for future studies.

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Poster

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Topic: G.04. Emotion

Support: We acknowledge the support of the Natural Sciences and Engineering Research Council of Canada (NSERC).
Alberta Innovates Health Solutions

Title: Spike-field interactions in human subgenual cingulate related to emotional decision making

Authors: *N. A. ZALASKY[1], D. L. CLARK[1], L. H. KIM[1], M. S. NOOR[1], F. LUO[1], A. J. GRUBER[3], *Z. H. KISS[2];
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Abstract: The subgenual cingulate gyrus (SCG) sits at the intersection of important emotional processing and regulation circuits. Because of its connectivity, it is a deep brain stimulation (DBS) target for treatment resistant depression. Network oscillations in this area may influence cognitive emotional regulation through coherence in the beta frequency band (13-30 Hz). How network dynamics influence single neuron activity in this area has never been studied in humans but is critical in linking SCG contributions to depression. Thus, we sought to determine the relationship between beta oscillations and single neuron activity in the SCG. We hypothesized that spiking activity of single neurons would be

modulated by network dynamics via beta-band spike-field synchronization.
Microelectrode recordings collected during SCG-DBS surgeries were used to compare single neuron spiking activity (filtered at 100Hz-10kHz) to local field potential (LFP) beta band (13-30Hz) dynamics during an emotional faces Stroop task. Spike-phase interactions were quantified using several measures. Instantaneous phase was calculated from the filtered signal in relation to spike times, and **phase-locking distributions** were determined for each cell. Rayleigh's test for non-uniformity was used to quantify **phase preference**. To measure the magnitude of coupling between single cells and beta oscillations, relative phase-locking was also computed. These **modulation indices (MI)** estimate the strength of beta modulation compared to an unsynchronized control sample.
Twelve patients participated in this study, for which 33 recording sites in SCG were obtained with 41 distinct cells isolated (21 cells with sufficient spontaneous firing). 83% of SCG neurons demonstrated significant phase-locking during the task, compared to 43% during spontaneous firing. All phase-locked neurons showed a preferred phase between 180 and 360 degrees, falling within the troughs of the beta oscillation. Modulation indices ranged from -2 to +8, with a higher proportion of single SCG cells showing significant modulation (MI >3) by the beta band during the task (39%) compared to spontaneous activity (24%). No changes in the strength of modulation were observed.
Preliminary analysis suggests that single neurons in the SCG are, in part, modulated by synchronization in the beta band, being driven by dips in beta oscillatory activity. This study is the first to examine the relationship between network oscillations and single neuron activity within the human SCG. Further analysis will provide us with a novel understanding of the role of SCG in emotional processing, and could inform possible closed-loop DBS.

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Poster

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Topic: G.04. Emotion

Support: National Research Foundation of Korea(NRF) funded by Ministry of Science and ICT (No. NRF- 2020R1F1A105820012)

Title: Frontal theta/beta ratio predicts attentional bias to threat in individuals with high social anxiety

Authors: *N. KWON[1], J. KIM[1], K. KIM[2], S.-Y. KIM[1];
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Abstract: Previous studies have demonstrated abnormal attentional bias to socially threatening stimuli in individuals with social anxiety disorder (SAD). Recent studies reported the frontal alpha asymmetry (FAA) and the theta/beta ratio (TBR) are the most prominent EEG-based biomarkers in SAD. However, it is still undefined which of the two components (FFA and TBR) is a key factor to explain attentional bias

to threat in SAD. Thus, we aimed to examine attentional bias to threat in individuals with high social anxiety (HSA) both in behavioral and electrophysiological levels. Thirty-five neurotypical adults performed a continuous performance task to examine attentional bias patterns. In the task, participants were asked to detect a target ('T') while ignoring concurrently presenting face distractor (angry/neutral). Attentional bias patterns were defined as attentional capture and attentional holding effects. Anxiety levels of participants were also collected using State-Trait Anxiety Inventory (STAI), Social Phobia Scale (K-SPS), Social Interaction Anxiety Scale (K-SIAS), and Social Avoidance and Discomfort Scale (K-SADS). Finally, using resting state EEG, FAA and TBR were collected and analyzed. To identify EEG components related to high social anxiety, we divided our participants into two anxiety groups based on the three social anxiety scales (K-SPS, K-SIAS, K-SADS): High social anxiety (HSA; N=14) and Low social anxiety (LSA; N=21) groups. Results reveled that only the HSA group showed both attentional capture and holding effects to angry faces. In addition, only the HSA group showed significant positive correlation between attentional holding scores and social anxiety scores. Next, multiple regression analyses were performed to discover the neural biomarkers related to the attentional bias to threat in individuals with HSA. Results showed that both the FAA and TBR significantly explained the increased attention bias in HSA individuals who showed both attentional capture and holding effects. Importantly, increased TBR was revealed as a key component to explain the attentional bias; that is, the effects of TBR on attentional bias was significant after controlling for the effects of FAA. Notably, it has been suggested that higher TBR is related to inefficient emotional control, which may cause a vigilant response to threatening stimuli in individuals with HSA. In sum, our study demonstrated similar attentional bias patterns in non-diagnosed adults with HSA to those in people with SAD. Further, we found that increased TBR during rest can be an important electrophysiological biomarker related to excessive attentional bias to threat in people with HSA.

Disclosures: N. Kwon: None. **J. Kim:** None. **K. Kim:** None. **S. Kim:** None.

Poster

P696. Anxiety: Human Studies

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P696.01

Topic: G.06. Anxiety Disorders

Support: NIMH R15MH1109051

Title: Cerebellar seeded functional connectivity changes in anxious individuals undergoing attention bias modification training

Authors: *K. ELWELL[1], L. FANG[2], J. CARLSON[2];
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Abstract: A hallmark symptom of anxiety is attention bias to threatening stimuli, and an abundance of studies have indicated a significant relationship between attention bias and the maintenance of anxiety disorders—with similar neural mechanisms driving them. The majority of neuroimaging studies have fixated on the roles of the anterior cingulate cortex, the prefrontal cortex, and the amygdala as key regions

for neural correlates of attention bias. However, new and converging research provides empirical evidence that the cerebellum's functional connectivity and shared network structure with threat processing regions contribute to anxiety. Attention Bias Modification (ABM) is a newly-emerging promising treatment for anxiety disorders in which participants are unconsciously trained to divert their attention away from threatening stimuli, with the goal to reduce attention bias towards threat. Therefore, the aim of the current study was to assess the effect of six-weeks of ABM training on cerebellar-seeded resting state functional connectivity changes in individuals exhibiting high trait anxiety and an attention bias towards threat. Participants (N = 41) were between the ages of 18 and 38, right-handed, free of any neurological history, and were not undergoing any form of psychological therapy, or taking any psychotropic medications. Functional connectivity was extracted from a 10-minute resting-state functional magnetic resonance imaging session. Resting-state functional magnetic resonance imaging scans were collected immediately prior to, and immediately following the conclusion of the six week ABM training. The results showed a decrease in both attention bias, as well as a decrease in cerebellar-seeded resting state functional connectivity. Specifically, relative to the control group, the ABM training group showed a decrease between cerebellum seeds to regions such as the anterior cingulate cortex, lateral occipital cortex, posterior cingulate cortex, thalamus, hippocampus, salience network, and default mode network. Our findings suggests that neural changes in cerebellar-based functional connectivity may underlie the ABM-related changes—such as decreased attention bias. This also implies that the cerebellum may contribute to the etiology and maintenance of anxiety and attention bias.

Disclosures: K. Elwell: None. **L. Fang:** None. **J. Carlson:** None.

Poster

P696. Anxiety: Human Studies

Location: Virtual Only

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Program #/Poster #: P696.02

Topic: G.06. Anxiety Disorders

Title: Impact of COVID 19 Pneumonia on the quality of life, mental health and autonomy of patients

Authors: *S. CHAKROUN[1,2], A. CHAKER[1,2], K. KCHAOU[1,2], S. MOKADDEM[1,2], S. BEN KHAMSSA[1,2];
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Abstract: Introduction Respiratory sequelae of COVID19 are now well identified but their impact on the quality of life, mental health and autonomy of patients is still unsufficiently studied.
Objective This prospective study was conducted to assess the quality of life, mental health, and independent living skills of COVID-19 pneumonia patients, 3 months after recovery .
Patients and methods This study included 154 patients who consulted the Respiratory Functional Explorations Department of the Abderrahmane MAMI Hospital in Ariana. Each patient undertook the Nottingham Health Profile (NHP) and SF-12 scales to assess quality of life, Hospital anxiety and depression (HAD) to assess mental health and the Lawton Instrumental Activities of Daily Living (IADL) Scale to estimate the level of autonomy in the instrumental activities of daily life

Results The sex ratio of our population was 1.3 with a mean age of 59.39 ± 11.76 years. On a scale of 100, the mean NHP different dimensions were distributed as follows: 34.34 for lack of energy, 19.87 for pain, 18.31 for sleep disturbance, 18.13 for exaggerated emotional reactions, 16.90 for mobility difficulties and 12.86 for social isolation. The average SF-12 score was 39% for the physical dimension and 50.73% for the mental dimension. The HAD scale confirmed anxiety in 23.4% and depression in 16.9% of patients. However, the average IADL score was 7.24 per 8, which is in favour of preserved autonomy in daily activities.

Conclusion

Our results revealed COVID-19 effects on the physical and mental health of patients and its negative impact on their quality of life contrasting with a preserved autonomy in daily life.

Disclosures: S. Chakroun: None. **A. Chaker:** None. **K. Kchaou:** None. **S. Mokaddem:** None. **S. Ben Khamssa:** None.

Poster

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Program #/Poster #: P696.03

Topic: G.06. Anxiety Disorders

Support: MICHR Pilot Grant: UL1TR002240

Title: Depression symptoms associated with brain function underlying attention bias in social anxiety disorder

Authors: *J. STOUT[1], S. GOLDBERG[1], S. JOSHI[1], J. ABELSON[1], I. LIBERZON[2], E. R. DUVAL[1]; [1]Univ. of Michigan, Ann Arbor, MI; [2]Texas A&M Med. Ctr., College Station, TX

Abstract: Social anxiety disorder (SAD) is often characterized by biased attention to threatening information, along with aberrant brain activation in regions associated with attentional control. People with SAD commonly experience comorbid depression symptoms; however, the brain activation underlying depression symptoms in people with SAD has not been well studied. This study aimed to investigate activation in brain regions associated with attentional control in people with SAD and a continuum of depressive symptoms measured on the Beck Depression Inventory (BDI-II). Participants include 29 right-handed adults ages 18-55. All participants have SAD, and depression symptoms ranging from minimal to severe. Participants completed a modified dot probe task during MRI scanning to assess attention bias and measure activation in brain regions involved in salience processing and attentional control. Participants indicated the direction of an arrow probe that randomly replaced a happy or threatening face. A trial is considered congruent when the arrow replaces the threatening face, and a trial is incongruent when the arrow replaces the happy face. We hypothesized that participants with SAD and more severe depressive symptoms will have increased activation in regions involved in attentional control and salience processing, including the right ventrolateral prefrontal cortex (vlPFC), dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC). Preliminary results indicate that higher depression symptoms were associated with greater activation in the dlPFC during all trials vs implicit

baseline (33, 9, 34, $p < .01$) and during incongruent vs congruent trials (-43, -0, -2, $p < .01$). Higher depression symptoms were also associated with less activation in the insula during all trials vs implicit baseline (-46, -1, 2, $p < .01$), and less activation in the dACC during incongruent vs congruent trials (18, 21, 26, $p < .01$). These results suggest that higher depression symptoms are associated with greater activation in regions involved in attention control (dlPFC) and less activation in regions involved in salience processing (insula, dACC). These findings suggest that people with SAD who have higher levels of depression demonstrate a compensatory response in attention control regions and a blunted response in salience processing regions.

Disclosures: J. Stout: None. **S. Goldberg:** A. Employment/Salary (full or part-time):; University of Michigan. **S. Joshi:** A. Employment/Salary (full or part-time):; University of Michigan. **J. Abelson:** A. Employment/Salary (full or part-time):; University of Michigan. **I. Liberzon:** A. Employment/Salary (full or part-time):; Texas A&M Medical Center. **E.R. Duval:** A. Employment/Salary (full or part-time):; University of Michigan.

Poster

P696. Anxiety: Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P696.04

Topic: G.06. Anxiety Disorders

Title: A Systematic Review on the Effects of Air Pollution on Anxiety and Depression

Authors: *D. H. DAHER[1], C. G. ZUNDEL[1], B. A. BORG[1], J. M. EVANSKI[1], P. RYAN[2], C. BROKAMP[2], J. R. STRAWN[2], H. A. MARUSAK[1];
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Abstract: Although the harmful effects of air pollution on human physical health (e.g., respiratory ailments) have been well established, the effects on mental health are less clear. Research shows that air pollutants can negatively impact the central nervous system, including inducing neuroinflammation and oxidative stress. Importantly, these mechanisms are also implicated in the pathophysiology of anxiety and depression, which are the most prevalent mental health disorders and affect 284 and 264 million individuals worldwide, respectively. Anxiety and depression are also associated with significant morbidity and disability. Given the public health significance of anxiety and depression, it is critical to understand the role of environmental factors, such as outdoor air pollution, in these disorders. Here, we performed a systematic review of the literature to examine the impact of outdoor air pollutants on anxiety and depression. The MEDLINE (PubMed) database for articles published before August 27th, 2020, and a total of 92articles was included in the review. Included articles focused on outdoor air pollutants (e.g.,PM2.5, PM10, and NO2) on anxiety and depressive symptoms or behaviors in humans or animal models. Sixty-eight percent (n = 62) of studies included humans, 22% included mice (n = 20),and 10% included rats (n = 9). PM2.5 was the most studied air pollutant and demonstrated consistent positive associations with anxiety (66%; n = 18 out of 27) and depression (75%; n =37 out of 49) across studies, particularly among adolescents and elderly populations. Although there were fewer studies, positive associations were also observed for PM10, O3, NO2, SO2, CO2,and PAH. This review demonstrates

consistent effects of outdoor air pollutants on anxiety and depression across studies. Evidence that outdoor air pollutants can increase the risk of mental health disorders, in addition to well-established effects on physical health, has implications for policy. Indeed, new legislation that sets restrictions on the sources of air pollution is needed to lower the environmental risk of mental health disorders, particularly in vulnerable populations(i.e., adolescents, elderly). As well as being a push for future studies that investigate the brain-behavioral mechanisms of the linkages between air pollution and mental health disorders. Given the rising prevalence of anxiety and depression over recent years, these data highlight the role of salient environmental factors — particularly air pollution — in influencing human health, which has implications for prevention and intervention.

Disclosures: D.H. Daher: None. **C.G. Zundel:** None. **B.A. Borg:** None. **J.M. Evanski:** None. **P. Ryan:** None. **C. Brokamp:** None. **J.R. Strawn:** None. **H.A. Marusak:** None.

Poster

P696. Anxiety: Human Studies

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Program #/Poster #: P696.05

Topic: G.06. Anxiety Disorders

Support: MNUMS cohort #20/05

Title: Anxiety and depression in Mongolia: translation, reliability, and structural validity of the hospital anxiety and depression scale in the Mongolian general population

Authors: *B. LKHAGVASUREN[1,2], E. TUMURBAATAR[3], O. JARGALSAIKHAN[4], R. ERKHEMBAYAR[5], G. TUMUR-OCHIR[6], T. JADAMBA[7], T. HIRAMOTO[8];
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Abstract: Anxiety and depression in Mongolia: translation, reliability, and structural validity of the hospital anxiety and depression scale in the Mongolian general population

Abstract Various psychological, biological, and social factors make people vulnerable to mental health issues. There has been no screening tool for the assessment of anxiety and depression available in Mongolia that is adequately validated for the use on mental health, and neuropsychiatric functions of the brain. Therefore, we aimed to translate and validate the hospital anxiety and depression scale (HADS) in the healthy general population in Mongolia. The HADS is reliable, valid, and practical for identifying the most common psychological disturbances, and a well-practiced scale. A test-retest study was carried out on 80 participants with an interval of 16.3±1.7 days between 2-time points. This observational comparative study for the validity of the self-reported measure was conducted between June and December 2020, 1094 participants were randomly selected, aged 13-75, mean age was 37.7±13.7, 60.9%

were females, and 63.9% were married. The HADS total score was 13.0±5.7, the HADS-Anxiety score was 6.8±3.6, and the HADS-Depression score was 6.0±3.1. The Intraclass correlation coefficient (ICC) values were 0.872, 0.837, and 0.801 for the HADS-T, the HADS-A, and the HADS-D, respectively. Indicating internal reliability, the Cronbach's alpha value was 0.776 for the HADS-T, 0.756 for the HADS-A, 0.582 for the HADS-D. External reliability was good in the whole scale, and both subscales using ICC. These findings suggest that the questionnaire can be considered a sufficiently homogenous measurement tool. The reliability of the both 2-factor and 3-factor structures of the HADS was confirmed using the confirmatory factor analysis with a satisfactory model fit on a separate sample. In conclusion, the Mongolian version of the HADS is a valid and reliable instrument to assess potential anxiety and depression cases in the Mongolian general population and can be used in various scientific practices.
KeywordsAnxiety, depression, population-based, validation, Mongolia

Disclosures: B. Lkhagvasuren: None. **E. Tumurbaatar:** None. **O. Jargalsaikhan:** None. **R. Erkhembayar:** None. **G. Tumur-Ochir:** None. **T. Jadamba:** None. **T. Hiramoto:** None.

Poster

P696. Anxiety: Human Studies

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Program #/Poster #: P696.06

Topic: G.06. Anxiety Disorders

Support: NINDS-K24 [K24-NS088568- 01A1]
Tiny Blue Dot Foundation
United States Department of Energy Computational Sciences Graduate Fellowship [DE-FG02- 97ER25308]

Title: Intersection of psychiatric disorders, epilepsy, and emotional conflict resolution

Authors: *D. SOPER, A. C. PAULK;
Massachusetts Gen. Hosp., Boston, MA

Abstract: Patients with epilepsy suffer from a high prevalence of psychiatric comorbidities, particularly anxiety, indicating an essential intersection between seizure disorders and psychological state. Understanding the mechanism underlying this comorbidity could help develop therapies for both epilepsy and psychiatric disorders and help understand the intersecting neural underpinnings. Through analyzing the relationship between intracranial neural activity, task data, self-report questionnaires, and neuropsychological evaluations, we tested the hypothesis that more anxious patients with epilepsy would have an impaired ability to resolve emotional conflict. We also hypothesized that connectivity between brain regions typically involved in emotion regulation and anxiety would be different depending on anxiety levels. We ran an emotional conflict resolution task (ECR) and Multi-Source Interference Task (MSIT) with two groups: patients with intractable epilepsy undergoing clinically invasive electrode placement to determine seizure onset (n=24) and healthy controls (n=36). ECR and MSIT, variants of the classic Stroop task, measure conflict resolution through changes in reaction time and accuracy for sequential presentations of congruent and incongruent trials, though ECR contains an emotional

component while MSIT does not (as a control). All participants also filled out self-report psychological questionnaires and a subset underwent neuropsychiatric testing. We show here, for incongruent trials, that participants with epilepsy (EPs) are less accurate with higher variability in the ECR task than healthy controls (HCs) (EP mean=81.79% +/-0.035, HC mean=93.24% +/-0.008, $p<0.05$, Wilcoxon Rank-Sum), while no accuracy difference was present during MSIT. Similarly, participants with higher Beck Anxiety Index (BAI) scores also had poorer accuracy on ECR. No such relationship existed between BAI scores and MSIT accuracy. We also examined differences in network connectivity in patients with epilepsy with low and high scores using coherence measures. These preliminary results suggest a deficit in emotional conflict resolution which corresponds with measured anxiety levels for patients with intractable epilepsy.

Disclosures: D. Soper: None. **A.C. Paulk:** None.

Poster

P696. Anxiety: Human Studies

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Program #/Poster #: P696.07

Topic: G.06. Anxiety Disorders

Support: ZIAMH002798 (clinical protocol 02-M-0321, NCT00047853)

Title: State anxiety differentiates value-driven and random exploration in an aversive multi-arm bandit experiment

Authors: *R. T. PHILIPS[1], K. FORAY[2], E. WEISS[1], C. GRILLON[1], M. ERNST[1];
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Abstract: Human decision making often involves exploration and exploitation, which may be impacted by anxiety. The goal of this study was to investigate the interaction between different exploration strategies (value-driven or random) and anxiety, using a computational model. 32 healthy volunteers (18 F, mean age 25) performed 2 versions of a 4-arm aversive (probabilistic shock) bandit task, in which participants were asked to choose the arm perceived to have the lowest probability of shock. In one version, the best strategy relied on purely value-driven exploration (choosing to explore only when there is a *perceived* better choice); whereas, in the other, it involved random exploration. Performance was analyzed using a reinforcement-learning model. The performance metrics included: 1) accuracies (defined as the proportion of choosing the lowest *true* shock probability option) and 2) persistent exploitation (defined as the proportion of repeatedly choosing the options with best *perceived* value). State-trait was measured using State-Trait Anxiety Inventory (STAI). While accuracies did not significantly differ between versions (paired t-test, $p = 0.1273$), persistent exploitation showed a significant difference between versions (paired t-test, $p = 0.0005$). Additionally, the persistent exploitation difference-score showed a strong negative correlation with the state STAI score ($R = -0.55$, $p = 0.0035$). Participants exhibited higher value-driven than random exploration, evidenced by higher persistent exploitation in the version favoring random exploration. Furthermore, individual differences in persistent exploitation between versions decrease as a function of state anxiety scores. In conclusion, state anxiety might influence exploratory behavior, suggesting an ambivalence between random and value-driven exploration

in higher state anxiety. These insights could help us understand the circuitry mediating explore/exploit decisions and aberrations in anxiety.

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Poster

P696. Anxiety: Human Studies

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Program #/Poster #: P696.08

Topic: G.06. Anxiety Disorders

Support: NIH Grant K01MH121777

Title: Using TMS to uncover the role of the intraparietal sulcus in in anxiety expression and hypervigilance.

Authors: *N. L. BALDERSTON, M. TEFERI, W. MAKHOUL, D. OATHES, Y. SHELINE; Univ. of Pennsylvania, Philadelphia, PA

Abstract: Neuromodulation is a promising avenue for novel anxiety treatment. However, optimal targets for treatment are not known. Our recent neuroimaging work suggests that the intraparietal sulcus (IPS) demonstrates elevated excitability and functional connectivity during periods of elevated arousal. We have also shown decreases in arousal by targeting the IPS with online 1 Hz stimulation. In the current work, we present data from two studies. The first study uses fMRI to examine the role of the IPS in hyperexcitability during a visual short term memory (VSTM) task. During each trial subjects see a cue pointing either left or right. They then see a bilateral array of squares, and are instructed to attend only to the squares in the cued hemifield. After a short delay they then see a response prompt with an example square that is either a match or a mismatch. Trials were grouped into blocks of safety and unpredictable threat. The second study uses simultaneous TMS/fMRI targeted at the right IPS to examine the role of the IPS in anxiety expression during unpredictable threat. The NPU threat task consists of Neutral, Predictable, and Unpredictable periods. During the neutral periods, subjects are not at risk for shock. During the predictable periods, subjects are only at risk for receiving a shock when a cue is present. During the unpredictable periods, subjects are at risk throughout. In the VSTM task, we sampled IPS activity using a 5mm sphere centered on coordinates from our previous IPS connectivity paper. We found marginally greater right IPS activity during threat compared to safe periods. Although preliminary, these results suggest that threat may have a stronger effect on right IPS BOLD activity during the VSTM task. In the unpredictable threat task, we extracted BOLD from the contralateral IPS, a measure of activity downstream elicited by the TMS pulse. We found marginally greater TMS-evoked BOLD responses during the threat compared to the safe periods. Although data collection is ongoing, these results suggest an increased responsiveness to IPS stimulation during unpredictable threat. Anxiety is known to impact attention control and anxiety patients have trouble focusing attention in a variety of cognitive tasks, including working memory. Threat-related hypervigilance is a prominent symptom of clinical anxiety, cutting across diagnoses, and this hypervigilance may be mediated by hyperactive orienting processes

mediated by the IPS. These results, combined with our previous work, offer promise that modulation of IPS excitability may reduce arousal and restore attention control in anxiety patients.

Disclosures: N.L. Balderston: None. **M. Teferi:** None. **W. Makhoul:** None. **D. Oathes:** None. **Y. Sheline:** None.

Poster

P696. Anxiety: Human Studies

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P696.09

Topic: G.06. Anxiety Disorders

Title: Pilot study demonstrates potential short-lived beneficial effects of the visuospatial interference task Tetris on subjective emotion

Authors: *V. RETTERHOLT, M. JERJOUS, A. JACOB, G. H. GOTTHARD;
Muhlenberg Col. Neurosci. Program, Allentown, PA

Abstract: Internationally, math anxiety is shown to affect many students (Luttenberger et al., 2018). However, little research has been done on methods of easing math-related anxiety This pilot study examined the effect of a visuospatial interference (VSI) task (Tetris) on subjective experience of mood in relation to math-related anxiety. When multiple cognitive tasks compete for working memory (WM) resources, there will be reduced information processing (Kessler et al., 2020). One way to induce this interference in information processing is by using a VSI task. The game Tetris was used in the current study because it has been shown to have an effect on the consolidation of traumatic memories and subjective recall of the traumatic event (Holmes, et al., 2010). Anecdotal evidence indicates that Tetris may produce calming effects on subjective emotion (Iyadurai et al., 2017). The current study extends the literature on VSI by examining the effects it has on subjective emotion.
Undergraduate students (n=24; 18-22 years old) participated in this pilot study (control: n=12; Tetris: n=12). Participants met with researchers via Zoom video calls to complete the study synchronously. In Session 1, participants were randomly assigned to a control or experimental group. They then completed a mood-assessment questionnaire, followed by a set of math problems. Upon completion of the math problems, participants in the control group answered true/false trivia questions (PubQuiz) for 10 minutes, and participants in the experimental group played Tetris for 10 minutes. Both groups then filled out the mood assessment a second time. During Session 2, which occurred one week later, participants completed the mood assessment one more time.
Mood assessments were analyzed at three time points: baseline, post-intervention, and one-week follow-up. While the n-sizes of this pilot study did not allow for significant differences to emerge, repeated measures ANOVA uncovered two findings that warrant further examination: (1) Tetris trended toward lower reports of “worry” post-intervention that increased one week later [$F(2,44)=2.15$, $p=.12$]; (2) Tetris maintained moderate levels of “relaxation” post-intervention that declined one week later [$F(2,44)=2.08$, $p=.14$]. These results may indicate that Tetris initially produces a calming effect that dissipates over the course of one week. Further examination with larger n-sizes will be necessary to further evaluate these data.

Disclosures: V. Retterholt: None. **M. Jerjous:** None. **A. Jacob:** None. **G.H. Gotthard:** None.

Poster

P696. Anxiety: Human Studies

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Program #/Poster #: P696.10

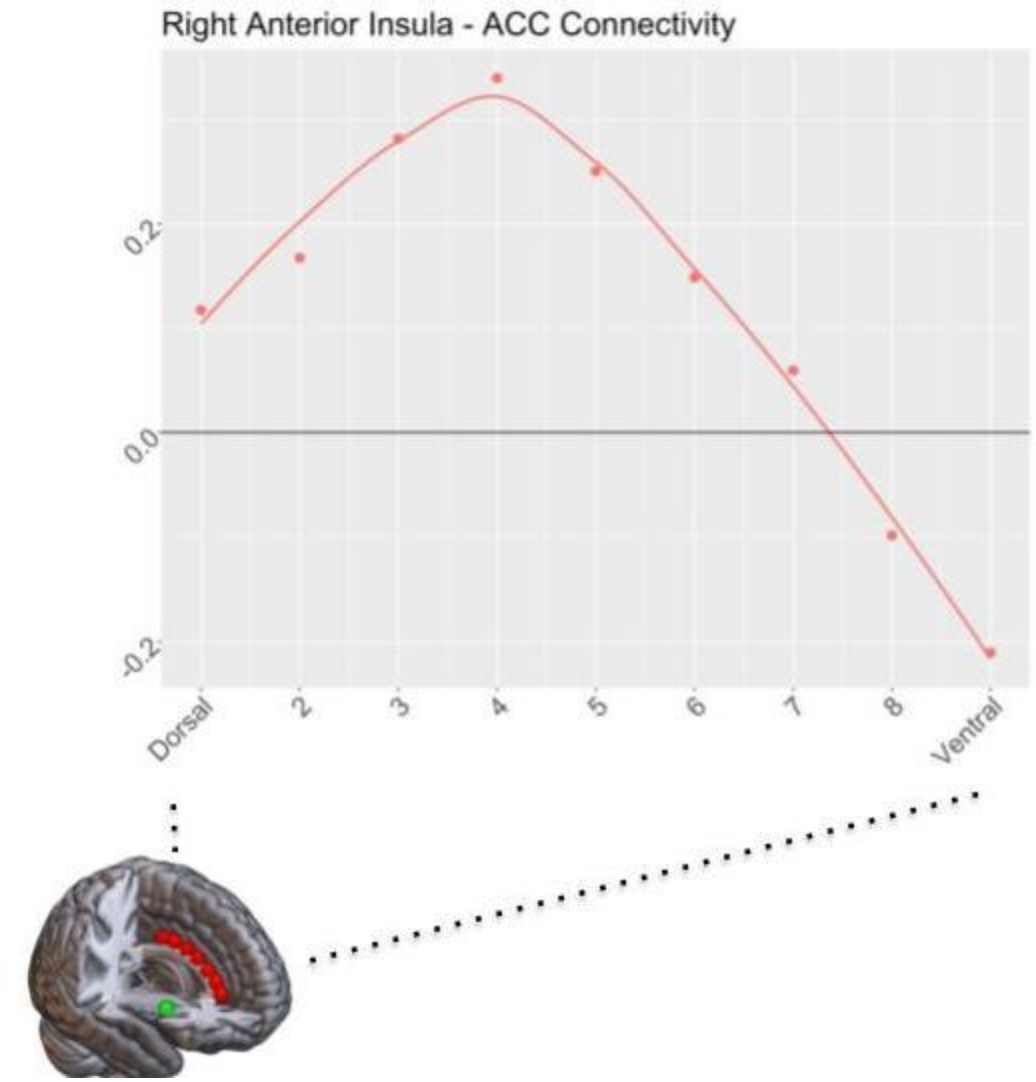
Topic: G.06. Anxiety Disorders

Support: SUNY Geneseo McNair Scholars Program
Geneseo Foundation Pre-Tenure Faculty Research Support Award

Title: Salience Network Topography in Pediatric Anxiety Disorders

Authors: E. CARLSON, ***B. TABER-THOMAS**;
SUNY Geneseo, Geneseo, NY

Abstract: Anxiety disorders are prevalent in people of all ages, often beginning in childhood or adolescence with 50% of diagnoses occurring by age 11 (Kessler et al., 2005). Due to the prevalence of pediatric anxiety disorders, early detection and intervention are advantageous for creating a positive prognosis for those who are affected. Here we examine salience network topography as a potential marker of anxiety, allowing for the implementation of earlier, personalized interventions. Taber-Thomas et al. (2016) found a topographical pattern of salience network connectivity related to anxiety risk in children. We further examined the robustness of this pattern using open source fMRI data in adults and children. In data from adults in the Brain Genomics Superstruct Project (n=1,000; Buckner et al., 2014) we found a normative pattern of salience network connectivity consistent with the pattern of children at low risk for anxiety (Fig. 1). In children with (n=8) and without (n=20) pediatric anxiety disorders, we hypothesized that, like shy children at risk for anxiety, children with an anxiety diagnosis will have less functional connectivity between the dorsal anterior cingulate cortex and the anterior insula compared to children without anxiety. Participants were children between ages 5.5 to 9.5 who had taken part in a previously published early childhood brain development and anxiety disorders study (Carpenter et al., 2015) for which open source data are available at OpenNeuro. Data were preprocessed and analyzed using AFNI. A psychophysiological interaction analysis was conducted using the right anterior insula as the seed region. Connectivity values were extracted for ROIs spanning ACC. Results show anxious children, like shy children at risk for anxiety, had significantly lower functional connectivity between the insula and dorsal anterior cingulate cortex than non-anxious children ($t(27) = 2.473$, $p = 0.02$). Consistent with the pattern found in children at risk for anxiety (Taber-Thomas et al., 2016), anxious children show altered salience network connectivity.



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Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

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Topic: G.05. Mood Disorders

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Title: The developmental effects of prenatal exposure to curcumin on anxiety- and depressive-like behavior in mice

Authors: *M. Y. ROBERTS[1], S. HANIF[1], A. VILLEGAS[1], N. S. BURGHARDT[1,2];
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Abstract: Curcumin, the primary active ingredient in the turmeric root, has been used for decades in Chinese and Indian traditional medicine. In the United States, it has recently become popular to take curcumin as a dietary supplement, because of its anti-inflammatory, tumor-suppressing, and antidepressant properties. These beneficial effects have been identified in adults taking curcumin, but it is not known if consumption during pregnancy is safe for offspring. We tested the effects of prenatal exposure to curcumin on the development of emotional behavior in mice. This involved giving female mice a rodent chow containing 1.5% curcumin or a control chow throughout pregnancy and replacing each chow with regular colony pellets shortly before birth. Offspring (n=18-22 males/group; n=17-29 females/group) remained on regular colony chow for the remainder of their development and were weighed weekly from 4-8 weeks of age. At approximately 9 weeks of age, behavioral testing began in the open field, novelty suppressed feeding test, and forced swim test. In addition, fear learning was tested with auditory fear conditioning. We found that prenatal exposure to curcumin significantly reduced bodyweight throughout development and promoted immobility in the forced swim test, effects that were more pronounced in females than males. In contrast, only males exposed to curcumin exhibited decreased exploration in the open field test and increased latency to feed in the novelty suppressed feeding test, indicating enhanced anxiety. Prenatal exposure to curcumin in males also led to an impairment in extinction learning, an effect that was not found in females. Our data indicate that exposure to curcumin *in utero* promotes the development of depression-like behavior in mice of both sexes, but increases anxiety-like behavior and affects learned fear in males only. Consumption of curcumin during pregnancy may therefore have detrimental effects on the development of neural circuits underlying emotional behavior in offspring.

Disclosures: M.Y. Roberts: None. **S. Hanif:** None. **A. Villegas:** None. **N.S. Burghardt:** None.

Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P704.02

Topic: G.05. Mood Disorders

Title: Exploring Sex Differences in Affective and Cognitive Symptoms in a Streptozotocin Model of Diabetes

Authors: *K. GILLEY, H. RODGERS, K. JENSEN, R. MCCREADY, P. SHARMA, E. G. VICHAYA; Baylor Univ., Waco, TX

Abstract: Diabetes is a common metabolic disorder associated with low grade systemic inflammation as well as an increased risk of developing affective and cognitive symptoms. Results indicate that symptom

risk is sex specific, suggesting sex-related divergent mechanisms. However, few preclinical studies have been conducted in female mice due, in part, to their greater resistance to diabetic induction. Therefore, we examined behavior in male and female mice following chemical induction of diabetes using streptozotocin (STZ). We hypothesized that male mice would have more severe hyperglycemia and cognitive deficits following STZ, while female mice would display higher depressive-like symptoms. We used a 2 (+/- STZ) x 2 (male vs female) factorial design (n = 4-6/group). Fasting blood glucose was measured by handheld glucometer. As expected, male mice exhibited more severe hyperglycemia (393.3 +/- 15.3 vs 318.0 +/- 38.49, $p<0.001$). We did not observe cognitive impairment in the spontaneous alternations Y-maze task in this cohort, but we did observe a main effect of STZ in the forced swim task (FST) ($p = 0.01$). We also observed a main effect of sex, such that male mice had higher immobility irrespective of STZ ($p = .001$). In a separate experiment, conducted in one year old mice using a 2 (+/- STZ) x 2 (male vs female) experimental design (n= 4 mice/group), we investigated the impact of STZ on willingness to work for rewards in a fixed ratio 5 task. There was a trend for mice to show a great reduction in number of rewards earned following STZ ($p < 0.1$), this effect was more robust in male mice. Our data indicate that despite lower levels of hyperglycemia in the STZ model, female mice are still vulnerable to developing affective symptoms with relatively equal severity to male mice, but may be more resilient to developing motivational deficits. Due to the sex-specific contrast in hyperglycemia severity, it will be necessary to consider severity when interpreting the data. Future research will confirm and extend these behavioral findings as well as examine potential mechanisms.

Disclosures: K. Gilley: None. **H. Rodgers:** None. **K. Jensen:** None. **R. McCready:** None. **P. Sharma:** None. **E.G. Vichaya:** None.

Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P704.03

Topic: G.05. Mood Disorders

Support: Hope College Biology, Chemistry and Neuroscience Program
A. Paul and Carol Schaap

Title: Early prenatal exposure to homocysteic acid leads to alterations in behavior and gene expression that are consistent with bipolar disorder

Authors: *K. BOSIS, G. TAYLOR, A. LUNDERBERG, S. SIMKO, L. CHASE;
Hope Col., Holland, MI

Abstract: We have previously demonstrated that early post-natal exposure of rat pups to the NMDA receptor agonist, homocysteic acid (HCA) from P3-P21 leads to the development of mixed manic/depressive behaviors following puberty. The manic behaviors are effectively reversed by lithium treatment, and the depressive behaviors are reversed by acute ketamine treatment. Thus, HCA appears to induce a bipolar-like phenotype in rats. The goal of this study was to determine whether HCA exposure also induces gene expression changes that are consistent with a bipolar phenotype. Microarray analyses

were performed on tissue obtained from the prefrontal cortices saline- and HCA-treated rats at 3 weeks and 32-weeks of age. At 3 weeks, HCA rats exhibited 132 differentially expressed genes relative to control, many of which suggest there is a delay in oligodendrocyte development. Interestingly, several genes that have been identified as exhibiting reduced expression in bipolar disorder and schizophrenia, including MBP, PLP1, MAG, MOG, ERMN, and GSN. At 32-weeks, 316 differentially expressed genes were identified, including many genes which are associated with GABAergic interneuron function or regulate excitatory/inhibitory balance including SST, PVLB, GABRB2, GABRA6, KCNA1. We confirmed several of these alterations in gene expression using qPCR. Collectively, these results suggest that HCA treatment leads to changes in gene expression that mirror those previously identified in GWAS and microarray studies in post-mortem BD patients.

Disclosures: K. Bosis: None. **G. Taylor:** None. **A. Lunderberg:** None. **S. Simko:** None. **L. Chase:** None.

Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

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Topic: G.05. Mood Disorders

Support: Natural Science Foundation of Shanghai (No.16ZR1410100 to C.L.)
National Natural Science Foundation of China (No. 31271134 to H.W.)
the James and Patricia Poitras Center for Psychiatric Disorders Research at MIT

Title: Sapap4 deficiency leads to postsynaptic defects and abnormal behaviors relevant to hyperkinetic neuropsychiatric disorder in mice

Authors: *T. WANG, **Y. BAI**, X. ZHENG, X. LIU, S. XING, L. WANG, Y. XIE, H. WANG, *C. LI; Key Lab. of Brain Functional Genomics (STCSM & MOE), Sch. of Psychology and Cognitive Science, East China Normal Univ., Shanghai, China

Abstract: Postsynaptic proteins play critical roles in synaptic development, function, and plasticity. Dysfunction of postsynaptic proteins is strongly linked to neurodevelopmental and psychiatric disorders. SAP90/PSD95-associated protein 4 (SAPAP4; also known as DLGAP4) is a key component of the PSD95-SAPAP-SHANK excitatory postsynaptic scaffolding complex which plays important roles at synapses. In the brain, SAPAP4 is highly expressed in cerebral cortex, the CA1 and CA3 regions of hippocampus, thalamus, striatum, amygdala and Purkinje cells of the cerebellum and localized to excitatory synapses. Recent studies have found that the mRNA or the protein expression levels of SAPAP4 were changed in neurological and psychiatric disorders. A microarray analysis indicates that SAPAP4 mRNA is a FRMP (fragile X mental retardation protein) target, translationally repressed in fragile X syndrome cells, and activity-dependent dendritic SAPAP4 mRNA transport is regulated by FMRP and impaired in a fragile X syndrome mouse model. High-density SNP genome-wide linkage analyses in one of the largest known autism pedigrees have suggested SAPAP4 is a potential candidate gene for autism in the chromosomal 20q11.21–q13.12 region. Truncation of the CG-

rich SAPAP4 promoter region triggered by the chromosome translocation t(8;20)(p12;q11.23) was also shown to induce epigenetic modifications at SAPAP4, perturb its expression, and segregate with cerebellar ataxia. In addition, a recent study has identified and validated SAPAP4 as a novel target gene of miR-1908-5p, a bipolar disorder-associated microRNA. However, the physiological role of SAPAP4 at excitatory synapses remains poorly understood. In this study, to understand the function of SAPAP4 in the brain, we generated Sapap4 gene KO mice. The analysis of our mouse model reveals structural alterations of excitatory synapses and postsynaptic composition changes of postsynaptic density in the prefrontal cortex. These synaptic defects are accompanied by a cluster of abnormal behaviors including hyperactivity, impulsivity, reduced despair/depression-like behavior, hypersensitivity to low dose of amphetamine, memory deficits and decreased pre-pulse inhibition, that are reminiscent of mania. Furthermore, the hyperactivity of Sapap4 KO mice could be partially rescued by valproate, a mood stabilizer used for mania treatment in humans. Together, our findings provide evidence that SAPAP4 plays an important role at synapses and reinforce the view that dysfunction of the postsynaptic scaffolding protein SAPAP4 may contribute to the pathogenesis of hyperkinetic neuropsychiatric disorder.

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Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

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Program #/Poster #: P704.05

Topic: G.05. Mood Disorders

Support: NIH NS034007
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NARSAD YI 26696

Title: Stress induced emotional dysregulation in a mouse model of Tuberous Sclerosis Complex

Authors: *P. SHRESTHA[1], C.-Y. JUAN[2], M. M. OLIVEIRA[2], K. S. A. RUIZ[2], M. MAMCARZ[2], M. SINGH[2], R. TRIANA-DEL RIO[2], M. HOU[2], C. FARB[2], A. CHIME[2], N. PENA[3], A. FRASER[1], J. E. LEDOUX[2], E. KLANN[2];
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Abstract: Tuberous Sclerosis Complex (TSC) is a neurodevelopmental disorder caused by mutations in Tsc1 or Tsc2, the genes that encode the protein components of TSC complex. TSC is one of the leading monogenic causes of autism spectrum disorder, and is associated with several neuropsychiatric disorders, collectively referred to as TSC associated neuropsychiatric disorders (TAND). TSC protein complex acts as an intracellular signal integrator and puts a brake on anabolic signaling mediated by mammalian target of Rapamycin complex (mTORC1), this occurs through its inhibition of small GTP-ase Rheb, which is a direct activator of mTORC1. Aside from the canonical TSC-Rheb-mTORC1 pathway, TSC complex has

recently been identified as a regulator of integrated stress response via TSC-Rheb mediated activation of eIF2alpha kinase PERK. Here, we show that heterozygous deletion of Tsc2 in Oxytocin receptor expressing cells (OxtRCs) precipitates behavioral susceptibility to social isolation stress. The manifestation of this behavioral susceptibility to stress is sex-specific. Male heterozygous null mice, upon prolonged social isolation, exhibit anxiety in tests that involve exploration of the environmental context or novel objects, specifically the open field test and marble burying test. On the other hand, social isolation reveals social anxiety in the female heterozygous null mice. We did not detect any impairment in associative learning and memory in the mutant mice, or motor stereotypy, indicating that OxtRC-specific haploinsufficiency of Tsc2 leads to aggravation of distinct indices of anxiety while sparing other behavior modules. Systemic administration of PERK inhibitor, GSK2606414, rescued all indices of anxiety-like behavior in male and female mutant mice whereas systemic Rapamycin, an mTORC1 inhibitor, only rescued anxiety in the marble-burying test for male mutants. Further, cell type-specific knockdown of Rheb in prefrontal OxtRCs rescued arena-related exploratory anxiety in male mice as well as social anxiety in female mutant mice. Our data indicate that aberrant behavior responses to stress are primarily mediated by TSC-Rheb-PERK signaling axis in Oxytocin responsive cells in the medial prefrontal cortex, and provide insight into the molecular underpinnings for emotional dysregulation evident in TSC.

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Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

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Program #/Poster #: P704.06

Topic: G.05. Mood Disorders

Support: NIH Grant R25 NS 80686

Title: Rescuing stress induced anxiety in a mouse model of tuberous sclerosis complex

Authors: *K. SAN AGUSTIN RUIZ[1], M. M. OLIVEIRA[1], M. MAMCARZ[1], C.-Y. JUAN[1], M. SINGH[1], A. CHIME[1], P. SHRESTHA[3], E. KLANN[2];
[1]Ctr. for Neural Sci., New York Univ., NY, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Neurobio. and Behavior, Stonybrook Univ., New York, NY

Abstract: The mammalian target of rapamycin complex (mTORC1)pathway is implicated in integrating and responding to various cues including cellular stress and growth factors. Tuberous Sclerosis Complex (TSC) is involved in mediating the mTORC1 pathway by inhibiting Rheb, an mTORC1 activator. However, when a ligand binds to an oxytocin receptor, it leads to Akt activation which phosphorylates Tsc2, effectively releasing the block of TSC on to mTORC1, allowing for increased translation. Thus, given that oxytocin receptors mediate the mTORC1 pathway through TSC, we chose to look into the role of Tsc2 in Oxytocin receptor neurons and what happens when you delete Tsc2 in these cells. Given that there is sexual dimorphism in oxytocin receptor expression we postulated that there could be sex

differences in how TSC manifest when Tsc2 is selectively deleted in oxytocin receptor neurons. In order to answer this question, we carried out different behavioral protocols with male and female heterozygote Tsc2 mutant mice. We used social isolation stress because oxytocin is thought to play a role in anxiety related behavior and we wanted to induce a stress related phenotype. Amongst the behaviors carried out, we found that socially isolated mutant male mice display more anxiety-like behavior in the open field test as they spend less time in the center of the field and in the marble burying test as they bury less marbles. On the other hand, female mice displayed social anxiety such that socially isolated females showed no preference for the object or mouse in a three chamber social interaction test. We tried to rescue these behavioral phenotypes using a PERK inhibitor given that TSC also plays a role in the integrated stress response through the activation of eIf2alpha kinase PERK. We found that PERK inhibitor was able to rescue all behavioral phenotypes of anxiety-like behavior in male and female mutant mice.

Disclosures: K. San Agustin Ruiz: None. **M.M. Oliveira:** None. **M. Mamcarz:** None. **C. Juan:** None. **M. Singh:** None. **A. Chime:** None. **P. Shrestha:** None. **E. Klann:** None.

Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

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Program #/Poster #: P704.07

Topic: G.05. Mood Disorders

Support: NIH Grant R15MH125282

Title: The impact of postpartum estrogen withdrawal following a hormone-simulated pseudopregnancy on anxiety and motivational behaviors in adult female mice

Authors: *R. C. SIMAMORA, B. L. ALONSO, L. T. COSTA, L. E. BEEN;
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Abstract: During pregnancy, estradiol levels increase 100 to 1000-fold higher than baseline levels. However, following birth and the expulsion of the placenta, estradiol levels plummet to below baseline levels and remain suppressed until ovulation resumes. Ongoing studies are investigating how this tremendous endocrine change generates a behavioral profile associated with peripartum mood and anxiety disorders. We used a hormone-simulated pseudopregnancy (HSP) in C57BL/6 adult female mice to model the impact of postpartum estrogen withdrawal on changes in behavior. In this model, ovariectomized mice receive daily injections that simulate estradiol and progesterone levels during early pregnancy, late pregnancy, and the postpartum period. Specifically, an estrogen-withdrawn group, which models the the drop in estradiol seen during the postpartum period, can be compared to an estrogen-sustained group, which continues to receive high levels of estradiol, and a control group, which receives vehicle injections throughout the simulated pregnancy and postpartum period. Previously, we have shown that estrogen withdrawal following HSP increases ΔFosB, a marker of plasticity, within the nucleus accumbens (NAc). Given that the NAc is associated with affect and motivation, we hypothesized that an estrogen-withdrawn state following HSP would also be correlated with behavioral deficits in anxiety and motivation. An open field test and elevated plus maze were used to quantify anxiety in the postpartum period in one cohort of

mice (n=32). In a separate cohort of mice (n=23), we performed a sucrose preference test and social motivation test. Estrogen withdrawal increased anxiety-like behavior in the elevated plus, as evidenced by more time spent in the closed arms than the open arms. Behavior in the open field did not vary with hormone condition. Behavioral data collection for the sucrose preference and social motivation tests is ongoing, but we hypothesize that the estrogen-withdrawn mice will display deficits in motivational behaviors through reduced sucrose preference and less interaction with the social stimulus. This would support the conclusion that estrogen withdrawal is implicated in postpartum reductions in motivation, which is a core feature of depression, and would complement our finding of increased ΔFosB in the NAc. Future research will look further into mechanisms of neural plasticity that may account for differences in motivation and mood.

Disclosures: R.C. Simamora: None. **B.L. Alonso:** None. **L.T. Costa:** None. **L.E. Been:** None.

Poster

P704. Developmental, Stress-Induced, and Sex-Specific Effects on Brain and Behavior

Location: Virtual Only

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Program #/Poster #: P704.08

Topic: G.05. Mood Disorders

Support: Davee Foundation
Northwestern Office of Undergraduate Research
WCAS Baker Program in Undergraduate Research

Title: Sexually dimorphic effects of adolescent stress in an X-linked congenic strain showing passive coping and increased anxiety

Authors: *M. T. JI, N. PASHANKAR, K. J. PRZYBYL, E. E. REDEI;
Dept. of Psychiatry and Behavioral Sci., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL

Abstract: Individual variations in stress vulnerability are connected to stress-coping behaviors and influenced by both genetics and the environment. The adolescent period is particularly vulnerable to stress; however, how genetic vulnerabilities can alter the long-term consequences of adolescent stress is not well known. This study aimed to investigate the effects of acute adolescent stress on adult behavior, using the F344.WKY-*Stresp3*/Eer (F.WX) inbred congenic strain. The F.WX shows passive coping and anxiety-like behaviors. During adolescence, male and female F.WX rats were exposed to a modified Forced Swim Test (FST), while controls were undisturbed. In adulthood, learning and memory were assessed by Contextual Fear Conditioning (CFC) and Novel Object Recognition (NOR), anxiety-like behavior through the performance in the Open Field Test (OFT), and finally, coping behavior was tested in the classic FST. It is hypothesized that F.WX animals with adolescent stress will show more passive coping and anxiety-like behaviors than F.WX animals without adolescent stress, and the behavioral differences could be associated with expression of genes within the QTL region. Furthermore, both adult males and females were hypothesized to be made equally vulnerable by stress during adolescence. The results did not confirm these hypotheses. Instead, this study found that the consequences of adolescent stress were sex-dependent in adulthood. In females, adolescent stress significantly increased inactivity in

the OFT (stress, $F[1,35]=5.54$, $p<0.05$) but decreased fear memory in the CFC (sex x stress, $F[1,43]=4.75$, $p<0.05$). It also significantly decreased the high innate passive coping of females in the FST as measured by immobility (sex, $F[1,34]=44.38$; $p<0.001$; sex x stress, $F[1,34]=5.39$, $p<0.05$). In contrast, stressed males appeared to be positively influenced by adolescent stress, having shown increased spatial recognitions in NOR and increased active coping in the FST (spatial recognition; sex x stress $F[1,28]=4.21$, $p<0.05$; coping, sex x stress, $F[1,36]=4.73$, $p<0.05$). Sequence variations between F344 and WKY genetically mapped within the QTL region were identified. The expression of three genes with sequence variations in their coding regions, along with glucocorticoid (*Nr3c1)* and mineralocorticoid (*Nr3c2)* receptor expressions of the adolescent stressed and non-stressed adult male and female F.WX animals were measured in multiple brain regions and showed association with behavioral measures. Thus, stress during adolescence can lead to resilience or vulnerability to distinct environmental challenges in males and females differently.

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Poster

P777. Modeling and Behavior II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P777.01

Topic: H.03. Decision Making

Title: A Game-Theoretic Computational Approach for Identifying the Neurobiological Basis of Multi-Person Social Interactions

Authors: *V. KURTZ DAVID[1], A. BRANDENBURGER[2], P. W. GLIMCHER[3,4];
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Abstract: Objective and Rationale: Seminal work in social neuroscience identified the role of the temporo-parietal junction (TPj) in reasoning about the mental state, actions and goals of others, a process usually referred to as “mentalizing”. Nonetheless, the study of mentalizing behavior is still lacking a strictly computational approach, which could lay the foundation for a neuronal-mechanistic account of social interactions. Here, we present a novel framework to examine the cognitive basis of strategic social interactions. Our goal is to investigate how the brain decodes social interactions into subclasses of cognitive functions associated with different cortical modules. Leveraging modelling architectures from game theory, alongside experimental design concepts from computational psychology, we identify orthogonal cognitive modules that we hypothesize play a role in mentalizing.
Methods and results: The complexity level of any social interaction is effectively the product of the social-representation complexity itself, and the number of options or outcomes that must be represented independent of social factors. When complexity level increases sufficiently, subjects struggle to fully represent the social setting and hence tradeoff the representation of valuation and mentalizing demands according to subject-specific capabilities and/or preferences. We utilize the Ring Game (Kneeland, 2015) to directly measure the allocation strategies of human subjects managing varying demands across these domains. In the Ring Game, each subject’s payoff depends on her own choices and the choices of all

other players in the ring. The number of players in each ring on a given trial determines the mentalizing requirements on that trial, while the complexity of the choice structure on a given trial imposes domain-general valuation demands. By varying the number of players in each ring (to manipulate mentalizing demands), as well as the number of choice options and choice structure (to manipulate domain-general representation requirements) from trial to trial, we develop a full, subject-specific, psychometric characterization of behavior in an array of social interactions. We identify subject-specific capacity constraints, namely, the percentage of games she was able to reason about, and then point at each subject's position along the valuation-social tradeoff axes.
Conclusions: This framework suggests a novel approach for examining social interactions, and can be applied to neuroimaging, to study tradeoff mechanisms between reward and social cognition networks in the brain, as well as to the study of pathologies in disorders of social cognition.

Disclosures: V. Kurtz David: None. **A. Brandenburger:** None. **P.W. Glimcher:** A. Employment/Salary (full or part-time):; New York University.

Poster

P777. Modeling and Behavior II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P777.02

Topic: H.03. Decision Making

Support: Horizon 2020 785907 SGA2

Title: Action Consequence during Reward-Driven Decision-Making

Authors: M. DEPASS, G. CECCHINI, ***I. COS**;
Univ. de Barcelona, Barcelona, Spain

Abstract: Characterizing Action Consequence During Reward-driven Decision MakingAuthors*M. A. DePass, G. Cecchini, I. Cos; Faculty of Mathematics & Informatics, University ofBarcelona, Barcelona, ES**DisclosuresM. A. DePass:** None. **G. Cecchini:** None. **I. Cos:** None.**Abstract**Previous research reported neurobehavioral correlates of reward signals, reward prediction error,and even state-space representation throughout the learning process of stimulus-response anddecisional patterns. However, a detailed characterization how the consequences of makingspecific actions influences decisions between them, remains to be properly formalized (Palidis etal., 2020; An et al., 2019; Akam et al., 2021). To this end, we developed a novel decision-makingparadigm, to be performed by human participants. We explicitly parameterized consequencewhich we defined as the change a decision may exert on subsequent ones, which could assumeone of four levels (zero, low, medium, high). A Latin square design was used to reduce potentialorder effects. We then fit reinforcement learning models to the behavioral data. We found model-free models could fit the behavioral data in the absence of consequence; however, in the presenceof consequence, a model combining model-free & model-based learning best replicated ourbehavioral data. Moreover, we found the RL learning rates correlated to the magnitude of actionconsequence. For some participants (n=2), LFP and EEG were recorded during task executionfrom the anterior insular, hippocampal, and orbitofrontal brain regions. We found the magnitudeof action

consequence could be decoded from power spectral density, spectral magnitude, andfrom electrode pair-wise correlation in these brain regions (with the largest contribution comingfrom the anterior insula). Network-like representations of the functional connectivity underlyingeach consequence level were also calculated. Finally, we fit generalized linear models to the dataand determined that consequence and reward can, in fact, be disambiguated as they havedifferential influences on several neurobehavioral metrics. Our results support the notion thataction consequence, though seldom analyzed, is a key metric that should be investigated; and,though it is often related to reward, can be disambiguated from it.

Disclosures: M. Depass: None. **G. Cecchini:** None. **I. Cos:** None.

Poster

P777. Modeling and Behavior II

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Program #/Poster #: P777.03

Topic: H.03. Decision Making

Title: Inverse reinforcement learning to infer multiple intentions behind decision-making in a bandit task

Authors: *K. NAKANISHI[1], S. KOTANI[1], S. HIROSE[1], Y. YAMASHITA[2], K. KATAHIRA[3], S. SUZUKI[4], M. FUKUSHIMA[1];
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Abstract: Computational psychiatry has attempted to uncover individual characteristics of computations in decision-making (i.e., computational phenotypes) associated with psychiatric symptoms by computational modeling in order to overcome the imprecise nature of psychiatric nosology. In this study, we propose an inverse reinforcement learning (IRL) algorithm combined with a clustering method, aiming to provide novel insights on the computational phenotypes in decision-making tasks. IRL is a promising technique to infer intention behind decision-making from a reward/cost function under a Markov decision process (MDP) formalism. The proposed algorithm is based on a well-known probabilistic maximum entropy IRL technique, the guide cost learning (GCL). Our approach estimates a reward/cost function for each cluster representing a group of state-action trajectories associated with decision-making. Although our approach applies to a broad class of decision-making tasks, the current study focuses on a three-armed bandit task with time-varying reward probabilities. When people play the bandit task, they can act based on obtained information that is updated as the task progresses. To represent such a process and formulate an IRL problem, we introduce an information state. Specifically, we apply the volatile Kalman filter (VKF) to calculate the information state for each participant playing the task. The VKF is an extended Kalman filter algorithm for a volatile environment as in the bandit task. The proposed algorithm takes the information states and actions (i.e. selected arms) of multiple participants as the input of state-action trajectories. Then, it alternately performs clustering the trajectories and estimating the reward/cost functions until the cluster assignment becomes stable. Here, we take a non-parametric Bayesian approach for the clustering, using the Dirichlet process mixture model without

pre-specifying the number of clusters (i.e. the number of distinct reward/cost functions). We confirmed that the proposed algorithm groups the state-action trajectories of the multiple simulation agents (e.g. greedy agent) correctly into the clusters, each corresponding to the known intention. Finally, we apply the proposed method for the data obtained from human participants performing the bandit task. Thus, our approach suggests a new computational phenotype to evaluate information processing underlying decision-making in both psychiatric and normal populations.

Disclosures: K. Nakanishi: A. Employment/Salary (full or part-time):; Deloitte Touche Tohmatsu LLC. **S. Kotani:** A. Employment/Salary (full or part-time):; Deloitte Touche Tohmatsu LLC. **S. Hirose:** A. Employment/Salary (full or part-time):; Deloitte Touche Tohmatsu LLC. **Y. Yamashita:** None. **K. Katahira:** None. **S. Suzuki:** None. **M. Fukushima:** A. Employment/Salary (full or part-time):; Deloitte Touche Tohmatsu LLC.

Poster

P777. Modeling and Behavior II

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Title: Using process models to disentangle stimulus-driven and controlled processes during value-based decision making

Authors: *H. RITZ, R. FRÖMER, A. SHENHAV;
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Abstract: There is growing interest in neuroeconomics in how cognitive control over value based decision making allows people to flexibly change how they make choices. Grounded in motivated control research, a recent theory by Vassena, Deraeve, & Alexander (2020) proposed that people recruit cognitive control to invigorate responses when difficult decisions won't make a deadline. To support this proposal, the authors fit a drift diffusion model (DDM) to participants (n=22) making value-based decisions under a short response deadline (750ms). They show that participants had a lower response threshold for difficult decisions, and interpret this as an index of controlled invigoration. Here, we critically examine the theoretical and empirical support for this proposal. First, we reanalyzed data from this study, and found that previous evidence for value-based invigoration (threshold changes) was an artifact of model misspecification. Once accounting for features of these data that were overlooked in the original DDM implementation (e.g., influences of decision urgency and overall set value), we no longer find that thresholds decreased with decision difficulty. Second, we show that a well-characterized and biologically plausible model of value-based choice (the leaky competing accumulator) can parsimoniously account for the features of these and similar datasets, without requiring an additional vigor-based controller. Together, our results suggest that the controlled invigoration theory of decision-making currently lacks empirical

support, and that its proposed mechanism may in most instances be obviated by existing models of value-based choice that lack such a control mechanism. More generally, our work demonstrates potential sources of mimicry between parameters of decision models that may lead to misattributions of control to evidence accumulation processes that are instead primarily stimulus-driven.

Disclosures: H. Ritz: None. **R. Frömer:** None. **A. Shenhav:** None.

Poster

P777. Modeling and Behavior II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P777.05

Topic: H.03. Decision Making

Support: Simons Foundation for Autism Research, Bridge to Independence Award

Title: Information sampling for trust decisions in children with autism

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Abstract: In humans, a significant shift in trust and cooperation is expected to occur in pre-adolescence but the changes in underlying strategies remain unknown. It is also unknown whether typically developing (TD) children differ from children with Autism Spectrum Disorder (ASD) in their cooperation strategies.To address this question, we used an information sampling trust game. Participants were told that trustees played the trust game 25 times with other players. They were then given the opportunity to sequentially sample information about each trustee's reciprocation history before deciding to invest or not. Unknown to them, trustee's reciprocation probabilities were computer generated and varied between 0 and 1.Our preliminary sample includes 42 TD (9.8 ± 1.8y) and 12 ASD children (11.2 ± 2.1y). We found that both TD and ASD groups invested more frequently when trustees reciprocated more in the past. This effect is modulated by age (older children invest more) and group (TD invested more) when trustee is more trustworthy. We also tested whether children's decisions to continue sampling was affected by the uncertainty about the trustee's intention to reciprocate. We found that both TD and ASD children sampled more when information was less conclusive, i.e., when the trustees made a similar number of decisions to reciprocate and defect in the past. This information sampling strategy was modulated by age. In the TD group, a quadratic age effect indicated that the youngest and oldest participants differentiated most between high and low uncertainty trials. In ASD, we found a linear age effect. Older participants sampled more information with higher information uncertainty. We investigate age and group related shifts in information sampling strategies in TD group only, due to our current smaller sample of ASD group. To test whether our models are robust and can be differentiated, we conducted model recovery and all models were recovered 100% on their own simulated data. We found that the behavior of TD participants was best described by a full Bayesian information updating model. To confirm our results, we performed a 10-fold cross validation, and our model predictions can generalize beyond the model fitted data. Overall, we found children adapt information sampling and cooperation decisions to the reciprocation probability of their partners differently based on their age and social

cognition. A normative Bayesian model best described TD participants' strategy. In a next step, we will describe differences in sampling strategies of children with ASD and investigate whether strategies predict behavioral and neural signatures of sustained cooperation and autistic traits.

Disclosures: W. Liu: None. **N. Shah:** None. **I. Ma:** None. **G. Rosenblau:** None.

Poster

P777. Modeling and Behavior II

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P777.06

Topic: H.03. Decision Making

Title: An online game to assess evidence accumulation and rule learning in humans

Authors: *Q. DO[1], G. KANE[2], J. T. MCGUIRE[3], B. B. SCOTT[4];
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Abstract: Pulse-based accumulation of evidence tasks have been used in human and animal studies to evaluate working memory and perceptual decision making. Here we developed an online game that trained humans with feedback on a visual pulse-based evidence accumulation task. We evaluated the performance of human subjects on this task, and compared the performance of those trained with feedback alone versus those who were given explicit written instructions and feedback. Across both groups, human performance was well described by a model in which choices were determined by the difference in the number of flashes, previous reward location and a side bias. Error rates were consistent with a scalar variability model of perceptual noise accumulation. No significant difference between subjects trained with feedback versus those given both feedback and written instructions was observed and learning through feedback could be achieved in 10 trials. These results suggest that online games inspired by pulse-based accumulation tasks provide a valuable behavioral assessment platform to examine perceptual decision making and learning in humans. In addition, the feedback-based training pipeline developed for this game may be useful in evaluating perceptual decision making in human populations with difficulty following verbal instructions.

Disclosures: Q. Do: None. **G. Kane:** None. **J.T. McGuire:** None. **B.B. Scott:** None.

Poster

P777. Modeling and Behavior II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P777.07

Topic: H.03. Decision Making

Title: The effect of memorability on food choice: do people prefer more memorable foods?

Authors: *X. LI, W. A. BAINBRIDGE, A. BAKKOUR;
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Abstract: Making adaptive decisions often relies on memory; the latter allows past experiences with choice options to guide actions. But not all memories are created equal. Some items are better encoded into memory than others; i.e. some choice options are more memorable. However, the effect of memorability on choice is unknown. We propose that more memorable food items are more likely to be chosen than less memorable foods of equal subjective value. To test this prediction, we first measured the memorability scores of 138 images of food. Participants (N = 199, 35% women, age ranges between 18-35) were presented with a series of images and asked to respond with a button press when the image on the screen was seen before (i.e., when the image is old). The memorability score for each image was calculated as Corrected Recognition, which was significantly consistent across people ($p < 0.014$). We then conducted a value-based food choice experiment; a different sample of 44 participants (30% women, M = 30.93, SD = 4.17) viewed the same 138 food images in random order, and were asked to rate how much they prefer to eat each item (a measure of subjective value). After the rating phase, participants chose between two food items based on their personal preferences. The pairs of items were generated based on ranking of the indicated subjective values across items for each individual. Mixed-effects regression models replicated previous findings and showed that participants' choices were associated with their stated subjective values for food (*Odds Ratio (OR)* = 3.32, *CI* = 2.81 - 3.92, $p < .001$) and that participants spent more time making choices between options that were similarly valued (β = -0.04, *CI* = -0.06 - 0.02, $p < .001$). Exploratory analyses revealed that more memorable items tended to be perceived as tastier (β = 0.083, p = 0.004), and tastier foods tended to be rated higher on subjective value (β = 0.65, $p < 0.001$). However, contrary to our prediction, there was no significant relationship between item memorability and choice behavior (p = 0.91). This result suggests that intrinsic item memorability of foods does not influence decisions about what to eat, and perhaps value-based decisions more generally. We proffer that, rather than a unique attribute that drives choice, memorability may constitute but one attribute among many used for the construction of subjective value of individual items during decision making.

Disclosures: X. Li: None. **W.A. Bainbridge:** None. **A. Bakkour:** None.

Poster

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Program #/Poster #: P777.08

Topic: H.03. Decision Making

Support: ONR N00014-19-1-2571
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NSF 1829398

NSF 1625552

Title: Virtual Human Foraging Behavior Follows Predictions for Heavy-Tailed Search

Authors: *K. N. MOORE, C. YI, M. F. DUNNE, C. E. STERN, J. T. MCGUIRE;
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Abstract: Studies suggest humans and animals favor foraging strategies that allow them to broadly explore the global search environment in large "steps" punctuated by periods of concentrated local search ("heavy-tailed search"). Despite a variety of studies on human foraging, few studies have sought to replicate evidence for this search strategy, as opposed to random diffuse search, in a virtual open-field foraging task. To investigate the extent to which humans engage in heavy-tailed search strategies in a virtual environment, we studied human participants (ages 18-35, N=5, F=4) as they completed 2 sessions of a virtual coin foraging task. Participants were instructed to freely explore and to collect coins in the virtual field, which was surrounded by four walls. In each foraging bout, 100 coins were randomly dispersed, and 225 coins were predictably clustered in four Gaussian-distributed patches. Trajectory step lengths were extracted from 8 min foraging bouts (total N=100) by segmenting trajectories where turn angles exceeded 40 degrees. Maximum Likelihood Estimation was used to fit step-length distributions for participants' foraging bouts to probability density functions of common models in foraging literature including power law, lognormal, and exponential distributions. We analyzed frequency distributions for goodness-of-fit using Akaike Information Criterion (AIC). Frequency distributions of participants' search trajectories were best fit by the power law model for 8 out of 10 sessions. Participants' trajectories from individual foraging bouts were also best fit by power law models, fitting 54% of all foraging bout step length distributions (N=100), while the exponential model fit 41% of the foraging bouts, and the lognormal fit just 5% of the bouts. Analyses of the best fitting parameters of the power law model suggested that virtually all estimated power law exponents (μ=1.43, SD=0.12) fell within the predicted range for Lévy walks: $1 < \mu \leq 3$. These results indicate that virtual human foraging behavior, much like in the natural world, can be described as a heavy-tailed search process. The emergence of the power law model as the best fitting model for search trajectories and corresponding estimated model parameters suggest that power law distributions (e.g. Lévy walks) approximate foraging step lengths at a large scale. However, exponential (Brownian) movement patterns were also apparent in this data set. Additional analyses are necessary to better understand the conditions in which Lévy vs. Brownian motion predominates distributions of step lengths in a virtual environment.

Disclosures: K.N. Moore: None. **C. Yi:** None. **M.F. Dunne:** None. **C.E. Stern:** None. **J.T. McGuire:** None.

Poster

P780. Modeling and Behavior V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P780.01

Topic: H.03. Decision Making

Title: Inferential reasoning in monkeys

Authors: *F. BOUCHACOURT[1], S. TAFAZOLI[2], M. G. MATTAR[4], N. D. DAW[5], T. BUSCHMAN[3]; [1]Princeton Neurosci. Inst., Princeton, NJ; [2]Princeton Neurosci. Inst., [3]Princeton Neurosci. Inst. & Dept of Psychology, Princeton Univ., Princeton, NJ; [4]Dept. of Cognitive Sci., Univ. of California San Diego, San Diego, CA; [5]Princeton Neurosci. Inst. & Dept of Psychology, Princeton Universiry, Princeton, NJ

Abstract: When in a new situation, we have to infer which set of rules to use. For example, when entering a new restaurant, we use contextual cues to infer whether it is a sit-down or a fast-food restaurant. Once this is determined, we can apply a set of previously learned rules to guide our behavior in each context. In humans and monkeys, inferring a behavior is believed to happen in the prefrontal cortex. To understand how one learns to infer which rule is in effect, we trained two monkeys to perform a category-response task with multiple latent rules. The monkeys were trained on three different rules; each requiring them to categorize the color or shape of a stimulus. Changes in the rule were not cued, forcing the animals to determine which rule was in effect on each block based on reward feedback alone. The animals performed the task well, quickly switching between rules. To understand the mechanisms supporting behavior, we compared several classes of models including incremental learning and Bayesian inference models. Both classes of models produce learning effects - i.e., experience-driven changes in behavior - but with different patterns and neural predictions. However, only a noisy version of the inference model captures the key qualitative features of the data, including differences in performance and learning following stimuli that either had congruent or incongruent responses across the rules. These results suggest monkeys can use inferential reasoning when determining how to behave in an uncertain world.

Disclosures: F. Bouchacourt: None. **S. Tafazoli:** None. **M.G. Mattar:** None. **N.D. Daw:** None. **T. Buschman:** None.

Poster

P780. Modeling and Behavior V

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Program #/Poster #: P780.02

Topic: H.03. Decision Making

Title: Temporal Analysis of Learning Negative Values in Non-Human Primates

Authors: *H. STEALEY, Y. ZHAO, E. CONTRERAS-HERNANDEZ, SR, S. R. SANTACRUZ; Biomed. Engin., Univ. of Texas at Austin, Austin, TX

Abstract: Frequently, decision-making tasks are between two positive outcomes of which one is relatively more valuable. In tasks where negative outcomes are considered, often the “value” associated with it cannot be quantified with the task value system. However, recent work has demonstrated a behavioral task that allows negative outcomes to be quantified in terms of units of the positive outcomes, such as juice volumes (see Fiorillo, 2013). In this task, alternative juice volumes are presented to determine how much the subject is willing to sacrifice to avoid the negative outcome (bitter juice solution). Here, we expand on this work by developing a temporally precise reinforcement learning (RL) model, including parameters that account for total fluid intake, daily task learning, and changes in

aversiveness over shorter timescales (e.g. on the order of trials). First, we determined a concentration of denatonium benzoate (bitter agent) so that the subject was equally likely to choose the standard option (e.g. 180 µL bitter juice) over an alternative option (e.g. 110 µL juice only) to determine the relative difference or "negative value" of the denatonium (e.g. -70 µL). Then, our subject performed a decision-making task in which they were presented with one of five trials types every five trials in which each trial type was the standard juice only option (180 µL bitter juice) against one of the five alternative juice only options with relative differences of -210 µL, -140 µL, -70 µL, 0 µL, or +70 µL. Each trial type was denoted by a specific stimulus color, and colors were not changed between experimental days. With our RL model, we demonstrate the relative influences that aversiveness, relative value, time, and learning have on changes in choice behavior for each trial type. This is a powerful framework to determine neural correlates of choice behavior with negative outcomes.

Disclosures: H. Stealey: None. **Y. Zhao:** None. **E. Contreras-Hernandez:** None. **S.R. Santacruz:** None.

Poster

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Program #/Poster #: P780.03

Topic: H.03. Decision Making

Support: NRF2021R1F1A105202011
2018R1A4A1025891

Title: Distinct patterns of serial dependence of binary decision making in classification and categorization tasks

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Abstract: Distinct patterns of serial dependence of binary decision making in classification and categorization tasks
Classification and categorization have long been favored as task platforms for studying cognitive operations underlying perceptual decision-making. Despite their similarity on the surface, the two tasks fundamentally differ in statistical structure: classification requires sorting the items within a single population into two halves according to their relative quantities (e.g., "His pet seems big for a pet") whereas categorization requires selecting between two alternative populations from which given items are sampled based on their quantities (e.g., "It seems a dog rather than a cat by its size"). Thus, according to the Bayesian decision-making theory, which posits that ideal observers combine their knowledge about the statistical structure of a given task with the present evidence to infer the world state of interest, ideal classifiers and categorizers should learn differently as they make a sequence of decisions. Specifically, the former classifier always updates the single population distribution for each instance (e.g., the average size of pet animals increases whenever seeing a pet of an above-average size) whereas the latter categorizer selectively updates only one of the two population distributions to which a given instance belongs (e.g.,

only the average size of dogs, but not that of cats, increases after seeing a dog of an above-average size). Consequentially, it is implied that Bayesian observers' choices show distinct patterns of serial dependence on previous stimuli and choices depending on whether they perform a classification or categorization task: (i) classifiers either alternate or repeat choices depending on memory noise whereas categorizers repeat choices; (ii) classifiers' and categorizers' choices are both repelled against previous stimuli, but repulsion being more pronounced in the former. We subjected these implications to empirical tests by regressing human observers' binary choices onto previous choices and stimuli, respectively in classification and categorization tasks. The observed regression coefficients were highly consistent with the model implications on serial dependence. Our findings suggest that humans indeed deploy distinct cognitive algorithms when classifying and categorizing, as implicated by the distinct statistical structures of the two tasks.

Disclosures: H. Lee: None. **S. Lee:** None. **H. Lee:** None. **K. Choe:** None.

Poster

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Program #/Poster #: P780.04

Topic: H.03. Decision Making

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Title: Tdcs restores natural decision-making performance in simulated network with excitatory-inhibitory balance

Authors: *P. ADKISSON[1], S. XU[3], G. FRIDMAN[1], C. R. STEINHARDT[2];
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Abstract: Transcranial DC stimulation (tDCS) has been shown to affect decision-making tasks, despite open questions regarding its mechanism of action. Recent evidence suggests that the behavioral effects of tDCS may be largely explained by stimulation-induced changes in the effective excitatory-inhibitory (E-I) balance of the targeted brain region. In this study, we developed a computational model to more closely emulate the natural cortical physiology subjected to tDCS. We extended a standard attractor model to one with two excitatory cortical populations connected via an inhibitory intercortical population, where each cortical population had a mixture of excitatory and inhibitory neurons. The E-I balance of each cortical population was varied in steps of 0.2 between 0-0.8 (portion of inhibitory neurons), while the intercortical population remained entirely inhibitory. The extended model was used to replicate the Javadi et al. (2015) visual two alternative forced choice task decision-making study, where left versus right choice indicated a gradient from a tall to long rectangle. The model took object "tall-ness" saliency as direct excitatory input to cortical populations, and tDCS was introduced an ionic current input to cortical neurons. We found that increasing the proportion of inhibitory neurons increases network decision time. Physiologically relevant

decision-making times (0.2-1 sec) were observed only when E-I balance was less than 0.4. Cortical populations with E-I balance of 0.6 (emulating pathological E-I imbalance) resulted in a 5-fold increase in decision time. When tDCS was introduced to the network with an E-I balance of 0.6, it reduced the decision time by 1.5 times (N=50 trials), suggesting that tDCS can reverse the network-level effects of E-I imbalance. At E-I balance of 0.4 and lower, tDCS had reduced effects that nevertheless matched those observed experimentally. These findings suggest tDCS may act as a target treatment that can reverse network-level pathologies deriving from E-I imbalance. They also provide concrete testable hypotheses about how tDCS affects both healthy and those suffering from neural disorders.

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Poster

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Topic: H.03. Decision Making

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2R01EY022979

Title: Choice-tuned inhibition supports decision-making though competition in recurrent neural networks.

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Abstract: In decision-making circuits, the firing rates of choice-tuned neurons are modulated by an upcoming choice. Neural circuit are an indispensable tool for understanding how choice-tuning accounts for decision-making computations. These models have primarily considered excitatory choice-tuning and have highlighted the importance of highly structured connections between choice-tuned excitatory populations. However, these models treat inhibitory neurons as an untuned and nonselective pool within these circuits. There is growing evidence for inhibitory choice and stimulus tuning in cortical areas important for perceptual decision-making. Here we aim to expand the explanatory power of decision-making circuit models by considering cases where inhibitory neurons are choice-tuned. We trained recurrent neural networks (RNNs), consisting of excitatory and inhibitory neurons, to perform a decision-making task. The task required the network to compare two inputs to the excitatory populations and report which is higher by increasing one of two outputs. We found that RNNs had similar fractions of choice-tuned excitatory and inhibitory neurons. Networks displayed a consistent circuit structure where excitatory-to-excitatory (EE) and excitatory-to-inhibitory (EI) connections tended to link similarly tuned neurons and inhibitory-to-excitatory (IE) connections tended to link oppositely tuned neurons. This result reveals a common motif where decisions are driven by recurrent excitation and competitive inhibition. To evaluate the importance of this common motif on the decision-making function of the circuit we shuffled the outputs of the top 10% of choice-tuned neurons. Shuffling EE connections lead to a large decrease in

performance, while shuffling EI and IE connections lead to a more moderate decrease in performance. In each case the performance reduction resulted from an increased rate of trials without a choice. When shuffling the outputs of neurons that were active, but were in the bottom 10% of choice-tuned neurons a significantly smaller performance reduction was observed. These results indicate that RNNs find a common solution to a decision-making task driven by selective recurrent excitation within choice-tuned populations and supported by competitive inhibition from choice-tuned inhibitory neurons. Inhibitory choice-tuning emerges naturally in the training process, even though these neurons receive no direct stimulus information, suggesting that dedicated pools of inhibition for each choice-tuned subpopulation could be a requirement for decision-making circuits.

Disclosures: J.P. Roach: None. **A.K. Churchland:** None. **T.A. Engel:** None.

Poster

P780. Modeling and Behavior V

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Program #/Poster #: P780.06

Topic: H.03. Decision Making

Title: A meta-reinforcement learning network exhibits model-based behavior via an augmented state representation in the two-step decision making task

Authors: *J.-A. LI, M. G. MATTAR;
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Abstract: Striatum and prefrontal cortex (PFC) both play critical roles in reward-driven reinforcement learning (RL). In the striatum, phasic dopamine driving synaptic plasticity represents prediction errors of model-free temporal-difference RL algorithms. In comparison, the neuronal dynamics in PFC is thought to implement flexible model-based RL algorithms. The meta-RL framework offers a promising perspective to reconcile the roles of striatum and PFC on decision making (Wang et al., 2018). In this framework, striatal model-free prediction errors are used to adjust the synaptic weights of the PFC network to implement a model-based algorithm through neural dynamics. However, it is not clear which model-based algorithm emerges from the learning process of meta-RL networks. To address this question, we trained a recurrent neural network (LSTM units with Advantage Actor-Critic architecture) on the two-step task (Daw et al., 2011). In this task, each trial consists of two stages: in the first stage, the agent selects one of two actions (A1 or A2), which probabilistically leads to one of two second-stage states, S1 or S2. Each second-stage state leads to a different probability of a unit reward, with the most valuable state switching stochastically. Our networks achieve near-optimal performance in this task. Projecting the neural dynamics onto the top three principal components of the hidden-layer state space, we found that the neural activity lies on four approximately parallel lines (edges) of a cube spanned by three roughly orthogonal axes: a second-stage state axis (S1 or S2), a reward axis (reward of 0 or 1), and an action axis encoding action probability favoring A1 or A2. To elucidate the mechanism determining these lines, we fit cognitive models to the networks' behavior (following Akam et al., 2015), including model-free Q(0), model-free Q(1), model-based (MB), reward-as-cue, and latent-state (LS) models. The MB and LS models provided the best fits. Surprisingly, the trial-by-trial choice probability in the LS model, but not in

the MB model, was consistent with the action probability on each line. Together, these results suggest that our meta-RL networks use an augmented state representation to exhibit apparent model-based behavior in the two-step task.

Disclosures: J. Li: None. **M.G. Mattar:** None.

Poster

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Program #/Poster #: P780.07

Topic: H.03. Decision Making

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Title: Neural mechanisms of optimism bias in learning

Authors: *F. TALEB[1,2], S. FARASHAHI[3], A. SOLTANI[4];
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Abstract: There is growing behavioral evidence that reward learning is adjusted according to different aspects of the reward environment. Such adjustments in learning are often measured by estimating the so-called learning rates via fitting choice behavior with different reinforcement learning (RL) models. Although the estimated learning rates vary between tasks and experimental conditions, there is recent evidence that their values exhibit certain regularities. For example, it has been shown that the learning rate for updating the reward value of the chosen option is larger for rewarded than unrewarded outcomes, a phenomenon referred to as optimism bias. Although a few normative accounts (mainly based on reward optimization) for such asymmetry in learning rates have been proposed, the underlying neural mechanisms are still unknown. To address this, we re-examined behavioral data during three related learning tasks but with different levels of complexity and across three species: (1) probabilistic reversal learning in mice in which two choice options provided reward with different probabilities that reversed between blocks of trials; (2) probabilistic reversal learning with additional reward magnitude in monkeys where in addition to reversals in reward probabilities, different reward magnitudes were presented on the two options in each trial; (3) multi-dimensional probabilistic reversal learning (MdPRL) in humans in which choice options had two features predicting reward probabilities that underwent reversals. Moreover, we tested the ability of two different mechanisms for explaining the observed adjustments in learning: reward-dependent metaplasticity (RDMP) and mixture of experts (MoE). By fitting choice behavior using standard RL models but with either two learning rates (α_+ and α_- for rewarded and unrewarded outcomes) or four learning rates (α_{b+}, α_{b-}, α_{w+}, α_{w-} for rewarded and unrewarded outcomes on the better and worse options) we found evidence for optimism bias ($\alpha_+ > \alpha_-$) in all three tasks. Importantly, we found that this asymmetry was accompanied by opposing patterns of the learning rates for the better and worse options: $\alpha_{b+} > \alpha_{b-}$ and $\alpha_{w-} > \alpha_{w+}$. These results were compatible with simulations based on the

RDMP model that adjusts learning according to regularities of the reward environment. Moreover, simulations of choice behavior during the three tasks using the MoE model revealed consistent results but based on very different mechanisms: i.e., larger weighting of experts with $\alpha_+ > \alpha_-$ on choice behavior. Together, our results suggest that very different mechanisms could account for the observed optimism bias in learning.

Disclosures: F. Taleb: None. **S. Farashahi:** None. **A. Soltani:** None.

Poster

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Topic: H.03. Decision Making

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Title: Evolving Memory: From Simple Foraging Associations to Cognitive Map Construction

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Abstract: Cognitive mapping builds internal representations of the world and is essential to episodic memory and mental imagery. Here we show how circuitry of basic foraging decision can be straightforwardly expanded for affective valuation and cognitive map construction in the agent-based foraging simulation, ASIMOV, reproducing likely evolution.
Behavioral choice in foraging is governed by reward learning and motivation, which interact to assign subjective value to sensory stimuli. These qualities characterize foraging generalists that hunt in variable environments, and are precursors to more complex memory systems. ASIMOV's core decision network is based on neuronal circuitry of cost-benefit decision in the predatory sea-slug *Pleurobranchaea californica*. ASIMOV's virtual forager affectively integrates sensation, motivation (hunger), and learning to make cost-benefit decisions for approach or avoidance of prey, providing reward and nutrition upon consumption. Olfaction is used for both odorant discrimination and spatial navigation.
We developed a Feature Association Matrix (FAM) with reward learning and hippocampus-like sequence learning to map and establish relations. It does the basic tasks as most models of hippocampal function, but with much less computational demand. For sets of inputs or features, like sensation and reward, the FAM memorizes presented sequences by changing associative strengths between pairs of inputs. Expected reward values are assigned to each association, allowing replay of memorized sequences. Memorized sequences may be unlearned if no longer presented or rewarded, and if there are other presentations of competing sequences.
We show how sequence memorization is achieved by chaining pair-wise associations made through simple higher-order conditioning mechanisms. Spatial learning for distant landmarks in terms of direction and distance is enabled by a simple path integration system. Addition of the FAM's spatial and episodic

memory to ASIMOV's forager shows how the neuronal circuitry of foraging decision can serve as the framework for cognitive mapping in evolution.

Disclosures: E.D. Gribkova: None. **R. Gillette:** None.

Poster

P780. Modeling and Behavior V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P780.09

Topic: H.03. Decision Making

Support: NIH Grant MH118925

Title: Planning in monkeys during an abstract strategy board game

Authors: *M.-Y. PARK[1], B. V. OPHEUSDEN[2], H. LIANG[1], M. OEMISCH[1], K. OSBORNE[1], W. MA[3], D. LEE[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Princeton Univ., Princeton, NJ; [3]New York Univ., New York, NY

Abstract: Making sequential decisions in dynamic social settings requires agents to search, evaluate, and optimize alternative strategies according to the current state and desired outcomes. To investigate the dynamics of learning and sequential decisions and the underlying neural mechanisms, we trained two monkeys to perform a simplified form of Go-Moku, namely Four-in-a-Row (different from Connect Four). The monkeys used a joystick to place their pieces on a 4-by-9 board, one at a time, taking turns with a computer opponent. A player could win by placing four pieces in a row horizontally, vertically, or diagonally. The game outcome could be a win, loss, or tie for the animal, which was rewarded only for wins.
We trained both monkeys to gradually become familiar with the rules of the game, by using stages of increasing difficulty. In the beginning, the monkeys were given two or three pieces that were already connected, and learned to complete a pattern of 3 or 4 in a row by choosing one of several cued locations in the board. Both animals learned to choose the locations to complete the desired patterns even if the distance of the choice from the existing pieces was not the closest compared to the other choices. Throughout training, both animals also tended to complete the 4-in-a-row patterns horizontally more frequently than vertically or diagonally.
Good performance in the Four-in-a-Row game requires a player to prevent the opponent from winning by predicting the future states of the game resulting from the opponent's choices. We found that the proportion of winning in which the animal actively blocked the opponent's winning move steadily increased from 26% to 41% during training. These results demonstrate that an abstract board game can provide a useful platform to investigate the neural mechanisms of sequential decision making.

Disclosures: M. Park: None. **B.V. Opheusden:** None. **H. Liang:** None. **M. Oemisch:** None. **K. Osborne:** None. **W. Ma:** None. **D. Lee:** None.

Poster

P780. Modeling and Behavior V

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Program #/Poster #: P780.10

Topic: H.03. Decision Making

Support: P50MH119569
R01MH123661

Title: Sex modulates the role of noradrenergic signaling in the exploration-exploitation tradeoff

Authors: *C. S. CHEN[1], E. KNEP[1], D. MUELLER[1], B. A. EBITZ[3], N. M. GRISSOM[2];
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Abstract: In an uncertain world, we balance two goals: exploiting rewarding options when they are available, and exploring potential better alternatives. Individuals approach this problem with divergent explore-exploit strategies, but we know little about the neural bases of this interindividual variability. One major axis of interindividual variability in executive function and decision-making is sex. Sex significamtly modulates the locus coeruleus-norepinephrine (LC-NE) system, which has long been thought to underpin exploration and learning. However, it remains unclear how the balance between exploration and exploitation differs across sexes, and whether noradrenergic signaling contributes to these sex differences. Here, we systemically administered propranolol (5mg/kg), a non-selective β-adrenergic receptor antagonist, and isoproterenol (0.3 mg/kg), a non-selective β-adrenergic receptor agonist, in male and female mice in a restless two-arm bandit task, using a within-subject design. In this restless bandit task, mice chose from two options that were associated with certain reward probabilities, which changed independently and stochastically over trials. Thus, animals could only infer values through sampling and integrating reward and choice history. We found that propranolol administration (NE antagonist) resulted in "stickier" choice behaviors, reflected in increased win-stay behaviors and decreased lose-shift behaviors compared to controls. The modulatory effects of propranolol on choices were stronger in males than females. On the other hand, there was no significant difference in win-stay behaviors between control and isoproterenol (NE agonist) group. A Hidden Markov model (HMM) was fitted to infer latent state of exploration and exploitation. The result suggested that propranolol decreased the probability of exploration in both males and females, with a stronger modulatory effect on males than females. Fitting reinforcement learning models revealed that blocking noradrenergic beta receptors with propranolol reduced the level of decision noise without affecting learning rate. Together, these results suggest that a novel, sex-modulated role for LC-NE system in differentially regulating exploration via regulating behavioral stickiness, rather than the rate of learning, across sexes.

Disclosures: C.S. Chen: None. **B.A. Ebitz:** None. **N.M. Grissom:** None.

Poster

P780. Modeling and Behavior V

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Program #/Poster #: P780.11

Topic: H.08. Learning and Memory

Support: NIH Grant 1R01MH126351
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NIH Grant K99EB027706
Paul and Lilah Newton Brain Science Research Award

Title: Shifts in learning strategies underlie rodent behavior during dynamic foraging

Authors: *N. M. LE[1], M. YILDIRIM[2], H. SUGIHARA[2], Y. WANG[1], M. SUR[1];
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Abstract: In uncertain foraging environments, a critical problem agents face is how to adapt their learning in accordance with the uncertainty of the environment and knowledge of the hidden structure of the world. In this context, previous studies distinguished between two modes of learning: model-free learning updates action values while balancing between exploration and exploitation, while inference-based behavior leverages knowledge of world's dynamics to infer the current state of the world. However, it is unclear how these behavioral strategies can be cleanly distinguished based on behavioral data and how animals transition between these modes during training. Here, we tackled these questions by examining rodent behavior in a dynamic foraging task. We trained head-fixed mice to select between two choices, left and right wheel turns. Only one direction was rewarded in each trial, and the target direction changed in blocks of 15-25 trials. To determine whether rodent behavior was better described by the model-free or inference-based strategies during learning, we simulated choice sequences of model-free and inference-based agents to gain insights into their behavioral signatures. Our model-free agent implements a Q-learning algorithm, while the inference-based agent performs Bayesian inference assuming a 2-state model of the world. We identified four criteria to characterize the behavior of these agents and used them to fit rodent behavioral data: the slope and offset of their switching decisions, the degree of exploration, and the relationship between switching and the performance in the previous block. Across all animals, we observed a consistent decrease in the times to switch the wheel turn direction, and a decrease in the degree of exploration with training. By performing a model comparison using log-likelihoods, these observations were better explained by a transition from model-free to inference-based mode of learning, as opposed to an increase in learning rate in a model-free agent. A 3-state Hidden-Markov model was fitted to the rodent behavioral data, revealing transitions between left-exploit, right-exploit and exploratory states. The duration of exploratory states decreased with training, consistent with the transition to the inference-based strategy. These analyses and characterizations form the basis of understanding shifts in behavioral strategies during dynamic foraging. Together with widefield calcium imaging across the whole cortex during the task, they will be important for identifying unique neural signatures of global brain states that are associated with distinct modes of learning.

Disclosures: N.M. Le: None. **M. Yildirim:** None. **H. Sugihara:** None. **Y. Wang:** None. **M. Sur:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P789.01

Topic: H.03. Decision Making

Support: NSFC (32071095, 31671171, and 31630034 to L.Z.)

Title: Separable neurocognitive changes underlie the development of communicative reasoning in adolescence

Authors: *C. WANG, M. CONG, Q. MI, G. YU, Y. SU, L. ZHU;
Peking Univ., Beijing City, China

Abstract: Humans possess a remarkable ability to read between the lines. Prior research suggests that decoding what is meant from what is said involves intertwining cognitive operations, such as inhibiting the literal interpretation of a communicative signal, and recovering the speaker's most probable intention based on context. Despite recent progress in understanding the neural bases of communicative reasoning, little is known about when and how humans acquire this ability, and whether basic cognitive functions such as executive control and social reasoning would interact with one another in support of its development. Combining computational modeling, cross-sectional and longitudinal fMRI data, we examined the neurobehavioral changes in communicative reasoning during the transition in and out of adolescence—a period critical for the development of both cognitive and social functioning.
A total of 316 subjects (ages 8-24, fMRI N = 141, behavior N = 175) participated in the experiment, among which 53 fMRI subjects were scanned twice, spanning 1.7-year. The ability of communicative reasoning was assessed using the combination of a well-established referential communication game, previously used to elucidate the neurocomputations underlying communicative reasoning in adults.
The accuracy of communicative reasoning continuously increases with age in both cross-sectional and longitudinal data. According to results from the cross-sectional fMRI data, such age-related performance changes are related to (i) increased involvement of reasoning about speaker's choices when interpreting speakers' messages, subserved by the changes in the engagement of ventromedial prefrontal cortex across age, and (ii) decreased egocentric processing of communicative contexts, subserved by the changes in sensory cortical activity. Importantly, longitudinal data further suggest that the contributions of the two processes are differentially modulated by changes in the activation of the frontoparietal network (FPN) during communicative interpretation.
These results suggest a prolonged development of communicative reasoning over the entire period of adolescence. It likely involves a delicate balance between the egocentric processing of sensory information and the reasoning about social partners, which is likely linked with the development of FPN functioning, previously implicated in executive control in adolescence. These results suggest a potential mechanism by which the maturation of communicative reasoning is shaped by separable, yet interacting neurocognitive processes.

Disclosures: C. Wang: None. **M. Cong:** None. **Q. Mi:** None. **G. Yu:** None. **Y. Su:** None. **L. Zhu:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P789.02

Topic: H.03. Decision Making

Title: Neural correlates of responsibility for inequality

Authors: *J. SCHULTZ;
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Abstract: People dislike inequality. More specifically, people are averse to unequal outcome distributions, and experience negative social emotions when subjected to unequal outcomes. Being responsible for negative social outcomes also leads to negative social emotions, such as guilt (Berndsen et al., 2004; Zeelenberg & Breugelmans, 2008). Together with inequity aversion (Bolton & Ockenfels, 2000; Charness & Rabin, 2002; Fehr & Schmidt, 1999), guilt aversion is considered one of the major factors influencing social decision-making (Fehr & Schmidt, 2006). Better understanding the neural mechanisms involved in experiencing such social emotions may allow to better understand human social behaviour and its variations. Here, we aimed to study the neural mechanisms involved in experiencing responsibility for inequal outcomes using a risky social choice task about monetary rewards. In a series of trials performed during functional magnetic resonance imaging, participants or a partner repeatedly chose between a lottery or a safe option. The outcome of each decision affected both participant and partner. If the lottery was chosen, unequal outcomes (either advantageous or disadvantageous for the participant) ensued in 50% of cases. Outcomes were revealed after each choice, and participants reported their momentary happiness every second trial. Linear mixed models revealed that both advantageous and disadvantageous inequality reduced participants' happiness [$t(458) = -8.02$, $p << 0.001$; $t(465) = -15.64$, $p << 0.001$, respectively]. Crucially, participants' happiness was lower after advantageous inequality resulting from their own rather than their partner's decisions [$t(457) = -3.1488$, $p < 0.002$]. Analysis of fMRI data revealed clusters of voxels in dorsomedial prefrontal cortex (dmPFC), precuneus, bilateral temporo-parietal junction, insula and inferior frontal gyrus with significantly higher BOLD signal when participants experienced unequal compared to equal outcomes. Among those regions, a cluster in dmPFC (peak MNI coordinates = 4, 48, 44; $Z = 4.49$) showed higher activity during the occurrence of unequal than equal outcomes when these outcomes resulted from decisions of the participant rather than the partner (interaction). All reported neuroimaging results survive thresholding at $p = 0.05$ corrected for multiple comparisons (FWE) at the voxel or cluster level. Our results thus suggest that the dmPFC is a part of the neural mechanisms engaged when experiencing unequal outcomes for which one is responsible.

Disclosures: J. Schultz: None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P789.03

Topic: H.03. Decision Making

Support: W911NF-10-2-0022

Title: Shifting Expectations: Criterion shift association of Electroencephalography, in a recognition memory security patrol paradigm.

Authors: *C. G. BOARDMAN[1], E. A. LAYHER[1], M. B. MILLER[1], J. M. VETTEL[2];
[1]Univ. of California Santa Barbara Neurosci., Santa Barbara, CA; [2]CCDC Army Reserch Labratory, Adelphi, MD

Abstract: Depending on the situation, it may be prudent to switch between a liberal and a conservative criterion. For instance, security personnel should maintain a liberal criterion when questioning individuals at a security checkpoint. However, when use of physical force on suspected individuals is anticipated, a conservative criterion should be used to minimize the risk of harming a potentially innocent person. Here we use EEG to explore the temporal and oscillatory dynamics associated with maintaining a conservative versus liberal criterion during a recognition security patrol task. We predicted that maintaining a conservative versus liberal criterion would be associated with a large positive event-related potential (ERP) peak around 300ms after stimulus onset (P3) and the more loosely defined late positive potential (LPP). Previously our work had indicated that the tendency to shift varies greatly between individuals, some shift easily while others do not shift at all. However individual tendency to shift is highly stable. We predicted that EEG oscillation power over time would be correlated with individual tendency to shift between liberal and conservative criterion placement.
In a screening task, we identified 31 EEG participants (aged 17-28, 7 male) who sufficiently shifted their criterion when instructed to focus on avoiding targeting innocent people in the conservative condition and to focus on avoiding missing suspicious people in the liberal condition. We found that maintaining a conservative versus liberal criterion is associated with a modest increase in frontal power ($F=10.54$, $p<0.003$, $r^2=0.20$) in the P3 range (600-850ms post stimulus), coinciding with large positive peaks in conservative>liberal contrast waveforms. Additionally, we created correlations between ERSP power (1-30 Hz) and individual tendency to shift. We averaged ERSP power over 193ms intervals, adjusted correlation p values using the Benjimaini and Hochberg method (fdr=0.05), and averaged over 9 brain regions (left, midline, and right, frontal, central, and posterior). We found high alpha and beta power was negatively correlated with individual tendency to shift across for hits and correct rejections, but not for misses or false alarms. This effect appeared in all brain regions when maintaining a liberal criterion, with the largest liberal correct rejection correlations around 13-21 Hz in the right prefrontal cortex (mean r=-0.59, mean adjusted p=0.006), from 300-3,000ms post stimulus. Overall, our results show maintaining a conservative criterion is associated with P3 and individual criterion shifting affects may be observed in oscillatory dynamics.

Disclosures: C.G. Boardman: None. **E.A. Layher:** None. **M.B. Miller:** None. **J.M. Vettel:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

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Program #/Poster #: P789.04

Topic: H.03. Decision Making

Support: NSERC Grant 2019-05786

Title: The resolution of stimulus- and action-based choices is mediated by different dynamics of brain oscillations.

Authors: *E. PIERRIEAU, J.-F. LEPAGE, P.-M. BERNIER;
Univ. de Sherbrooke, Sherbrooke, QC, Canada

Abstract: It has been shown that conflict processing in the context of instructed choices is associated with increased midfrontal theta, possibly driven by a microcircuit including the supplementary motor area and the midcingulate cortex, and involved in conflict detection and signaling through synchronization with task-relevant regions. Here we test whether similar modulations are also observed when conflict arises from action costs. 31 participants (15 females) performed an action selection task by reaching with their right arm toward one of two visual targets. In instructed choice trials, participants had to reach the target indicated by a central arrow, surrounded by peripheral arrows which directions could be congruent or not, thus manipulating the level of conflict (flanker task). In free choice trials, the presented stimulus was non-directional and participants could reach the target they preferred. Target positions were manipulated so that one target was biomechanically preferable or both targets were similarly preferable, thus inducing low and high conflict, respectively. Results showed that in spite of similar sensory input and motor output, brain oscillations were differently modulated by the context of choice. In instructed choices, conflict was associated with higher midfrontal theta power and lower contralateral sensorimotor beta power, a finding consistent with results from previous studies. However, these results were not observed in free choices, as conflict was rather associated with lower parieto-occipital beta power. Overall, these results indicate that the resolution of stimulus and action-based conflicts involves distinct circuitries, suggesting that this process is not centralized in the brain but instead differs depending on the level of abstraction of decisional variables.

Disclosures: E. Pierrieau: None. **J. Lepage:** None. **P. Bernier:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

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Program #/Poster #: P789.05

Topic: H.03. Decision Making

Support: Grant in Aid Japanese Government 20K20749
Grant in Aid Japanese Government 18H03612

Title: Functional connectivity of human risk decisions: Cognitive control and systematic deviation from risk neutrality

Authors: T. ASAMIZUYA[1], H. TAKESUE[2], S. OTA[3], *J. KATO[4];
[1]The Univ. of Tokyo, Tokyo, Japan; [2]Tokyo Metropolitan Univ., Tokyo, Japan; [3]Meiji Univ., Tokyo, Japan; [4]Grad. Sch. of Law and Politics, Tokyo, Japan

Abstract: <META NAME="author" CONTENT="加藤 淳子">Functional connectivity of human risk decisions: Cognitive control and systematic deviation from risk neutrality
Takeshi Asamizuya, Hirofumi Takesue, Shozo Ota, and Junko Kato
Human rational decision making is often considered based on objective evaluation of probabilities and outcomes. Prospect theory challenges this presumption and illuminates the systematic deviation of human decisions, i.e., risk aversions and risk seeking, respectively, when outcomes are framed as gain and loss. The psychological principles have attracted much attention of cognitive scientists, but the underlying brain mechanism is still unknown. This fMRI study estimated the value functions of risk decisions when subjects drew the lotteries both in the gain and loss framings and examined the functional connectivity across activated regions. Activation was found when making risk decisions in the BA 10, BA 32, the bilateral, ventral anterior insula, and the precuneus. When decisions were made along with prospect theory, i.e., risk aversion to gain outcomes and risk seeking of loss outcomes, the functional connectivity was strengthened from BA32 to BA10. The result implies that systematical deviation from risk neutral choices result from the connectivity of the regions implicated with cognitive control. Moreover, stronger connectivity from BA10 to BA32 was specific to risk seeking in expectation of losses, but the bilateral connectivity between the right anterior insula and BA32 was strengthened only by risk aversion expecting gains. Connectivity between the precuneus and the left anterior insula was just the opposite, i.e., strengthened from the precuneus in risk aversion for gains but from the left anterior insula in risk seeking to avoid losses. Overall, our functional connectivity analyses imply that the systematic deviation from risk neutrality result from the working of cognitive control. Social cognition might play a role in risk aversion in gain framing, but metacognition, that is, high executive control, in risk seeking in loss framing.

Disclosures: T. Asamizuya: None. **H. Takesue:** None. **S. Ota:** None. **J. Kato:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P789.06

Topic: H.03. Decision Making

Title: The value of politics: Neurobiological representations of political valuation

Authors: *B. B. LU, P. W. GLIMCHER;
Ctr. Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Unlike value-based decisions, it is unclear if political decisions are made using a principled evaluation of alternatives. Social scientists have long considered political preferences to be a privileged class of decision-making, much like religious beliefs, that defy logical thought processes. It is thus tempting to assume that political preferences are represented in the brain by a unique set of neural processes or structures. Broadly-based studies of valuation, however, have revealed that nearly all valuations that guide decision-making are represented in the medial prefrontal cortex and striatum. These areas are known to accurately represent individual-specific subjective values for monetary rewards, lotteries, consumer goods, aesthetic judgements, charitable contributions, and social interactions. In this

study we asked whether a construct as complex as a political preference uses the same neural machinery that seems to represent all previously studied subjective valuations using a "common neural currency". Building on prior work our lab, we scanned forty participants with political preferences that span the American political spectrum using a novel psychophysical task that orthogonalizes partisanship and political information. Functional MRI scans were completed while subjects made preference ratings on real proposed laws that have appeared before US Congress. They first reported their preferences based solely on a synopsis of the law, and about 30m later reevaluated those preferences (all while in the scanner) after learning about the actual percent of members of Congress in each party who voted in favor of the law. Subjects thus stated their preferences for each law before and after receiving information about the true partisan support for each law. The laws' true congressional support were, by design, completely uncorrelated with the participants' estimates of that support.
We observed that participants' political preferences shifted dramatically when the true partisan support was revealed. These data allow us to identify the neural representation of political valuation both before and after partisan information was revealed. Preliminary results suggest that political valuation is represented in the common subjective value network.

Disclosures: B.B. Lu: None. **P.W. Glimcher:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

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Program #/Poster #: P789.07

Topic: H.03. Decision Making

Support: NSFC Grant 32071095
NSFC Grant 31671171
NSFC Grant 31630034

Title: Talk informatively: shared dmPFC coding of informativity in listener and speaker

Authors: *Q. MI, L. ZHU;
Peking Univ., Beijing, China

Abstract: Objective Human communicates informatively. Recent development in computational linguistics has proposed that--similar to value-based decisions--a speaker selects an expression to deliver certain intention based on the amount of information contained in the expressions, and a listener interprets the received expression as a rational decision made by the speaker. Although these theories highlight the central role of informativeness in communication in a manner analogous to value in goal-directed behavior, no direct evidence is available that the brain indeed evaluates informativeness of expressions in conservational contexts. Here, by combing fMRI, computational linguistics, and game theory, we investigate whether and how expression informativeness, as quantified by Shannon information, is represented in patterns of neural activity in listeners, and whether listeners and speakers have similar or distinct underlying patterns in coding communicative informativeness. **Methods** Employing a well-established communicative game previously used to investigate neurocomputations of intentional

communication, we conducted two independent fMRI experiments (N1=34, N2=26). The first is to establish the informativeness representations in listeners, and the second is to replicate the listeners results and then to evaluate the degree to which the identified patterns could be generalized across contexts and to speakers. **Results** Multivariate analyses show that expression informativeness, derived on a trial-by-trial basis, is robustly represented in patterns of neural activity in the listener's dorsal medial prefrontal cortex (dmPFC). Interestingly, further analyses suggest that the listener and speaker dmPFC use a common neural coding to represent the same amount of expression informativeness across different communicative contexts. **Conclusion** These results support a model of intentional communication whereby the effective interpretation and production of communicative signals arises from evaluating expression informativeness, providing a neurocognitive basis for rational communication accounts.

Disclosures: Q. Mi: None. **L. Zhu:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

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Program #/Poster #: P789.08

Topic: H.03. Decision Making

Support: Stanford Neuroscience Institute NeuroChoice Initiative grant to Brian Knutson

Title: Convergent evidence indicates that activity in distinct neural circuits predicts risk seeking versus avoidant choices

Authors: *L. MORTAZAVI[1], C. C. WU[1], B. D. KNUTSON[2];
[1]Stanford Univ., Stanford, CA; [2]Dept Psychology, Stanford Univ. Dept. of Psychology, Stanford, CA

Abstract: Functional Magnetic Resonance Imaging (FMRI) evidence has implicated cortical and subcortical circuits in risky choice, but whether activity in one or more circuits predict risky choice remains unclear. We convergently analyzed original data using a temporally staged risky gambling task to identify neural activity that predicted risk seeking versus averse choice (Leong et al., 2018), and then applied a classifier derived from that data to predict risky choice in a different risky gamble dataset (Tom et al., 2007). For original data, healthy participants (n=20) were scanned using FMRI as they chose between risky gambles for actual money or a no-risk/no-outcome option. Risky options were equated for expected value and variance but varied with respect to skewness (i.e., positive skew: 25% +$5.25, 75% -$1.25; symmetric: 50-50% +/-$3.05; negative skew: 75% +$1.25, 25% -$5.25). Based on the Affect-Integration-Motivation framework, activity immediately prior to choice was extracted from targeted Volumes Of Interest (VOIs) in the Nucleus Accumbens (NAcc), Anterior Insula (AIns), and Medial PreFrontal Cortex (MPFC) and submitted to models that predicted risky choice on a trial-to-trial basis. As predicted, NAcc and MPFC activity predicted risk-seeking choices but AIns activity instead predicted risk-averse choices. A whole-brain linear model as well as a model-free classifier (i.e., Support Vector Machine with Recursive Feature Elimination) confirmed that activity in these regions (but not sensorimotor regions) predicted risky choice. To test the features' generalizability, the classifier was applied to a distinct risky choice dataset (i.e., the Mixed Gambles Task of Tom et al (2007)). Despite

differences in task, sample, and scanner, activity from the same regions predicted risky choice with comparable effect sizes. Thus, neural features that predict risk-seeking choices are distinguishable from those that predict risk-averse choices, and each may be associated with different types of anticipatory affect. Together, these findings also further identify and refine a “risk matrix” of reliable, valid, and generalizable neural features that predict risky choice.

Disclosures: L. Mortazavi: None. **C.C. Wu:** None. **B.D. Knutson:** None.

Poster

P789. Neural Mechanisms Underlying Human Behavior and Cognitive Processes

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Program #/Poster #: P789.09

Topic: H.03. Decision Making

Support: NIH Grant EB026549

Title: Neural Representation of Expectations on Somatic Pain, Vicarious Pain, and Cognitive Effort

Authors: *H. JUNG[1], L. SLIPSKI[1], M. AMINI[1], M. HEILICHER[2], B. J. HUNT[1], E. I. MURPHY[1], X. HAN[1], P. A. KRAGEL[3], M. A. LINDQUIST[4], T. D. WAGER[1];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Univ. of Colorado Boulder, University of Colorado Boulder, CO; [3]Dept. of Psychology, Emory Univ., Atlanta, GA; [4]Dept. of Biostatistics, Johns Hopkins Univ., Baltimore, MD

Abstract: Expectations can shape the way we perceive the world. For example, word of mouth on a difficult math exam may shape one's test performance. However, studies to date have examined expectations in separate domains, i.e. cognitive and affective, which does not allow for comparing or contrasting neural representations of expectation across different domains. These neural representations may be strikingly different ("domain-specific"), or they may indicate the existence of a common representation that acts upon different experiences ("domain-general"). We used fMRI to compare the neural representation of expectations and their influence on stimulus perception across domains: via thermal pain, vicariously observed pain and cognitive mental rotation tasks. On each trial, participants were presented with perceived social cues (high/low) and then asked to rate their expectations to a subsequent stimulus intensity (pain/vicarious/cognitive); afterwards, they would experience the stimulus and subsequently rate their experience. We preregistered an analysis plan for a target sample of 120 participants; here, we present preliminary results from 18 participants. We compared the 1) non-modulated stimulus experience phase and 2) cue-modulated stimulus experience phase across three tasks, within-participants. The non-modulated pattern of activation in response to the stimuli, averaged across seven networks (Buckner et al., 2008), was different across task domains. In addition, the patterns of cue-modulated activations were also found to be significantly different across task domains, suggesting that cue-modulated expectation effects are domain-specific. From this, we plan to conduct a mediation analysis using the univariate/multivariate x domain-specific/domain-general parametric modulation maps, per our pre-registered plan. By identifying the neural mediators that link expectation cues and experience,

these findings will advance our understanding of the neural representation of expectations and modulated experiences.

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Poster

P799. Network Activity

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Program #/Poster #: P799.01

Topic: H.04. Executive Functions

Support: NIH R01 MH111424
U01 N2094358

Title: Overlapping functional networks in the mouse brain

Authors: *H. VAFAII[1], F. MANDINO[3], D. O'CONNOR[4], X. PAPADEMETRIS[3], T. CONSTABLE[3], E. M. R. LAKE[3], L. PESSOA[2];
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Abstract: Large-scale functional connectivity analysis has revealed a highly modular community structure. A common strategy in studying these networks is using disjoint community detection algorithms that assign a binary membership value to each region. Recent findings suggest this may not be the most effective approach, as some regions (e.g., hubs) likely participate in multiple networks. Here, we studied overlapping community organization in a functional MRI dataset of N=10 mice scanned under light anesthesia using a mixed-membership Bayesian model. This model allows each brain region to belong to all communities simultaneously with varying membership values — a measure of a region's "belonging" strength to communities. The results showed that the majority of regions resided on dense overlaps between communities, and only a minority of regions exhibited sharp memberships to a single network. To test the reliability of our approach, we collapsed the membership distribution of each node to its maximum value and obtained disjoint communities as a special case. Doing so allowed us to recover the network structure observed by other researchers that used standard disjoint algorithms. Thus, our approach finds reproducible results that provide information lost by using standard alternatives. Next, we identified the most prominent networks, including a Default Mode Network (DMN), a latero-cortical network, and a visual network. Our analysis suggests that the mouse DMN involves three different subnetworks: 1) a cortical component that contains anatomical hubs such as Retrosplenial and Anterior Cingulate areas; 2) a midline subnetwork that partially intersects with somatosensory and motor areas; and 3) a network containing bridges between cortex and subcortical areas including Agranular Insula, Ectorhinal, and Perirhinal areas. Furthermore, we used Shannon entropy to quantify the membership diversity of regions. Combining the entropy measure with the measure of degree centrality revealed three major brain region types: i) low degree, high entropy: hubs in the DMN joined by long-range anatomical

pathways; ii) high degree, high entropy: mostly belonging to the midline subnetwork of DMN; and iii) high degree, low entropy: exclusively from sensory networks with dense, local connectivity. Such characterization illustrates the type of information that is gained by using the proposed approach, and which is lost by standard non-overlapping methods. Taken together, our results demonstrate the utility of overlapping community detection in quantifying the membership diversity of brain regions and understanding the rich patterns of functional interactions in the brain.

Disclosures: H. Vafaii: None. **F. Mandino:** None. **D. O'Connor:** None. **X. Papademetris:** None. **T. Constable:** None. **E.M.R. Lake:** None. **L. Pessoa:** None.

Poster

P799. Network Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P799.02

Topic: H.03. Decision Making

Support: NIMH - BRAIN RF1 MH114276-01 (Hillman)
NIH (NINDS) R01NS076628
R01NS063226 (Hillman)

Title: Investigating the neural and behavioral basis of Dynamic Functional Connectivity

Authors: *D. THIBODEAUX[1], S. SHAHSAVARANI[3], C. J. NWOKEABIA[1], W. XU[1], F. LODGHER[1], D. A. HANDWERKER[4], J. GONZALEZ CASTILLO[5], P. BANDETTINI[6], E. M. HILLMAN[2]; [2]Biomed. Engineer, [1]Columbia Univ., New York, NY; [3]Univ. of Illinois At Urbana-Champaign, Urbana, IL; [4]SFIM/LBC, Natl. Inst. of Mental Hlth., Bethesda, MD; [5]SFIM/LBC/NIMH/NIH, Bethesda, MD; [6]Section on Functional Imaging Methods, NIMH-NIH, Bethesda, MD

Abstract: Resting state functional magnetic resonance imaging (rs-fMRI) has revealed brain-wide correlation patterns throughout the human brain, interpreted as functional connectivity. Dynamic Functional Connectivity (dFC) expanded on this technique via sliding window correlation analysis, revealing moment-to-moment changes in functional connectivity across an imaging session. However, the meaning of these transitions in terms of neural activity and behavior are not well understood.
In this work, we utilized dFC analytical techniques in conjunction with Wide Field Optical Mapping (WFOM) in the awake, behaving and anesthetized mouse. We hypothesized that the neural activity observed with WFOM would exhibit similar transitions between functional connectivity states as reported by fMRI dFC studies. We also explored whether changes in functional connectivity would correspond to changes in behavioral state, during both awake and anesthetized conditions.
Simultaneous neural and hemodynamic activity was collected using WFOM from 5 freely behaving head-fixed Thy1-jRGECO1a mice. Behavioral metrics such as movement, whisking and pupillometry were also acquired simultaneously. Raw neuroimaging data was dimensionally reduced to 92 representative time courses across the dorsal surface of the cortex for each subject utilizing a semi-supervised clustering technique. A 10 second sliding window was then used to calculate moment-to-moment dFC maps across each session. These dynamic correlation maps were k-means clustered into 7 dynamic states, which could

then be used to calculate the most representative state for any given epoch.
dFC analysis revealed a diverse set of brain states, with some states exhibiting a notable desynchrony between visual and frontal motor regions. Behavioral metrics during state transitions revealed consistent, unique trends within dynamic state changes. States with low, desynchronous correlations had little to no movement and exhibited pupil constriction. Alternatively, other states exhibited elevated behavioral metrics with differing temporal trends, indicating that some dynamic states represent specific behavioral sequences, such as movement onset. During anesthesia-induced immobility, dFC analysis revealed systematic changes in brain state metrics that closely matched awake states during voluntary immobility, a property that was quickly reversed after recovery. These results suggest that dFC analysis is capturing stereotyped spontaneous neural fluctuations and that movement has an immediate and widespread impact on neuronal Functional Connectivity.

Disclosures: D. Thibodeaux: None. **S. Shahsavarani:** None. **C.J. Nwokeabia:** None. **W. Xu:** None. **F. Lodgher:** None. **D.A. Handwerker:** None. **J. Gonzalez Castillo:** None. **P. Bandettini:** None. **E.M. Hillman:** None.

Poster

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Program #/Poster #: P799.03

Topic: H.04. Executive Functions

Support: R01MH118370
T32NS047987

Title: Bridges or Mirages Connector Hubs and Inter-Subject Variation in Connectivity Profiles

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Abstract: Connector hubs (hubs) are regions with connections evenly distributed across functional brain networks, found most commonly in association cortex. Because of these characteristics, hubs are hypothesized to play a critical role in network structure and in contributing to higher-level cognitive control functions. However, the hub literature is primarily based on group average functional connectivity and recent work has demonstrated that association regions of the brain can also show substantial inter-individual variation. This raises the question of whether putative hubs are mirages, only appearing hub-like due to their correspondence with locations of pronounced individual differences in connectivity profiles. To answer this question, we compared the locations of typical (group-level) hubs and regions of idiosyncratic functional connectivity ("network variants") in both the Midnight Scan Club and Human Connectome Project datasets. Group hubs defined based on participation coefficient (a measure of how evenly distributed a node's connections are between networks) did not overlap strongly with network variants. In contrast, group hubs defined based on community density (a measure of the number of networks present within a certain radius) were shown to overlap substantially with network variant locations. Additionally, in single subjects, typical hubs showed connectivity profiles with a good degree

of similarity to the group average. Our results demonstrate that group hubs are not simply driven by the presence of large inter-subject variations in connectivity profiles, suggesting that they may represent real elements of brain networks. In contrast, our findings suggest caution is warranted when defining hubs based on community density, which may be associated with inter-subject variation in the boundaries of functional brain networks.

Disclosures: D.M. Smith: None. **A. Dworetsky:** None. **B. Kraus:** None. **E.M. Gordon:** None. **C. Gratton:** None.

Poster

P799. Network Activity

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Program #/Poster #: P799.04

Topic: H.04. Executive Functions

Support: NIH Grant K99-R00 MH096901
NIH Grant R01 MH109520

Title: The functional relevance of flexible hub connectivity in cognitive control networks

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Abstract: Increasing evidence suggests that cognitive processes are shaped by brain network interactions, yet it remains unclear how task-driven changes in those interactions relate to changes in cognitive information processing. We sought to address this gap in the context of cognitive control, which is the flexible implementation of goal-directed cognition and behavior. In prior work we established that connectivity patterns in two large-scale cognitive control networks - the frontoparietal and cingulo-opercular networks - exhibit flexible hub mechanisms in support of cognitive control. We have observed that cognitive control network regions dynamically reweight their connectivity in a systematic, task-relevant manner, which prompts the question of how such reconfigurations instantiate cognitive control. To address this, we utilized a recently developed approach for mapping activity flow processes: the movement of task-evoked activity between neural populations. Importantly, these models are constrained by empirical connectivity estimates, which allows us to probe the functional relevance of task-based connectivity changes. To determine the network mechanisms underlying cognitive control, we used resting- and task-state fMRI data of N=41 healthy adult participants. During task fMRI participants engaged with a rapid instructed task learning (RITL) paradigm that demanded high levels of cognitive control via rapid switching amongst 64 permuted rule sets (all participants performed with above-chance accuracy: mean=76.84% correct, S.E.M.=1.99). The activity flow model exhibited high prediction accuracy of task-evoked activations across RITL states and cortical regions (r=0.82, p<0.01), which suggests that distributed processes specified by task-state functional connectivity changes have a dominant influence upon cognitive-control-related activity across the cortex. We found preliminary evidence that activity-flow-based prediction accuracy was higher for cognitive control network regions

exhibiting stronger flexible hub properties, suggesting a particularly important functional role for flexible hubs in the generation of task-evoked activations during cognitive control tasks. Together these results provide a mechanistic framework for understanding the functional role of task connectivity changes implemented via flexible hubs in the generation of cognitive control.

Disclosures: C.V. Cocuzza: None. **R.D. Mill:** None. **M.W. Cole:** None.

Poster

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Program #/Poster #: P799.05

Topic: H.04. Executive Functions

Support: NIH Grant F32MH119761

Title: Evaluating the reliability, validity, and utility of overlapping networks: implications for cognitive control

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Abstract: The Dual Networks model posits that two whole-brain networks, the frontoparietal (FPN) and cinguloopercular (CON), subserve distinct aspects of cognitive control (Dosenbach et al, 2008). While this model has been a fruitful basis for ongoing study, it does not propose a defined mechanism for integration between the FPN and CON, nor does it capture the role of other potentially relevant networks. The model's incompleteness is in part due to a common assumption in network neuroscience - namely, the implicit assumption that regions are members of one primary network, i.e., that networks do not overlap. The methods borne out of this assumption lose crucial information not only about individual regions' connections to multiple networks but also the specific networks they bridge between. Here, we explore the between-sample reliability, relative validity, and practical utility for a method of assigning regions to multiple overlapping networks, using the Dual-Networks model as an example case for potential applications. This method, the "mixed membership algorithm", assigns regions a probability distribution across a predefined number of overlapping "communities" (Najafi et al, 2016). Using a 200-subject sample of 15-minute resting state data from the Human Connectome Project (van Essen et al, 2013), we conducted a series of topographic comparisons with the communities generated by this algorithm using a bootstrapped Dice coefficient analysis. To assess reliability, we split the data into two halves and compared the communities generated for each, showing good agreement between samples. To assess validity with the greater literature, we compared the communities from the full 200 subjects with nonoverlapping networks generated using established methods (Yeo et al, 2011), revealing a close 1:1 relationship between most of the networks and a single unique community. Finally, to demonstrate the utility of overlapping networks for cognitive applications, we assessed the community membership of the regions of the FPN and CON. These regions were revealed to be members of more than two communities

and that all of them were members of multiple communities, suggesting potential areas of overlap between the FPN, CON, and other networks that may support their integration.

Disclosures: S. Cookson: None. **M. D'Esposito:** None.

Poster

P799. Network Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P799.06

Topic: H.04. Executive Functions

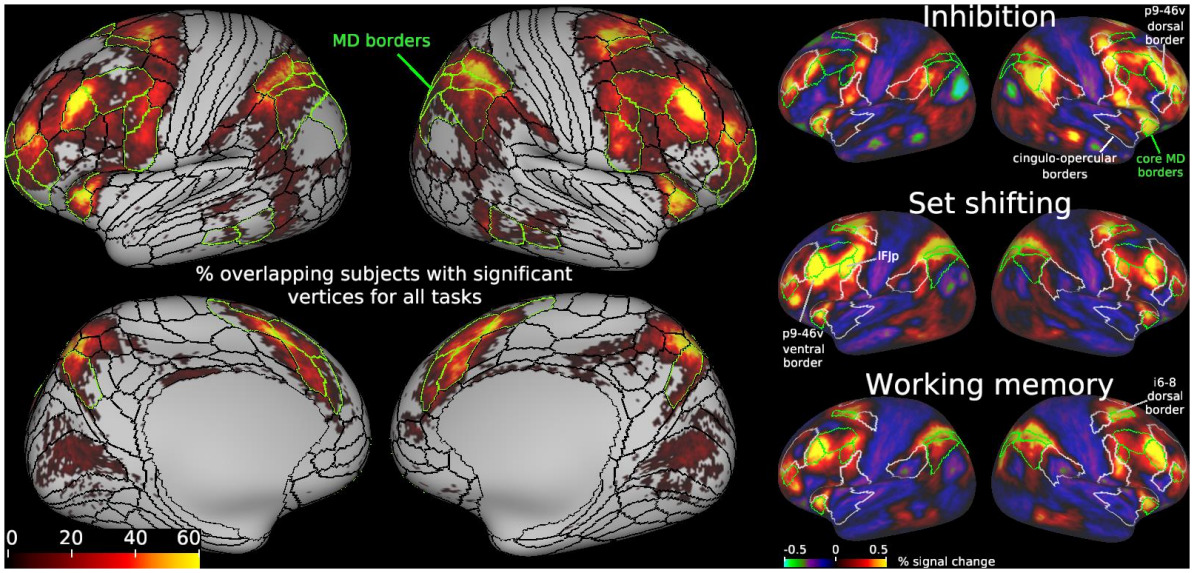
Support: MRC Grant SUAG/045.G101400
NIH Grant R01MH060974

Title: Executive task fMRI activations overlap and diverge in domain-general cortex following fine-grained resting-state architecture

Authors: *M. ASSEM[1], S. SHASHIDHARA[2], M. F. GLASSER[3], J. DUNCAN[4];
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Abstract: Domain-general or multiple-demand (MD) cortex refer to a set of frontal, parietal and occipito-temporal cortical patches that are co-activated by many different kinds of demanding cognitive tasks. Numerous studies of tasks targeting different components of executive functions show co-activations of MD cortex, but the limited spatial resolution of traditional imaging methods blurred the line between overlapping and segregated activations for the different components. Here we used state-of-the-art multimodal MRI techniques of the Human Connectome Project (HCP) to scan subjects performing three kinds of executive tasks: working memory, set shifting and inhibition; each with a hard and easy version. In line with a “common” executive function component, the hard>easy contrast showed robust overlaps in MD cortex at the single subject level. But in line with relatively specialized components, each task showed different and precise quantitative variations in MD activations. Peaks of activation for each task often lay at the borders between MD and more specialized regions, with different peaks for different executive demands.
Using an independent HCP resting-state dataset, we found that seed regions within MD cortex show differential connectivity patterns that closely predict each task’s precise topography. Most prominently, inhibition showed right lateralized activations at the borders between MD and cingulo-opercular networks (e.g. dorsal frontal border between p9-46v (MD) and 46). Set shifting showed left lateralized activations prominent in IFJp and the ventral border of p9-46v. Working memory showed overlaps between MD and dorsal attention networks (e.g. dorsal frontal i6-8 (MD) and 6a).
Collectively, these results show that the three executive tasks engage a common cortical MD network. The detailed pattern of activity, however, is modulated according to each task’s content. Using precise

imaging methods, the results suggest domain-specific networks closely interact with their neighbouring MD cortex to generate distinct executive functions.



Disclosures: M. Assem: None. **S. Shashidhara:** None. **M.F. Glasser:** None. **J. Duncan:** None.

Poster

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Topic: H.04. Executive Functions

Support: NIH Grant R01MH122613

Title: Human thalamic hubs shape task-evoked activity across multiple cognitive domains

Authors: E. SORENSON, ***K. HWANG**;
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Abstract: Evidence from resting-state functional connectivity studies suggests that the human thalamus is a network hub well suited for promoting integrative functions (Hwang et al. 2017; Greene et al. 2020). Such connectivity properties predict that a single thalamus hub integrates multiple cognitive functions, and thus a diverse range of cognitive and behavioral tasks should induce a common converging activation profile in thalamic hubs. The goal of our study is to evaluate this prediction. Our study used the Multi-Domain Task Battery dataset (MDTB; King et al. 2019) that included 24 participants, who performed 26 unique tasks across multiple domains. We then used PCA to identify thalamic evoked response patterns that are associated with task-general activities across multiple domains. The PCA summarized multi-task activity with 10 components, with the first three PCA components collectively explaining 78.8% of the variance. The first PCA component shows significant activation in the posterior thalamus while the

second component shows strong activation in the medial thalamus. Using the loadings from PCA, the second component was shown to have the least variance across tasks and likely represents a task-general activity pattern in the thalamus. The activation of the posterior and medial regions of the thalamus overlap with thalamic connector hubs previously identified using resting-state functional connectivity data. Furthermore, the calculated connector hub values, estimated using the task activation data and hierarchical clustering of task activation patterns, are similar to those calculated using resting-state functional connectivity data. To determine to what extent task-general thalamic activity influences task-evoked cortical activity, we performed thalamocortical activity-flow analysis (Cole et al., 2016) to compare observed cortical task-evoked responses with responses predicted by thalamocortical activity. We found that thalamic evoked response propagated through thalamocortical functional connectivity can significantly predict cortical evoked responses across different tasks (averaged r across tasks = 0.4149, std = 0.1884, $p<.001$). Our findings suggest that thalamic hubs support a wide range of cognitive tasks and shape cortical cognitive task activations. Specifically, task-general evoked responses in the medial thalamus can influence region-wide cortical evoked responses via the thalamic hub's extensive connectivity with cortical systems.

Disclosures: E. Sorenson: None. **K. Hwang:** None.

Poster

P799. Network Activity

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Program #/Poster #: P799.08

Topic: H.04. Executive Functions

Support: NIH R01 MH121509

Title: Interactions among frontal-parietal and cingulo-opercular networks supporting cognitive control

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Abstract: Cognitive control involves directing one's actions based on current and future relevant demands. The frontoparietal control network (FPCN) has been shown to fractionate as a function of cognitive control demands such that rostral-most regions are selective for future-oriented planning or temporal control, mid-regions for adapting behavior according to contextual circumstances or contextual control, and caudal regions for linking stimulus to action or sensory-motor control. Furthermore, this somatomotor distal to somatomotor proximal control demand organization maps onto an abstraction gradient representing future to current behavioral demands, respectively. Concurrently, the cinguloopercular network (CON) is engaged during control tasks, yet the organization of the regions therein and their specific interactions with the FPCN remain unknown. This study analyzed fMRI data on two separate groups of young, healthy participants who completed a comprehensive control task designed to elicit the three proposed control demands: temporal control, contextual control, and sensory-motor control. Areas within the CON fractionated as a function of temporal and contextual control – the dorsal medial prefrontal cortex (dmPFC) mirrored the FPCN in a rostro-caudal manner, while the anterior Insula

(aI) showed a ventral-dorsal gradient. We next considered the brain-behavior relationships through each region's correlation with current and future behavior. CON temporal control regions were positively correlated with future trial reaction time while contextual control regions were positively correlated with current trial reaction time, a pattern mirroring the FPCN. To further distinguish the CON and FPCN interactions on behavior we employed a set of mediation analyses within- and between-networks. Results showed that the relationship between CON contextual regions and current trial reaction time was fully mediated by the FPCN contextual regions. Likewise, the relationship between CON temporal regions and future trial reaction time was fully mediated by FPCN temporal regions. Further dividing the CON regions showed a serial order of the dmPFC and the FPCN mediating the relationship between the aI upon relevant control behavior. Collectively, the data indicate separable aI to dmPFC to FPCN to behavior interactions for temporal and contextual control, respectively. These results show an important separation between the highly interconnected CON regions as well as the interactive relationship between the FPCN and CON during cognitive control.

Disclosures: J.L. Wood: None. **D.E. Nee:** None.

Poster

P799. Network Activity

Location: Virtual Only

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Program #/Poster #: P799.09

Topic: H.04. Executive Functions

Support: NHMRC GNT1156536

Title: Noradrenergic modulation of brain network topology and energy landscape dynamics mediates conscious perception under perceptual ambiguity

Authors: *G. WAINSTEIN[1], K. A. EHGOETZ MARTENS[2], V. MEDEL[3], E. J. MÜLLER[4], B. MUNN[4], B. ANDERSON[2], E. STÖTTINGER[5], J. DANCKERT[2], J. M. SHINE[3];
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Abstract: Previous studies investigating the perceptual updating and bistable perception have consistently implicated a distributed set of regions within the cerebral cortex. Indeed, its activity is consistent with the broader notion that cognitive capacities arise from the coordinated interactions amongst interconnected networks. Despite these clear links, less is known about the neurobiological basis of its modulation in shaping the large-scale network. On this matter, the Locus Coeruleus noradrenaline system is well-suited to mediate the large-scale brain state switches required to flexibly alter conscious perception. In previous work, it has been argued that phasic release of noradrenaline from the LC acts as a "network reset" signal, which effectively disrupts ongoing processing allowing animals to reconfigure their ongoing neural dynamics. Based on these concepts, we hypothesized that the resolution of perceptual ambiguity is intricately related to LC activity which act as a 'network reset' to reconfigure conscious awareness to resolve perceptual uncertainty. To test this hypothesis, we used a cognitive task

designed to augment perceptual ambiguity. The task consisted on a set of transforming images that transition from an initial object (e.g., a plane) into a second object (e.g., a shark; Figure 1A) and subjects were instructed to press a button to indicate the perceptual change. Crucially, conscious awareness of a change in stimuli to a second object is known to 'pop out'. To test our hypothesis, we analyzed both pupillometric data (Figure 2B) - a robust marker of LC activity- and fMRI data to track the putative impact of LC on brain network dynamics in light of graph theory analysis such as network-level integration (Figure 2C-D) and energy landscape changes. We confirmed our hypothesis that phasic bursts of LC activity increases network integration and perceptual changes are related to peaks in pupil diameter, which leads to the resolution of perceptual ambiguity.

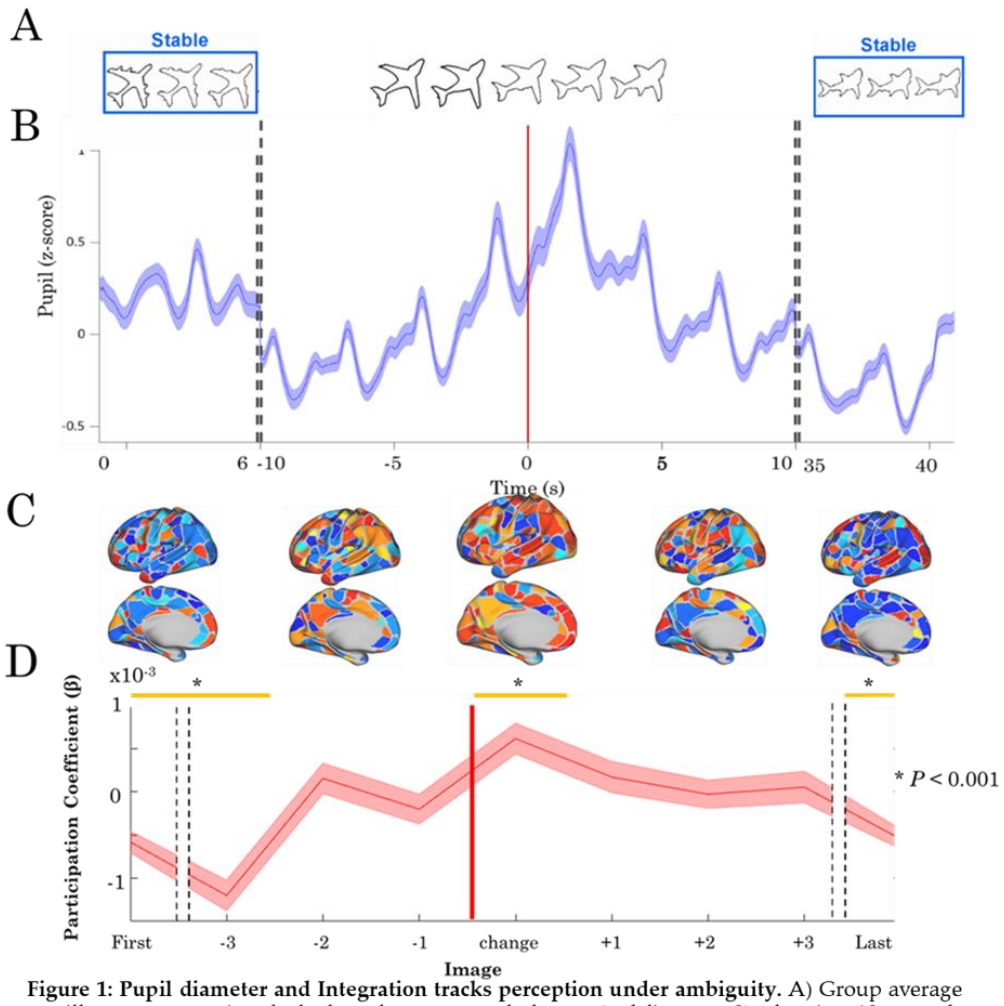


Figure 1: Pupil diameter and Integration tracks perception under ambiguity. A) Group average pupillary response time locked to the perceptual change (red line, t = 0), showing 10 seconds around that point. The first and last 6 seconds are shown in the left (right) section of the plot (dotted line). B) Brain cortical map representation of the evoked participation coefficient (i.e., βPC). Color represent the loading of the PC with red being positive and blue negative. C Average βPC for each regressor across all subjects and regions. Orange bars shows the significant regressors ($\beta \neq 0$, $p_{FDR} < 0.001$). Red vertical line represents the perceptual change.

Disclosures: G. Wainstein: None. **K.A. Ehgoetz Martens:** None. **V. Medel:** None. **E.J. Müller:** None. **B. Munn:** None. **B. Anderson:** None. **E. Stöttinger:** None. **J. Danckert:** None. **J.M. Shine:** None.

Poster

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Program #/Poster #: P799.10

Topic: H.04. Executive Functions

Support: NIH MH096773
NIH MH115357
NIH MH115357-02S1

Title: MIDB precision network atlas as a potential use case for targeted brain stimulation

Authors: *R. HERMOSILLO[1,2], L. A. MOORE[4], C. M. CARRASO[2], E. J. FECZKO[1], G. CONAN[2,5], B. ADEYEMO[6], E. EARL[5], A. PERRONE[2], A. DWORETSKY[7,8], C. GRATTON[9,10], S. E. PETERSEN[11,12,13,14], O. MIRANDA DOMINGUEZ[1,2], D. A. FAIR[2,1,3];
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Abstract: Non-invasive brain stimulation (NIBS) technologies such as transcranial direct current/alternating-current stimulation (TCDS/TCAS) and transcranial magnetic stimulation (TMS), have quickly outpaced advances in techniques for neuronavigation. Recent evidence suggests that the effectiveness of TMS for clinical depression treatment not only depends on the spatial accuracy of the area to be stimulated, but also on the patient's unique brain connectivity. Current methodologies for targeted brain stimulation rely on measuring a fixed distance from the motor cortex, based on the EEG 10-20 positioning system, or real-time, neuronavigation based on stereotactic image-guided positioning based upon the patient's neuroanatomy. However, recent evidence suggests that the spatial correspondence of functional topography is highly variable across participants, which could be a source of the variability in NIBS intervention outcomes. Using precision functional brain mapping methods from resting-state fMRI data in 6,106 9-10 year olds from the Adolescent Cognitive Brain Development (ABCD) study, we created a new open-source, method-flexible set of probabilistic network atlases: the Masonic Institute for the Developing Brain (MIDB) Precision Atlas.
Using a MIDB probabilistic map of the frontoparietal network, we demonstrate that a seed placed within a region of high network probability (0.75) within the dorsolateral prefrontal cortex (DLPFC) showed consistent anticorrelation with the subgenual cortex, (a connection targeted in NIBS treatment for clinical depression), both in the adults from Midnight Scan Club (n =10) and subset of ABCD subjects (n=10). However, when the seed was moved slightly outside of the region of high network consensus to a region

with high network heterogeneity (0.35 probability), the correlation with the subgenual cortex was inconsistent. These results provide one potential use case for the MIDB precision atlas and the associated probabilistic templates that provide a frame of reference for spatial location of a network of interest when conducting therapeutic brain stimulation.

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Poster

P799. Network Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P799.11

Topic: H.04. Executive Functions

Support: UC Santa Barbara Academic Senate

Title: Diurnal fluctuations in testosterone tied to variation in intrinsic functional connectivity in a densely sampled male

Authors: *H. GROTZINGER[1], L. PRITSCHET[1], T. SANTANDER[1], E. G. JACOBS[1,2];
[1]Psychological and Brain Sci., [2]Neurosci. Res. Inst., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Sex hormones are powerful neuromodulators of learning and memory, influencing the brain at the level of microscopic intracellular events to macroscopic brain organization. A central feature of the mammalian endocrine system is that hormone secretion varies over time. Human neuroimaging studies that densely sample individuals over timescales of days, weeks, and months provide unique insight into the role our endocrine system plays in regulating the dynamic properties of the human brain. For example, we recently established estrogen's ability to drive widespread patterns of connectivity and enhance the global efficiency of large-scale brain networks in a densely-sampled female (Pritschet et al., 2020). In men, sex hormone production follows a sinusoidal pattern with a peak in testosterone between 6-7am and nadir between 7-8pm. To capture these diurnal changes in hormone production, a male participant (age 26) underwent brain imaging (T1, T2 hippocampal, and resting state fMRI scans) and venipuncture every

12-24h for 30 consecutive days, resulting in 40 sessions. This dense-sampling, deep-phenotyping approach offers a unique opportunity to probe the relationship between testosterone and functional brain networks with high spatiotemporal precision. Results confirmed diurnal fluctuations in testosterone, cortisol, and estradiol, with decreases of ~63%, ~92%, and ~89%, respectively. Standardized regression revealed predominantly positive associations between whole-brain patterns of coherence and total testosterone, cortisol, and estradiol concentrations. In particular, nodes in the Salience/Ventral Attention and Dorsal Attention networks displayed the strongest associations with all three hormone concentrations. Stratifying the data by morning and evening reveals fewer whole-brain patterns of coherence associated with testosterone concentrations in the evening, when testosterone concentrations are low, compared to morning sessions. Together, findings from this study enhance our understanding of testosterone, cortisol, and estradiol as rapid neuromodulatory hormones, and provides evidence that diurnal changes in steroid hormone production impacts whole-brain functional network architecture.

Disclosures: H. Grotzinger: None. **L. Pritschet:** None. **T. Santander:** None. **E.G. Jacobs:** None.

Poster

P799. Network Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P799.12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: On the topochronic map of the human brain dynamics

Authors: *P. SORRENTINO[1], S. PETKOSKI[2], M. SPARACO[3], E. TROISI LOPEZ[4], R. RUCCO[4], E. SIGNORIELLO[3], F. BASELICE[4], S. BONAVITA[3], M. PIROZZI[5], M. QUARANTELLI[5], M. QUARANTELLI[5], G. SORRENTINO[4], V. K. JIRSA[6];
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Abstract: Large-scale brain activity evolves dynamically over time across multiple time-scales. The structural connectome imposes a spatial network constraint since two structurally connected brain regions are more likely to coordinate their activity (*1*). It also imposes a temporal network constraint by virtue of time delays via signal transmission, which has modulatory effects on oscillatory signals (*2*). Specifically, the lengths of the structural bundles, their widths, myelination, and the topology of the structural connectome influence the timing of the interactions across the brain network. (*3*). We introduce a novel in vivo approach for directly measuring functional delays across the whole brain using magneto/electroencephalography and integrating them with the structural connectome derived from magnetic resonance imaging. We developed a map of the functional delays characterizing the connections across the human brain and a map of the corresponding functional velocities. This yields a topochronic map of the human brain dynamics. The functional delays are tightly regulated, showing, as expected, that larger structural bundles had faster velocities, with the delays varying much less than expected if they only depended upon distance (permutation test, $p<0.001$), both at the group and individual level. Then, we estimated the delays from magnetoencephalography (MEG) data in a cohort of multiple sclerosis

patients, who have damaged myelin sheaths, and demonstrated that patients showed greater delays across the whole network than a matched control group (KS test, $p<0.001$). Furthermore, within each patient, individual lesioned connections were slowed down more than unaffected ones (permutation test, $p<0.001$). Our technique provides a practical approach for estimating functional transmission delays in vivo at the single-subject and single-fiber level and, thus, opens the possibility for novel diagnostic and curative interventions as well as providing empirical, subject-specific constraints to tailor brain models.

Bibliography.

1. P. Sorrentino, C. Seguin, R. Rucco, M. Liparoti, E. Troisi Lopez, S. Bonavita, M. Quarantelli MD, G. Sorrentino, V. Jirsa, A. Zalesky, The structural connectome constrains fast brain dynamics. *eLife*. **10**, e67400 (2021).2. G. Deco, V. Jirsa, A. R. McIntosh, O. Sporns, R. Kötter, Key role of coupling, delay, and noise in resting brain fluctuations. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 10302–10307 (2009).3. G. Deco, V. K. Jirsa, A. R. McIntosh, *Emerging concepts for the dynamical organization of resting-state activity in the brain* (Nature Publishing Group, 2011; https://www.nature.com/articles/nrn2961), vol. 12.

Disclosures: P. Sorrentino: A. Employment/Salary (full or part-time):; Aix-Marseille University. **S. Petkoski:** A. Employment/Salary (full or part-time):; Aix-Marseille University. **M. Sparaco:** A. Employment/Salary (full or part-time):; Luigi Vanvitelli University. **E. Troisi Lopez:** A. Employment/Salary (full or part-time):; University of Naples Parthenope. **R. Rucco:** A. Employment/Salary (full or part-time):; University of Naples Parthenope. **E. Signoriello:** A. Employment/Salary (full or part-time):; universita Luigi Vanvitelli. **F. Baselice:** A. Employment/Salary (full or part-time):; University of Naples Parthenope. **S. Bonavita:** A. Employment/Salary (full or part-time):; universita Luigi Vanvitelli. **M. Pirozzi:** A. Employment/Salary (full or part-time):; National Research Council of Italy. **M. Quarantelli:** A. Employment/Salary (full or part-time):; National Research Council of Italy. **M. Quarantelli:** A. Employment/Salary (full or part-time):; National Research Council of Italy. **G. Sorrentino:** A. Employment/Salary (full or part-time):; University of Naples Parthenope. **V.K. Jirsa:** A. Employment/Salary (full or part-time):; Aix-Marseille University.

Poster

P799. Network Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P799.13

Topic: H.04. Executive Functions

Title: Global brain connectivity reliably predicts individual differences in intelligence

Authors: *E. D. ANDERSON, A. K. BARBEY;
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Abstract: Individual differences in human intelligence can be predicted from patterns of neurobiological connectivity spanning multiple brain networks. Much current theorizing into the neural basis of intelligence, however, has adopted a localizationist perspective, mapping human intelligence to a single specialized brain region or brain network. Current neuroscience evidence points to the importance of both specialized neurobiological systems and global network topology for predicting individual differences in intelligence, suggesting that purely localizationist theories of intelligence may fail to fully capture or

explain important sources of individual variation in cognitive ability. To what extent does neuroscience evidence support either global or localized neurobiological connectivity as a key source of individual differences? To further explore the systems-level neurobiology identified by state-of-the-art neuroscience theories of intelligence, we deployed a connectome-based predictive modeling framework to systematically investigate the predictive power of both localized and global functional connectivity patterns theorized in the literature to underpin intelligence. We administered a comprehensive battery of fluid and crystallized intelligence tasks to a large sample of healthy young adults (N=297), including figure series completion, LSAT analogical reasoning, Shipley-2 Vocabulary, and the Adult Decision-Making Competence Battery. Structural equation modeling was used to generate confirmatory factor loadings and produce individual estimates of general intelligence from this battery. Using reproducibly processed resting-state data, our connectome-based predictive modeling study found that intelligence was best predicted from global, whole-brain patterns of resting functional connectivity. In contrast, we observed low or non-existent performance for predictive models trained only on localized connectivity profiles. Critically, we found that weakly-connected edges known to support functional segregation and small-world organization are important neurobiological predictors of individual differences in intelligence, and that these edges were distributed across the entire connectome. Our results point to a need for neuroscience theories of intelligence that integrate specialized and necessary neurobiological substrates of intelligence within a larger information-processing architecture, suggesting important future directions for research into the neurobiological properties that underlie individual differences in cognitive ability.

Disclosures: E.D. Anderson: None. **A.K. Barbey:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.01

Topic: H.04. Executive Functions

Support: KAKENHI Grant 18K07348
KAKENHI Grant 21K07255
Takeda Science Foundation

Title: Two processing streams in response inhibition revealed by fMRI and time-resolved TMS

Authors: *T. OSADA[1], A. OGAWA[1], A. SUDA[1,2], K. NAKAJIMA[1,4], M. TANAKA[1], S. OKA[1], K. KAMAGATA[3], S. AOKI[3], Y. OSHIMA[4], S. TANAKA[4], N. HATTORI[2], S. KONISHI[1];
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Abstract: Multiple cognitive processes are recruited to achieve adaptive behavior. However, it is poorly understood how such cognitive processes are implemented in temporal cascades of human cortical areas as processing streams to achieve behavior. In the present study, we used functional MRI (fMRI) and transcranial magnetic stimulation (TMS) to explore the multiple processing streams for response

inhibition. We first identified cortical areas critical for response inhibition in a stop-signal task with fMRI: the ventral posterior inferior frontal cortex (vpIFC), dorsal posterior inferior frontal cortex (dpIFC), presupplementary motor area (preSMA), and intraparietal sulcus area (IPS). To analyze the stream structure among the areas, network analyses with functional connectivity were performed: the vpIFC and preSMA belonged to the cinglo-opercular network whereas the dpIFC and IPS belonged to the fronto-parietal network. Next, single-pulse TMS (spTMS) was administered during performance of the stop-signal task by taking advantage of the high temporal resolution of spTMS. Each of the target areas was stimulated in half of the trials, and trials with and without stimulation were intermixed within runs. Prolonged stop-signal reaction time (SSRT), a behavioral index for response inhibition, was observed in spTMS to the vpIFC at the time window of -90 to -60 msec, with the end of the SSRT (i.e., stopping) for no-stimulation trials defied as zero (mean difference: 20.5 msec, $t(19) = 5.2$, $p = 4.9 \times 10^{-5}$, paired t-test). The dpIFC and preSMA showed a transient disruption effect at the subsequent time window of -60 to -30 msec (for the dpIFC, mean difference: 18.1 msec, $t(19) = 4.6$, $p = 2.1 \times 10^{-4}$, paired t-test; for the preSMA, mean difference: 17.2 msec, $t(19) = 4.6$, $p = 2.1 \times 10^{-4}$, paired t-test). The IPS showed a disruption effect at the time window of -30 to 0 msec (mean difference: 19.6 msec, $t(19) = 5.2$, $p = 4.7 \times 10^{-5}$, paired t-test). Finally, we tested whether or not the information flowed effectively from the vpIFC to the preSMA and from the vpIFC to the dpIFC during response inhibition. SpTMS following suppression of the vpIFC with repetitive TMS (rTMS) showed that prolonged SSRT was still observed by spTMS to the dpIFC, but not to the preSMA. A significant area (preSMA/dpIFC) × Pre/Post-rTMS interaction effect was observed in a two-way ANOVA of ΔSSRT ($F(1,19) = 11.9$, $p = 2.6 \times 10^{-3}$). These results indicate that the flow from the vpIFC to the preSMA was effective whereas the flow from the vpIFC to the dpIFC was not effective. Our study suggests two parallel processing streams for response inhibition (vpIFC-preSMA vs. dpIFC-IPS) where the vpIFC and dpIFC act as the origins, respectively.

Disclosures: T. Osada: None. **A. Ogawa:** None. **A. Suda:** None. **K. Nakajima:** None. **M. Tanaka:** None. **S. Oka:** None. **K. Kamagata:** None. **S. Aoki:** None. **Y. Oshima:** None. **S. Tanaka:** None. **N. Hattori:** None. **S. Konishi:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.02

Topic: H.04. Executive Functions

Support: FWF Grant KLI600B27

Title: Effects of slow cortical potential neurofeedback on the contingent negative variation in children and adolescents with autism spectrum disorder

Authors: *K. PRILLINGER[1], S. T. RADEV[2], P. L. PLENER[1], L. KONICAR[1];
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Abstract: The contingent negative variation (CNV) is a well studied indicator of attention- and expectancy-related processes in the human brain. However, its role as a potential biomarker of successful clinical interventions in autism spectrum disorder (ASD) remains unclear.
With this randomized controlled trial, we investigated how the CNV changes following an intensive neurofeedback training. Twenty-one adolescents with ASD in the experimental group underwent 24 sessions of EEG-based slow cortical potential (SCP) training and were compared to twenty adolescents with ASD in the control group receiving treatment as usual. During SCP training, feedback was provided at the participants' monitor as an object that participants had to direct upwards in negativity trials and downwards in positivity trials (50 % negativity and positivity trials in sessions 1-12 and 80 % negativity and 20 % positivity trials in sessions 13-24). CNV waveforms were obtained from a continuous performance test (CPT), which all adolescents performed before and after the corresponding three-month long intervention period.
In order to utilize all available neural time series, trial-based area under the curve (AUC) values for all four EEG channels were entered into a hierarchical multivariate Bayesian model. The model achieved considerable uncertainty reduction and revealed markedly different pre-post changes in both groups: CNV amplitudes increased slightly in the control group but decreased markedly in the experimental group. The effects of the intensive SCP neurofeedback intervention on the CNV in children and adolescents with ASD are discussed regarding the potential use of the CNV as a biomarker for treatment outcome and the role of attention-related comorbidities in ASD.

Disclosures: K. Prillinger: None. **S.T. Radev:** None. **P.L. Plener:** None. **L. Konicar:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.03

Topic: H.04. Executive Functions

Support: G20RR030883

Title: Executive functioning in college students with comorbid anxiety and depression symptoms

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[1]Interdisciplinary Neurosci. Program, [2]Dept. of Psychology, Univ. of Rhode Island, Kingston, RI; [3]Dept. of Exercise Sci., Elon Univ., Elon, NC

Abstract: *Background:* Few studies have investigated how comorbidity, the presence of two or more distinct disorders in an individual, is related to executive functioning. Impairments in executive functioning in young adults are associated with poorer academic performance and psychological disorders, such as depression and anxiety. The present study had two main hypotheses: hypothesis A) those with symptoms characteristic of comorbid major depressive disorder and anxiety would self-report worse executive functioning and a lower grade point average (GPA) compared to those with symptoms of either depression or anxiety alone, and hypothesis B) those with singular or comorbid symptoms would report worse executive functioning and a lower GPA than those without symptoms of anxiety and/or

depression. *Method:* A sample of 77 undergraduate college students completed self-report measures of anxiety symptoms, depression symptoms, executive functioning, and GPA. A multivariate analysis of variance (MANOVA) was conducted to test hypotheses A and B. *Results:* MANOVA results revealed significant differences in self-reported executive functioning according to level of symptomatology (F = 23.87, $p < .001$). While self-reported GPA decreased across groups, this trend was not statistically significant (F = 1.91, p = .156). *Limitations:* Limitations of the current study include a small sample size, additional comorbidities present in the sample, and lack of treatment information. *Conclusions:* Self-reported executive functioning was significantly different between symptomatology groups, with comorbid disorder symptoms resulting in worse executive functioning compared to singular disorder symptoms or no symptoms. There was no significant difference in GPA between groups based on symptomatology.

Disclosures: L.E. Thompson: None. **L.L. Weyandt:** None. **C.T. Schulz:** None. **A.T. Piepmeier:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.04

Topic: H.04. Executive Functions

Title: Test anxiety is associated with a decreased error-related negativity in tasks requiring top-down and bottom-up attention

Authors: *H. MATKINS, E. A. BOURASSA;
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Abstract: On electroencephalography (EEG), an incorrect motor response is followed by a sharp negative deflection most prominent in the frontal and central cortex (likely originating from the anterior cingulate cortex). This error-related negativity (ERN) can be elicited whether or not the participant is consciously aware of the error and is thought to reflect either an error detection system or a more general conflict-monitoring system. Previous research has shown that the ERN is more pronounced in people with anxiety. The attentional control theory of anxiety posits that a decrease in top-down attentional control causes an increase in bottom-up attentional capture, and previous work in our lab has shown that this is true in students with test anxiety (TA). This study hypothesized that students with TA would have a larger ERN than students without TA and that the change in ERN would be larger in tasks requiring top-down attentional control. Participants were screened for TA using the blue-box stress test. EEG was measured from students with and without TA during a modified go-no go task. The modification was that half of the trials required top-down attentional processing (search condition) whereas the other half of trials required bottom-up attentional processing (salient condition). Interestingly, ERNs, as a whole, were smaller in participants with TA compared to participants without TA. In both groups, the ERN was larger in the salient condition compared to the search condition. Event-related spectral perturbations (ERSPs) over the central cortex in students without TA showed that committing an error caused a significant decrease in early theta power followed by a decrease in alpha power compared to correct trials; these differences were not seen in students with TA. On correct trials, students with TA had lower early theta power than

students without TA; on error trials, students with TA had decreased low-beta power compared to students without TA. In a separate exploratory analysis, there was a large negative deflection in the parietal lobes following the commission of an error; this parietal negativity was also much more pronounced in students without TA compared to participants with TA and was more prominent in the salient condition. Taken together, these data suggest that in students with TA, the conflict monitoring system of the anterior cingulate cortex may be hypofunctional and therefore goal-oriented behavior may be less amenable to correction. Alternatively, the parietal lobe deflection may suggest that the conflict-monitoring system includes the frontoparietal attentional network, a system known to be altered in TA.

Disclosures: H. Matkins: None. **E.A. Bourassa:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

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Program #/Poster #: P801.05

Topic: H.04. Executive Functions

Support: I01BX004712

Title: Pilot Results From a Brief, Remote Use, Cognitive Exam In COVID-19 Cases

Authors: *T. BERESFORD[1], D. HIPP[2], P. J. RONAN[3];
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[3]Psychiatry and Basic Biomed. Sci., VA Research/USD Sanford Sch. of Med., Sioux Falls, SD

Abstract: Background: Early experience with the COVID-19 Pandemic has begun to elucidate brain function changes that may result in compromised cognition both acutely and during variable recovery periods. Reported cognitive assessment is often limited to orientation alone. Further assessment may seem an inappropriate burden in acute COVID-19 cases characterized by fatigue and confusion as well as examiner safety. Objective: To assess cognition in COVID-19 cases as comprehensively as possible in a brief format, all while observing safety; and to establish clear-face value of its external validity. Method: We adapted a brief cognitive assessment, previously applied to liver transplant candidates and medical/surgical inpatients, for remote use in patients hospitalized for COVID-19 treatment. Collecting quality assurance data from telephone-administered assessments, this report presents a series of six COVID-19 case vignettes to illustrate the 5-Minute Assessment use in diagnosis and treatment of brain effects. Primary medical teams referred the cases for neuropsychiatric consultation. Results: Varying over four decades in age, none were able to engage meaningfully with their surroundings on admission. On follow-up exam 6 to 10 days later, four of the six had recovered Working Memory, and only one had recovered calculation ability. Two were capable of complex Judgment responses while none of the cases completed frontal executive function testing in the normal range. Conclusions: Cognitive assessment in COVID-19 cases, using this remote examination, reveals patterns of cognitive recovery that vary among cases and are far more complex than loss of orientation. In this series, testing specific temporal, parietal, and three frontal lobe functions suggests that calculation ability, judgment, and especially frontal

executive functions, may characterize COVID-19 brain effects. Used widely, and serially, this exam method can potentially inform our understanding of COVID-19 brain effects with healing from the virus.

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Poster

P801. Executive Function and Inhibitory Control in Human Subjects

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Topic: H.04. Executive Functions

Support: NRF Grant 2020R1I1A1A01072492
KHIDI Grant HI18C1166

Title: A Preliminary Study to Evaluate Feasibility, Efficacy and Satisfaction of a mobile-based Cognitive Remediation Therapy (CRT) program for pediatric patients with chronic neurological disorders

Authors: *S. EOM[1], Y. LEE[2];
[1]Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [2]Univ. of Texas Dallas, Dallas, TX

Abstract: Pediatric patients with chronic neurological disorders have often problems in their nerocognitive function. Specially, the cognitive remediation therapy(CRT) may be beneficial for alleviating persisting neurocognitive deficits in pediatric neurological patients. This study aimed to evaluate the feasibility, efficacy and satisfaction of the developed mobile-based CRT program for cognitively dysfunctional pediatric patients. Based on the previous study results for investigating parents' concerns and necessity of CRT as well as various chief problems of pediatric neurological patients, a mobile-based CRT program for pediatric patients was developed, which was composed of 6 game-like friendly CRT programs for core neurocognitive training including auditory selective/sustained attention, auditory/spatial memory, and executive function. In addition, the executive web-dashboard for carrying out the study process of the patients' and their parents' participation in the CRT program was designed for providing the relevant information such as procedure manual and evaluating subjects' neurocognitive function at the pre & post CRT, and keeping a daily training log, as well as executing CRT program. For the feasibility, efficacy and satisfactory study of this CRT, one hundred adults were included in the study with a mean age of 23.5±3.5 years. Relating mobile-based neuropsychological tests of Digit Span, Stroop, Working memory and processing speed were also performed as the pre-and post-intervention evaluation. In addition, self-report for attention, impulsivity, meta-cognition, and satisfaction were administered at the time of pre-and post-intervention. Neuropsychological data and behavioral measure were analyzed as a within-subjects factor. The analysis of the feasibility test including compliance and participation rate demonstrate the high level of feasibility. Furthermore, neuropsychological and behavioral data including reaction time, accuracy, and interference ratio demonstrated the positive effect of mobile-based CRT on attention, working memory and executive function. And satisfactory results showed the high level of satisfaction. The pediatric patients-centered mobile-based CRT program and the executive web-dashboard were designed and produced, and the results of preliminary study suggest that the feasibility, efficacy and satisfaction of the CRT program are significantly good. With the availability of the executive web-

dashboard, hopefully CRT could be useful for a clinical study and a clinical intervention for cognitively dysfunctional pediatric patients as an evidence-based CRT intervention program.

Disclosures: S. Eom: None. **Y. Lee:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.07

Topic: H.04. Executive Functions

Title: Conflict Control in Patients with Essential Tremor Pre-and Post- Deep Brain Stimulation.

Authors: *J. KANE[1], J. S. NEIMAT[3], S. WYLIE[1], P. HEDERA[4], F. PHIBBS[4], N. C. VAN WOUWE[2]; [2]Neurosurg., [1]Univ. of Louisville, Louisville, KY; [3]Neurosurg., Vanderbilt Univ., Nashville, TN; [4]Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: Deep brain stimulation (DBS) of the regions known to be involved in the dysregulation of motor processes is a common treatment option for patients with Essential Tremor (ET), a movement disorder characterized by kinetic tremor and execution deficits. Disruptions in cerebellar-thalamo-cortical networks could affect inhibitory action control in ET, which is dependent upon the suppression of impulse and replacement of a more appropriate action. The current study investigated whether ET disrupts the proficiency of conflict control by having 41 ET patients (before DBS surgery) and 29 age-matched healthy controls (HC's) perform an action control task (SIMON task). A smaller subset of 8 ET patients [ongoing study] completed the task both pre- and post- DBS) surgery of electrodes in the thalamic ventral intermediate (VIM) nucleus. Patients completed blocks of the Simon task, which requires a left or right response to a feature (e.g., here arrow direction) of a spatially lateralized stimulus. When the action signaled by the spatial location and direction of the arrow are non-corresponding (i.e., induce conflict), the inappropriate action impulse must be suppressed. Overall, patient pre-DBS performance on non-corresponding (Nc) conflict trials was slower and less accurate than corresponding (Cs) trials in comparison to HC's. A focused analysis on fast impulsive response rates (accuracy in the fastest reaction time bin on Nc trials) showed that ET patients responded more erroneously compared to controls. In sum, these results suggest impaired conflict control in ET compared to HC's. When comparing preliminary results from pre and post DBS performance, we found no significant differences in patient's accuracy or reaction time (RT) pre- to post-DBS, however, there was a trend of overall faster reaction times post-DBS (p=.064). Lack of significant difference in performance may be due to greater surgical benefits on (gross) motor over cognitive performance, although data collection for this study continues as well. The larger number of pre-op impulsive errors in comparison to the HC could be explained by a reduction in performance monitoring potentially caused by cerebellar deficiencies in ET, since previous studies in patients with cerebellar damage have found that a reduction in performance monitoring could lead to more errors. Future studies should aim to investigate how cerebellar dysfunction in ET relates to action impulsivity and how this is affected by DBS.

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Poster

P801. Executive Function and Inhibitory Control in Human Subjects

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Program #/Poster #: P801.08

Topic: H.04. Executive Functions

Support: NSERC Postgraduate Scholarship-Doctoral
NSERC Discovery Grant

Title: Buffer for boredom: A pilot investigation of the protective effects of exercise against mental fatigue

Authors: *B. TARI, M. SHIRZAD, M. HEATH;
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Abstract: Mental fatigue occurs after prolonged periods of sustained attention and results in increased ratings of exertion, decreased physical performance and slowed reaction times. Mentally fatigued individuals also perform worse than non-fatigued individuals on executive tasks (i.e., tasks requiring the ability to rapidly reconfigure attentional and motor goals). In contrast, executive function has been shown to be improved following a single bout of moderate-to-heavy-intensity exercise for as little as 10-min; however, whether a single bout of aerobic exercise can mediate the negative effects of mental fatigue is unknown. Here, participants completed separate 20-min sessions of rest (i.e., reading) and heavy-intensity (i.e., 80% of estimated maximum heart rate) aerobic exercise (via running or combination of running and walking) immediately prior to performing the psychomotor vigilance task (PVT) for 20-min. The PVT is a sustained-attention reaction-time task that measures the speed with which subjects respond to a visual stimulus and has been shown to reliably induce mental fatigue. Executive function was assessed prior to and immediately following the control-PVT and exercise-PVT sessions via the antisaccade task. Antisaccades are non-standard goal-directed eye-movements requiring that an individual look mirror-symmetrical to a target stimulus, and are mediated via similar frontoparietal networks modulated by aerobic activity and mental fatigue. Results demonstrate that the PVT elicited a greater degree of mental fatigue after rest than after exercise. In terms of executive performance, antisaccade reaction times (RTs) were lengthened following the rest-PVT session; however, antisaccade RTs were reliably shortened following the exercise-PVT session. Accordingly, evidence suggests that acute aerobic exercise may shield executive function against the deleterious effects of mental fatigue.

Disclosures: B. Tari: None. **M. Shirzad:** None. **M. Heath:** None.

Poster

P801. Executive Function and Inhibitory Control in Human Subjects

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Program #/Poster #: P801.09

Topic: H.04. Executive Functions

Support: NIH Grant DA044749
NIH Grant DA045189

Title: Gray matter volumetric correlates of dimensional impulsivity traits in children: an adolescent brain cognition development project

Authors: *Y. CHEN[1], J. S. IDE[1], C. S. LI[1,3], W. WANG[1], S. ZHORNITSKY[1], S. CHAUDHARY[1], T. M. LE[1], S. ZHANG[1], C.-S. R. LI[1,2,4];
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Abstract: Previous research has investigated the cerebral volumetric correlates of impulsivity, largely in moderate-sized samples, and the findings varied extensively across studies. Further, few have examined the potentially distinct neural correlates of the various dimensions of impulsivity. Here, we followed published routines and performed voxel-based morphometry analysis of a data set (n=11,474; 5,452 girls, 9-10 years) curated from the Adolescent Brain Cognition Development project. Of the sample, 648 and 2,697 were identified as monozygotic twins and dizygotic twins/siblings, respectively. In a linear regression with all five subscores of the UPPS-P questionnaire as regressors and age in months, total intracranial volume, and scanner model as covariates, higher levels of lack of premeditation and sensation seeking were correlated with greater gray matter volumes (GMVs) in a wide array of cortical and subcortical regions that subserve impulse control, including the frontoparietal cortex, insula, thalamus, and dorsal striatum. In contrast, higher positive urgency was correlated with diminished GMVs in many of the same regions as well as the hippocampus and parahippocampus. Slope tests revealed that girls relative to boys showed stronger correlations of regional GMVs with sensation seeking and with positive urgency. The dimensional impulsivity traits were weakly to moderately heritable with lack of perseverance showing highest h^2 in girls and boys. The volumetric correlates were highly heritable in girls and boys combined, with those of sensation seeking and positive urgency showing highest h^2 in girls and in boys, respectively. These findings collectively suggest shared and distinct cerebral volumetric bases of dimensional impulsivity traits in children and may facilitate developmental neuroscience research of externalizing psychopathology.

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Poster

P801. Executive Function and Inhibitory Control in Human Subjects

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P801.10

Topic: H.04. Executive Functions

Title: A step over the horse race model: study of inhibitory control of gait initiation by a stop signal task.

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Abstract: Gait initiation triggers a chain of events leading our body to leave a stable position, in which the difference between the body's center of mass (COM) and the center of pressure (COP) is minimal. During the about 500 ms of anticipatory postural adjustments (APA), that precede the step onset, a set of muscles are recruited both to lift the foot and to stabilize the body as the difference between COM and COP increases. Then, it is during APAs that inhibitory commands should act for the interruption of the multisegmental control of the stepping. The Stop Signal Task (SST), requiring either to execute a movement in response to a go signal (Go trials) or to inhibit it, when a stop signal suddenly occurs after the go (Stop trials), is largely used to study action inhibition. The outcome in the task is accounted for by a model describing a race between Go and Stop process, triggered by go and stop signals respectively. In stop trials, movements are executed if the Go process runs sufficiently fast. This formulation of the model, mainly developed by studying movements completed in a very short period, as saccades or finger (key press) movements, approximates the occurrence of movements with the end of race. However, the overall process can be different for movements evolving in longer timescales, or requiring different steps, as gait initiation. We used an adapted version of SST to study gait inhibition and evaluate how well the race model accounts for its control. Nine healthy participants were tested, while the position of 31 markers fixed on their body, the ground reaction forces over 8 dynamometer platforms and the activation of 16 body muscles were simultaneously recorded. The recorded signals were used to compute the time course of COM and COP changes and to measure muscles activity modulations during APAs in Go (GT), Stop correct (SCT), and Stop error (SET) trials. Muscle activity was used to estimate trial by trial the reaction time to the go (GoRT) and to the stop (StopRT) signal. As predicted by the race model GoRTs in GT were longer than in SET. However, the difference between COM and COP, at the time of StopRT, resulted higher in SET than in SCT suggesting this as a further parameter to monitor for predicting gait inhibition. Our results suggest that the inhibitory command controlling postural adjustments before Gait initiation continues to be processed after muscular activation and that the inhibition of the programmed step takes place only if the COM-COP difference reaches a point of non-return. Our results suggest a revision of the go process for the race model that must account for the biomechanical variables influencing complex and multi-segmented movements.

Disclosures: L. Fiori: None. **S. Colangeli:** None. **A. Ranavolo:** None. **F. Draicchio:** None. **S. Ferraina:** None. **E. Brunamonti:** None.

Poster

P805. Studies of Working Memory

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P805.01

Topic: H.05. Working Memory

Support: NRF-2017M3C7A1048040

Title: Neural Correlates of Emotional Working Memory in Nonsuicidal Self-Injury

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Abstract: There is strong evidence that emotional working memory may play a crucial role in processing emotional regulation. However, little is known about the neural correlates of emotional working memory of nonsuicidal self-injury (NSSI), which is associated with emotion dysregulation. The present study aimed to investigate the potential neurophysiological mechanism of emotional working memory in individuals who engaged in NSSI.Thirty-two individuals who have engaged in NSSI 5 or more times in the last year (NSSI group) and 28 age-, sex-, handedness-, socioeconomic status-, education-, and IQ-matched controls (control group) completed the Emotional Face N-back (EFNBACK) task during fMRI scanning. The EFNBACK task is a working memory task with emotional stimuli as distracters, and which consists of two different memory load conditions (i.e., 0-back, 2-back) and three emotional distracter type conditions (i.e., no picture, neutral face, or negative face). Whole-brain analysis revealed that the individuals with NSSI showed greater activity relative to controls in the left inferior and superior frontal areas during the high attentional demand conditions with negative-face distracters (2-back negative *versus* 2-back fixation contrast). The NSSI group also showed hyperactivation of the subcortical system, including the globus pallidus and caudate nucleus, in response to the 0-back negative *versus* 0-back fixation contrast. Moreover, within the NSSI group, a significant negative correlation was found between neural activity in the caudate and EFNBACK response times.These results are the first evidence of the altered neural response to the emotional working memory tasks in NSSI that has not been previously explored. These neural activity patterns to both the emotional distraction and the degree of attentional demand may provide new insights into the pathophysiology of NSSI.

Disclosures: H. Shin: None. **G. Kim:** None. **H. Moon:** None. **J. Hur:** None.

Poster

P805. Studies of Working Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P805.02

Topic: H.05. Working Memory

Title: Longitudinal study of working memory in Neurocysticercosis

Authors: *L. BAQUEDANO SANTANA[1], E. G. BERNAL TERAN[2], A. D. DELGADO[3], M. VERASTEGUI[4];
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Abstract: Neurocysticercosis (NCC) is a disease caused by the larval stage of the *Taenia solium* parasite located in the central nervous system. Seizures are the most common clinical manifestations; however,

patients with NCC often present cognitive impairment, including memory and learning alterations. The aim of this study was to evaluate memory in a rat model for NCC associated with neuronal damage in the hippocampus. Female and male rats 14 days old were intracranially inoculated with *T. solium* oncospheres. The T-maze test and Neurobehavioral scale were employed to evaluate spatial working memory and sensorimotor capacity. The H&E stain and the Anti-NeuN immunostaining allowed evaluating the hippocampal cells. NCC Male rats had short-term spatial memory losses in T-maze compared to control male rats at one year of follow-up. In contrast, NCC female rats displayed learning deficits and spatial working memory deficits at 9 and 12 months post-infection, compared to control female rats. Hippocampus neuronal cells density in NCC-infected rats with deficit memory was significantly different than the control group ($p<0.05$). Also, we reported seizures, paresis, and deficit sensorimotor. Overall, this study supports the relationship between NCC and cognitive impairment demonstrated by memory deficit.

Disclosures: L. Baquedano Santana: None. **E.G. Bernal teran:** None. **A.D. Delgado:** None. **M. Verastegui:** None.

Poster

P805. Studies of Working Memory

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Program #/Poster #: P805.03

Topic: H.05. Working Memory

Support: R21MH117687

Title: Vicarious trial and error during encoding of a spatial working memory task facilitates accurate decision-making

Authors: *A. E. GEORGE, J. J. STOUT, Jr., A. L. GRIFFIN;
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Abstract: Spatial working memory, the ability to encode, temporally maintain, and retrieve spatial information, is necessary for goal-directed navigation. Within a spatial working memory-dependent T-maze task, rats need to accurately retrieve information about a previous trial in order to make an informed decision about their next trajectory. When faced with these decisions at a choice point, rats will occasionally exhibit complex behaviors, such as pausing and sweeping their head back and forth. These behaviors, called vicarious trial and error (VTE), are thought to be a behavioral manifestation of deliberation (Redish, 2016). For this experiment, we examined VTE in adult male rats ($n = 18$) during asymptotic performance of a delayed non-match to position T-maze task, a task that experimentally separates memory encoding and retrieval into ‘sample’ and ‘choice’ phases. Interestingly, we observed that rats sometimes exhibit similarly complex behaviors during sample phase traversals, despite the fact that these trajectories are forced and thus do not require a decision. Using established methods to identify VTE (Redish, 2016), we found that VTE can be readily extracted from sample-phase traversals. We hypothesized that execution of sample phase VTE (sVTE) reflected the application of a strategy that was aiding rats in task performance. To explore this hypothesis, we analyzed the relationship between sVTE

and choice accuracy. We reasoned that, if sVTE aids the rat in making a correct decision, we should observe a higher proportion of sVTE to occur across trials in which the rat subsequently makes a correct choice when compared to the proportion of sVTE that occur on the sample phase of trials following a correct choice. As predicted, our results show that sVTE significantly tended to precede correct choices rather than follow them ($t(17) = 3.15$, $p < 0.01$). Surprisingly, the opposite effect was observed for incorrect trials - sVTE tended to occur more often on the sample phase of the trial following an incorrect decision ($t(17) = -4.13$, $p < 0.01$). Specifically, sVTE occurred most often on the sample phase of the trial after an incorrect choice when the next choice was correct ($t(17) = -2.25$, $p < 0.05$) - suggesting that, after an incorrect decision, the application of sVTE assists the rat in making a correct choice on the next trial. Together, these findings imply that VTE behaviors may serve various purposes during spatial working memory, depending on recent past experiences and whether encoding or retrieval is presently required.

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Poster

P805. Studies of Working Memory

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Topic: H.05. Working Memory

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Title: When Working Memory fails: mechanisms underlying memory accuracy and errors

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Abstract: Working memory (WM) is an essential brain function, which is central for cognition and severely impaired in multiple brain disorders. To investigate the underlying mechanisms limiting WM we developed a two-alternative delayed response task in which head-fixed mice are presented with an acoustic stimulus coming from either a left or a right side speaker. Animals had to remember the prospective response during a variable delay (duration D=0, 1, 3 and 10s) after which, they had to lick the corresponding side port.To understand how the length of the delay period affected the mice's accuracy, we fitted a Generalized Linear Model that quantified the impact of the different factors on choice. The fitted model captured the forgetting process as a reduction of stimulus impact on choice as D increased. Mice also showed (1) an idiosyncratic fixed bias showing a side preference for one of the choices that was affected by the delay and (2) a repeating bias favoring the previously responded side that was independent of delay. Also, the repeating bias increased with trial index within a session whereas the interaction between stimulus and delay length was not affected. To recapitulate these findings, we propose a two-

state hidden Markov Model in which animals switch between two behavioral strategies: a WM and a history-based module (HB). The WM module is described as a double well potential where the planned response can be maintained in one of the two attractors and forgetting is captured by noise-driven escape transitions during the delay. Small asymmetries between the two wells can introduce a WM bias that increases with the delay. The HB one is a logistic function that only depends on previous responses and outcomes and is thus unaffected by the delay. Trial index results suggest that animals spend more time in the HB towards the end of the session. Moreover, pharmacological inactivation of NMDA receptors using NR2B antagonists caused a decrease of the stimulus weight and an increase of the repeating bias, without change in the stability of WM. Finally, we performed electrophysiological recordings in the anterolateral motor cortex (ALM) of behaving mice seeking to validate the proposed two-module model. We found that the stimulus selectivity degraded continuously during the delay period, establishing a neural correlate of the memory forgetting found behaviorally. Moreover, activity in ALM differed between inferred WM trials and HB trials. Our results show that the source of errors could be substantially different depending on the strategy that subjects are following: a memory trace decrease during the delay for WM related errors and a non-efficient repetition strategy for HB errors.

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Poster

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Topic: H.05. Working Memory

Support: NIH grant R01AG026158

Title: Activation patterns underlying verbal working-memory maintenance and Cognitive Reserve

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Abstract: To identify an fMRI-pattern underlying working-memory rehearsal in a verbal Sternberg-task, we imaged 183 people with age coverage in the ranges 20-30 and 55-70. Beyond task performance, participants were characterized in terms of demographics, and neuropsychological assessments of crystallized verbal intelligence, episodic memory, perceptual speed, and abstract fluid reasoning. Participants studied an array of either 1, 3, or 6 upper-case letters for 3 seconds (=encoding phase), then rehearsed the letters sub vocally for 7 seconds facing a blank screen (=maintenance phase), to be probed with a lower-case letter to which they responded with a differential button press whether the letter was part of the studied array or not (=retrieval phase). For the current study we focused on the maintenance phase, and first performed OrT-CVA analysis (Habeck et al, 2005, Neural Computation) to identify an activation pattern showing memory-load increases in pattern score for all but 3 participants ($p < 0.0001$). The pattern showed positive loadings at mid-line supplementary motor and left inferior frontal areas, and negative loadings at Default-Node-Network areas. Load-related increases in pattern score correlated

positively with age, but negatively with mean cortical thickness, episodic memory, fluid reasoning, and perceptual speed, but load-averaged pattern scores were positively related to verbal intelligence. (All p-values less than 0.01). However, since the pattern revealed no relationship to task performance, we combined all load levels by averaging, and used PCA-regression in an additional analysis to derive a pattern to predict mean reaction time (p=0.002). The regional composition of the pattern was sparse and consisted of positive loadings (=faster reaction) in bilateral thalamus and left orbitofrontal areas, with negative loadings (=slower reaction) in right mid-frontal and angular-gyrus areas. Load-averaged pattern scores only displayed a positive association with perceptual speed (p=0.002). These results demonstrate that a necessary load-related activation pattern manifested greater efficiency (=lower slope) for younger age, thicker cortices, and better fluid cognition, but no relation to performance. Instead, there was an additional performance-related pattern, independent of age or brain structure. Because the performance relation was not confounded by brain structure or age, the pattern fulfills the postulates of Cognitive Reserve, and maps out a dimension different from usual proxies like crystallized verbal ability, leisure activity, or education.

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Poster

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Title: Emergence of population dynamics causally driving delayed paired associations working memory

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Abstract: While a number of brain regions vital for working memory have been identified, and persistent activity in these regions recorded during working memory tasks, how these activity patterns emerge and the necessity of these activity patterns for behavioral performance is poorly understood. To gain more insight into these problem, we have trained head-fixed mice to perform an olfactory paired association working-memory task, during which head-fixed mice made decisions depending on the sequential identity of two odors presented separated by 5 seconds. As the secondary motor cortex (M2) has been found to be essential for the performance of motor preparation tasks, we asked if the M2 was also critical for performance of complex working memory tasks requiring the comparison of two distinct stimuli separated in time. We therefore utilized a highly efficient soma-targeted Guillardia theta anion-conducting channelrhodopsin (stGtACR2) to perform optogenetic silencing at different time intervals while the animal was performing the task. Single-unit recordings demonstrated that stGTACR2 silencing was highly effective and did not result in abnormal activity patterns beyond the stimulation period. Silencing of M2 neurons during delay and reward periods dramatically worsened behavioral performance, while stimulation at other time intervals had no effect. Therefore M2 is both important for maintaining the

working memory during the delay period, as well as comparing the memory of the first stimulus with the second stimulus to drive decision making. Future work will determine the mechanisms that drive the development of delay activity with learning.

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Poster

P805. Studies of Working Memory

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The National Research Council of Thailand grant
The KMUTT's Startup Fund for junior researchers

Title: The parallel neurodevelopment of selective filtering and visual working memory capacity from childhood to adulthood

Authors: *K. LERTLADALUCK[1,2], P. WIWATPHONTHANA[2], P. SOOKPRAO[2], P. PUVACHAROONKUL[3,2], K. NIRUNPONG[4], S. ITTHIPURIPAT[2,5,6];
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Abstract: It has been debated how attention and visual working memory (vWM) develop from childhood to adulthood. One prominent account has proposed that vWM capacity fully developed in late childhood as past research studies have reported children as early as 7 years old (or even younger) having a comparable level of vWM capacity similar to the adult level, distinct to the ability to filter out distraction which continues to develop throughout late childhood and adolescence. However, it has been argued that comparable working memory performance across children and adults could be due to the differences in experimental protocols used in different age groups. Moreover, recent research has shown that vWM continues to develop throughout adolescence. That said, it is still possible that vWM capacity could drop after late childhood and rise again during adolescence until it reaches a similar level in adulthood. Here, we measured the capacity of vWM and related EEG activity from typically developing children, teenagers, and healthy adults performing a delayed-matching-to-sample task where they selectively

remembered the colors of visual targets presented with and without distractors. Importantly, comparisons across age groups were performed using the data obtained from conditions where task parameters including encoding duration and set sizes of targets and distractors were carefully controlled. We found that vWM capacity continued to increase from late childhood to adolescence and adulthood in parallel with age-related improvement in selective filtering function. Moreover, the modulations of the contralateral delay activity and the frontal biasing EEG signals track the developmental trajectories of vWM capacity and filtering efficiency, respectively. Together, our data suggest that the continuing maturation of the parietal and frontal cortex plays a crucial role in supporting the parallel development of working memory and selective attention, which is extended throughout late childhood and adolescence.

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Poster

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Topic: H.05. Working Memory

Support: NIH Grant MH095984-06

Title: Flexible top-down control in the interaction between working memory and perception

Authors: *C. TENG[1], J. M. FULVIO[1], J. JIANG[2], B. R. POSTLE[1];
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Abstract: Working memory (WM) and perception are highly intertwined and interactive processes (e.g., Awh and Jonides, 2001; Chun, Golomb, Turk-Browne, 2011), and a considerable amount of research supports the idea that these two functions may rely on a common representational substrate (e.g., Teng & Kravitz, 2019; Teng & Postle, 2021). Here we examined how the interaction between WM and ongoing perception is controlled, by testing human performance on a dual-task that varied conflict between WM and perceptual representations. Subjects first viewed an orientation-grating memorandum, then performed orientation discrimination on a second item (the discriminandum), and then recalled the orientation of the memorandum. Congruity between memorandum and discriminandum was manipulated, and incongruent trials generated hallmarks of both proactive and reactive control in performance on the subsequent trial: The response-time cost of incongruity was reduced for the discrimination task (indicating increased proactive control) and the sign of the serial bias of the discriminandum on recall flipped, from attractive following congruent trials to repulsive following incongruent trials (a consequence of reactive control). A separate control experiment confirmed that the repulsive serial bias reflected top-down control (rather than, e.g., passive perceptual adaptation) because it was absent when the orientation of the discriminandum was made task-irrelevant. To formalize these observations, we fit the data using the Flexible Control Model (FCM; Jiang et al., 2014, 2015) and two model parameters were sensitive to trial-by-trial variation in conflict: fluctuation in “predicted conflict” quantified adjustments in the level of proactive control; the value of the “control prediction error” captured the strength of reactive control

recruited in response to memorandum-discriminandum congruity. Furthermore, the magnitude of the repulsive serial bias triggered by an incongruent trial was predicted by the magnitude of that trial's "control prediction error" (solidifying the link between repulsive bias and reactive control). Overall, these results illustrate that conflict between the current contents of WM and perception is governed by the flexible recruitment of two types of top-down control, proactive and reactive control. Model-based analysis of the results from a follow-up EEG experiment will investigate neural correlates of these two distinct forms of cognitive control.

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Poster

P805. Studies of Working Memory

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Program #/Poster #: P805.09

Topic: H.05. Working Memory

Title: Impaired spatial working memory by TRPC4 channel knockdown in the hippocampus CA1 area

Authors: *B. SABER MAROUF[1], R. KAUSHIK[2], A. DITYATEV[2], M. SAUVAGE[3], M. YOSHIDA[4]; [1]ESF graduate school ABINEP, Med. Faculty, Otto-von-Guericke Univ., Magdeburg, Germany; [2]Mol. Neuroplasticity, German Ctr. for Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [3]Leibniz Inst. for Neurobio. (LIN), Magdeburg, Germany; [4]DZNE Magdeburg, Haus 64, Magdeburg, Germany

Abstract: Working memory requires a maintenance of information in a readily accessible form in various cognitive tasks. Persistent firing of neurons is believed to be one of the neurophysiological mechanisms to retain information during working memory. It has been reported that transient receptor potential canonical 4 (TRPC4) channels support persistent firing in individual hippocampal CA1 pyramidal cells. To study the role of hippocampal TRPC4 channels on the spatial working memory, shRNA technique was used to knockdown the TRPC4 channels in the hippocampal CA1 neurons. TRPC4 knock down efficacy was confirmed in primary neuronal cell culture. A spatial-delayed alternation task (T-maze) was used to study the effect of TRPC4 knockdown in mice (12 weeks old, C57BL/6J) spatial working memory. The results showed a significant performance attenuation in the TRPC4 knockdown group compared to the control group that was injected with a scramble shRNA virus. In conclusion, our data suggests an indispensable role of hippocampal TRPC4 channels in spatial working memory.

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Poster

P805. Studies of Working Memory

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Program #/Poster #: P805.10

Topic: H.05. Working Memory

Title: Memory-guided continuous tracking reveals the spectrogram of working memory

Authors: *S. AHMAD[1], L. K. CORMACK[2], A. C. HUK[2];
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Abstract: Working memory is often studied in the laboratory using discrete items to be remembered, but in real life, continuous sensorimotor events are commonplace. We therefore developed a task in which subjects reconstruct a continuous (but noisy) visual trajectory from memory. We then adapted and extended the tools of continuous psychophysics (Bonnen et al, 2015) to analyze the effects of stimulus intensity and delay period on the accuracy of remembered trajectories. In our novel task, subjects used a mouse cursor to retrace the trajectory of a gaussian luminance blob after it moved in a one-dimensional random walk. The target's horizontal movement was specified by a sequence of gaussian white noise velocities that were cumulatively summed to generate the on-screen coordinates, while the vertical coordinates of the target and subject's cursor were defined by a constant rate. On each trial, subjects observed targets presented at 5% and 20% contrast levels travel trajectories of varying lengths (1, 2, or 4 s). Following each trajectory, the subject had an equivalent amount of time to retrace the previously seen path from memory. We adjusted the memory demand during the task by varying the length of the target trajectory. Longer trajectory lengths stressed the subjects mnemonic ability by increasing the amount of time between observing and reconstructing the target trajectory (delay period) as well as the amount of information to remember. Subjects were able to perform the task and completed a total of 162 tracking trials each. The spatial positions of the target and subject's cursor were used to compute trial-averaged cross-correlograms (CCGs) and measure the correlation between our target and response time series data as a function of the lag between them (Mulligan, Stevenson, & Cormack, 2013). Our CCGs showed that tracking performance on the task decreases when stimulus intensity is low and the delay length increases. We then generated time-frequency cross-correlation plots of the subject's response velocities to characterize the spectro-temporal representation of their memory-guided tracking performance and compare it to that of the target velocities. The resulting "spectrograms of memory" revealed the degree and time course to which coarser aspects of the target trajectory were remembered better than finer aspects of the trajectory. We found that the trajectories reconstructed from memory typically reflected frequencies below 10 Hz. This approach thus provides a means for characterizing more continuous aspects of working memory, and can do so in the context of a naturalistic behavior without requiring extensive task training.

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Poster

P823. Episodic and Episodic-Like Memory II

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Title: The effects of age on neural correlates of recognition memory: an fMRI study

Authors: *M. HOU, T. WANG, M. RUGG;
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Abstract: Prior studies examining the effects of age on the neural correlates of recognition memory have yielded mixed results. In the present study, we employed a modified remember-know paradigm to compare the fMRI correlates of recollection and familiarity in samples of healthy young (n = 16, mean age = 20.3, age range = 18-25, 8 female) and older adults (n = 22, mean age = 69.1, age range = 63-77, 13 female). After studying a series of concrete words, participants underwent fMRI scanning during a test phase in which they responded "remember" to a test word if any qualitative information could be recollected about the study event. When recollection failed, participants signaled how confident they were that the test item had been studied. Young and older adults demonstrated statistically equivalent estimates of recollection and familiarity strength, while overall recognition memory accuracy was significantly lower in the older adults. Robust, age-invariant fMRI effects were evident in two sets of *a priori* defined brain regions consistently reported in prior studies to be sensitive to recollection (the 'core recollection network') and familiarity respectively. In addition, the magnitudes of 'familiarity-attenuation effects' in perirhinal cortex demonstrated age-invariant correlations with estimates of familiarity strength and memory accuracy, replicating prior findings. Together, the present findings add to the evidence suggesting that the neural correlates of recognition memory are largely stable across much of the healthy human adult lifespan.

Disclosures: M. Hou: None. **T. Wang:** None. **M. Rugg:** None.

Poster

P823. Episodic and Episodic-Like Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.02

Topic: H.07. Long-Term Memory

Support: NIH Grant MH106512

Title: Cortical representations of decoded content in episodic memory encoding and reinstatement

Authors: *M. HEBSCHER[1,2], J. L. VOSS[1];
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Abstract: Everyday memory involves high overlap between the actors, locations, and objects of events. Such overlapping information can aid cueing of related memories or lead to memory interference. Little is known about how overlapping information is processed by different neural structures at the time of

encoding and how similarity between events affects their later recall. In the present study, we tested how the degree and content of similarity among naturalistic events affects how they are encoded and remembered. We used computational modeling to decode the content of naturalistic stimuli and measured the degree to which similarity between stimulus features predicts encoding and reinstatement by measuring multivoxel patterns of functional magnetic resonance imaging (fMRI) activity. Subjects (N=20) performed an episodic memory task in which they encoded and recalled naturalistic video stimuli in the fMRI scanner. Visual similarity between stimuli was assessed using a convolutional neural network and semantic similarity was measuring using a topic model applied to descriptive text of the videos. Visual similarity was found to positively predict multivoxel pattern similarity between stimuli at encoding in posterior temporal and occipital regions. Semantic similarity positively predicted pattern similarity at encoding in temporal and higher-level occipital regions, and negatively predicted neural similarity in lower-level occipital regions. These findings demonstrate that different event features derived from computational models map onto multivariate patterns of neural activity at the time of encoding in relevant cortical regions. We further found that greater pattern similarity at encoding was differentially related to later cortical reinstatement. Parietal and temporal regions tended to show a positive relationship, such that more neural similarity between stimuli at encoding predicted greater reinstatement of those stimuli. Occipital regions showed the opposite pattern, with greater neural similarity between stimuli at encoding negatively predicting later reinstatement of those stimuli. This suggests that greater neural similarity between events at the time of encoding, or integration, aids reinstatement in certain regions, while lower neural similarity, or differentiation, aids reinstatement in other regions. Together, these findings demonstrate that the degree and content of overlap between naturalistic events affects how they are encoded and reinstated by patterns of cortical activity.

Disclosures: M. Hebscher: None. **J.L. Voss:** None.

Poster

P823. Episodic and Episodic-Like Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.03

Topic: H.07. Long-Term Memory

Support: ESRC Grant ES/R010072/1

Title: The Impact of Externally Induced Gamma Oscillations on Human Episodic Memory Formation

Authors: *D. WANG[1,2], K. L. SHAPIRO[2], S. HANSLMAYR[1,2];
[1]Inst. of Neurosci. and Psychology, Univ. of Glasgow, Glasgow, United Kingdom; [2]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Episodic memories are past experiences that usually contain rich multisensory information. Previous studies using rhythmic sensory stimulation (RSS) show that synchronising multisensory brain regions at theta frequency facilitates binding multisensory information into long-term memory. These findings suggest that effective associative memory depends on finely tuned timing between cortical inputs. One of such timing mechanisms is spike timing dependent plasticity (STDP). If a pre-synaptic

neuron fires within a short delay before a post-synaptic neuron, the connection from the pre-synaptic neuron to the post-synaptic neuron will be strengthened. If the temporal order of the two spikes is reversed, then the synaptic connection will be weakened. Such a time window for synaptic modification (< 50 ms) falls within the gamma frequency range and synaptic modification is an exponential function of delay. However, evidence on the causal role of synchronising neural inputs at gamma frequency in human episodic memory formation is lacking. We investigated this using RSS to entrain visual and auditory cortices at gamma frequency (37.5 Hz). Luminance of video clips and volume of sound clips were modulated by a 37.5 Hz sine wave with four phase offsets: 0°, 90°, 180° and 270°, which corresponds to the delay of 0 ms, 6.67 ms, 13.33 ms and 20 ms between visual and auditory inputs. In Experiment 1, 48 young healthy participants (both sexes) were asked to remember associations between the video-sound pairs and later recall the corresponding video when they were cued with a sound. Recall accuracy for the 0° condition was significantly better than the 270° condition, which has the longest delay between visual and auditory stimuli, suggested by a paired sample t-test. However, whether this memory effect was indeed driven by STDP is not clear with regard to the directionality of the synapses. To better formulate the role of STDP, we conducted Experiment 2 with a new group of 48 participants. The only difference from Experiment 1 was that the participants were cued with a video in the memory test and asked to recall the corresponding sound. Recall accuracy was predicted to decay exponentially as a function of the phase offset between visual and auditory inputs, if STDP is the driving force. In each experiment, EEG activity was recorded in 24 participants. EEG data is predicted to reveal that sensory regions are entrained to the respective frequency and phases. Our findings provide causal evidence with regard to the role of gamma oscillations in supporting human episodic memory formation, which supports the notion that STDP may play an important role in human learning and memory.

Disclosures: D. Wang: None. **K.L. Shapiro:** None. **S. Hanslmayr:** None.

Poster

P823. Episodic and Episodic-Like Memory II

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.04

Topic: H.07. Long-Term Memory

Support: PID2019-111199GB-I00

Title: Post-encoding reactivation binds episodic sequences in long-term memory

Authors: *X. WU[1,2,3], B. STARESINA[4], L. FUENTEMILLA[1,2,3];
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Abstract: Prior animal and human work have shown that post-encoding reinstatement plays an important role in the formation of a memory for the unfolding experience. Here, we test whether the integration of the elements of an episodic sequence is promoted via neural reinstatement after one-shot exposure. We recorded scalp electroencephalography (EEG) while participants encoded trial-unique combinations of

face-object-scene picture triplets that were subsequently recalled in a test. We used representational similarity analysis on EEG data and found evidence for rapid memory reinstatement the just encoded triplet sequence (i.e., ~500 ms after the offset) , and that the magnitude of the neural reinstatement predicted recollection in the test. We then used a time-resolved pattern classification approach to quantify the degree to which EEG neural activity elicited during picture encoding and at sequence offset discriminated between image categories. This analysis revealed statistically validated classifier fidelity at approximately 180ms - 500ms during image presentation, and this time window also coincided with significantly increased magnitude of discriminability of the classifier output throughout the offset period. More importantly, later remembered triplets showed reduced discriminability value across offset period comparing to the later forgotten triplets. Altogether these results provide important evidence that episodic offset memory reinstatement is a mechanism engaged to support integration of episodic elements in long term memory, and that such integration is achieved by overcoming the representational gap between separate encoding stimuli.

Disclosures: X. Wu: None. **B. Staresina:** None. **L. Fuentemilla:** None.

Poster

P823. Episodic and Episodic-Like Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.05

Topic: H.07. Long-Term Memory

Support: ERC-STG-715714

Title: Tracking encoding-retrieval transformations using EEG-based representational structures

Authors: *C. POSTZICH[1], J. LINDE-DOMINGO[2], M. WIMBER[1];
[1]Univ. of Glasgow, Glasgow, United Kingdom; [2]Ctr. for Adaptive Rationality, Max Planck Inst. for Human Develop., Berlin, Germany

Abstract: Episodic memories contain sensory information about the events we encounter, and it is commonly assumed that successful recall of the event is supported by the neural reactivation of such information. A growing amount of evidence, however, indicates that stimulus information during the initial encoding and the subsequent retrieval are not represented in the same cortical location, suggesting an encoding-retrieval transformation rather than a veridic reinstatement of the original information (Rissman, J., & Wagner, A. D., 2012, Annu. Rev. Psychol.). While most of the evidence comes from fMRI, the present EEG study uses second-order representational similarity analyses to investigate this potential transformation with high temporal resolution. In our task, subjects learned associations between words and objects in an encoding phase and were later cued with the word to retrieve the object, and to classify it according to its perceptual or semantic content (e.g., was it an animate or an inanimate object). The ability of a multivariate pattern classifier to distinguish different object classes (e.g., insects vs mammals) was used as a measure of the representational dissimilarity between classes of objects. Time series of representational dissimilarity matrices (RDMs) during encoding showed early differentiation along the perceptual dimension followed by differentiation along the semantic dimension, indicating a

forward stream of processing, in line with previous results (Cichy, R. M., Pantazis, D., & Oliva, A., 2014, Nat. Neurosci.). Encoding and retrieval RDM time series were then cross correlated, yielding a temporally resolved encoding-retrieval similarity measure that does not depend on the reactivation of the exact original features. Additionally, we employed a novel approach to delineate perceptual and semantic influences on this encoding-retrieval similarity measure, and this approach provided evidence for a reverse semantic-to-perceptual reactivation stream during retrieval (Linde-Domingo, J., Treder, M. S., Kerrén, C., & Wimber, M., 2019, Nat. Commun.). Finally, topographical analyses of the classifier performances indicate that different sets of sensors contribute to encoding and retrieval classification, adding to the notion that stimulus representations are transformed from initial learning to later remembering.

Disclosures: C. Postzich: None. **J. Linde-Domingo:** None. **M. Wimber:** None.

Poster

P823. Episodic and Episodic-Like Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.06

Topic: H.07. Long-Term Memory

Support: UNAM DGAPA PAPIIT IG300121

Title: Influence of dietary nutrient intake on episodic memory across the adult life span

Authors: *S. CANSINO[1], F. TORRES-TREJO[2], *C. ESTRADA-MANILLA[1], A. FLORES-MENDOZA[1], G. RAMÍREZ-PÉREZ[1], S. RUIZ-VELASCO[3];
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Abstract: The aim of the study was to identify nutrients that have the ability to impact brain functioning and, as a consequence, influence episodic memory. In particular, we examined recollection, the ability to recall details of previous experiences, which is the episodic memory process most affected as age advances. A sample of 1550 healthy participants between 21 and 80 years old participated in the study. Nutritional intake was examined through a food frequency questionnaire and software developed to determine the daily consumption of 64 nutrients based on food intake during the last year. Recollection was measured through a computerized source memory paradigm. First, we identified which nutrients influence recollection across the entire adult life span. Then, moderator analyses were conducted by dividing the sample into young (21-40 years old), middle-aged (41-60 years old) and older (61-80 years old) adults to establish in which life stage nutrients influence episodic memory. Across the adult life span, recollection accuracy was shown to benefit from the intake of sodium, heme, vitamin E, niacin, vitamin B6, cholesterol, alcohol, fat, protein, and palmitic, stearic, palmitoleic, oleic, gadoleic, alpha-linoleic and linoleic acid. The effects of energy, maltose, lactose, calcium and several saturated fatty acids on recollection were modulated by age; in older adults, the consumption of these nutrients negatively influenced episodic memory performance, and in middle-aged adults, only lactose had negative effects.

Several brain mechanisms that support episodic memory were influenced by specific nutrients, demonstrating the ability of food to enhance or deteriorate episodic memory.

Disclosures: S. Cansino: None. **F. Torres-Trejo:** None. **C. Estrada-Manilla:** None. **A. Flores-Mendoza:** None. **G. Ramírez-Pérez:** None. **S. Ruiz-Velasco:** None.

Poster

P823. Episodic and Episodic-Like Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P823.07

Topic: H.07. Long-Term Memory

Title: Linear episodic chronometry in the macaque medio-posterior parietal cortex

Authors: *L. HUANG[1], L. WANG[1], Y. ZHENG[1], K. MAKOTO[2], S. KWOK[3,1,4];
[1]East China Normal Univ., Shanghai, China; [2]Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom; [3]Div. of Natural and Applied Sci., Duke Kunshan Univ., Kunshan, China; [4]Shanghai Key Lab. of Brain Functional Genomics, Shanghai, China

Abstract: Primate posterior parietal cortex (PPC) mediate memory consolidation and retrieval. While we previously reported that monkeys rely on a forward replay mechanism to support temporal-order judgement between cinematic events, it is unknown how PPC neurons deal with multiple events spanning across intertwined episodes. We recorded single-unit electrophysiology data from the monkeys PPC while having them learned 6 videos over 2 days and tested their temporal order judgement (TOJ) on third day: learning phase consisting of 3 10-s videos/day (in total 6 different videos), and testing phase on Day 3 consisting of TOJ trials without any video-watching. On day 3, they performed TOJ trials under three different conditions: (i) both frames from a single video; (ii) frames from two different videos learned within same day; (iii) frames from two different videos learned across two different days. We ran four 3-day sessions and recorded 61 neurons in total. We tested the hypotheses that (1) the animals recall the order of episodic events learned across the previous two days in a forward search, sequential manner, and (2) such a forward search retrieval mechanism is supported by PPC neurons. Behaviorally, a linear regression model showed that monkeys' response time for TOJ increased as a function of chosen frame location across the 6 videos spanning across the first two days (i.e., faster for video 1 and slower for video 6), with correct trials on Day 3: $r^2 = 0.018$, $p < 0.001$, suggesting that the six videos might have been integrated into a single temporal sequence and the animals retrieved the memory in a forward search sequential manner. Moreover, when considering the increment in RT between first and last chosen frame location, there is a compression factor of 2.14×10^{-6}. Correspondingly, the firing rate decreased significantly as a function of chosen frame location across the 6 videos spanning across the first two days (i.e., higher for video 1 and lower for video 6), with all neurons: $r^2 = 0.004$, $p < 0.001$, and with 36 out of 61 neurons showing this pattern. This result suggests firing rate of most of neurons are modulated by memory search. These results indicate that PPC neurons would reduce their firing rate when the memory search hit the memory target, suggesting that these neurons are involved in supporting the putative forward search. Altogether, our results suggest macaque monkeys can learn and maintain a linear, extended series of episodic experiences (over 48 hours), while PPC neurons are involved in supporting

this forward-replay memory search. These results support the presence of a memory chronometry for past episodes in the primate medio-posterior parietal memory system.

Disclosures: L. Huang: None. **L. Wang:** None. **Y. Zheng:** None. **K. Makoto:** None. **S. Kwok:** None.

Poster

P823. Episodic and Episodic-Like Memory II

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Program #/Poster #: P823.08

Topic: H.07. Long-Term Memory

Support: R37-MH065635
HHMI Gilliam Fellowship

Title: Oligodendrocyte mechanisms in the anterior cingulate cortex but not the hippocampus are critical for episodic memory formation

Authors: *L. BARBOZA, B. BESSIÈRES, O. NAZARZODA, C. M. ALBERINI;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The hippocampus and prefrontal cortex play an essential role in memory consolidation, the process by which an initially labile memory becomes stronger and resilient to disruption. While hippocampal biological mechanisms have been extensively investigated as the bases of memory consolidation, the biological changes in cortical areas contributing to memory consolidation and storage are less understood. Furthermore, while the hippocampus is generally known to play a transient, although critical, role in memory consolidation, cortical areas, and particularly the anterior cingulate cortex (ACC), is believed to be the site of long-term memory storage. Here we show that in the ACC, but not in the dorsal hippocampus (dHC), oligodendrocyte-specific transcripts are rapidly induced after a single episodic learning event and required for long-term memory formation. RT-qPCR time course analyses after inhibitory avoidance training in rats revealed a rapid upregulation of transcripts critical for oligodendrocyte differentiation and myelin biogenesis in the ACC but not the hippocampus. Western blot and immunohistochemistry analyses confirmed the upregulation of oligodendrogenesis-related proteins one day after training. ACC-targeted antisense-mediated knockdown of Myrf, a master transcription factor of oligodendrogenesis, impaired long-term memory retention but did not affect short-term memory. Likewise, either conditional global or ACC-targeted knockout of oligodendrogenesis in mice impaired long-term memory formation while dHC-targeted knockout had no effect. We conclude that oligodendrocyte-specific mechanisms are rapidly regulated and required for long-term memory formation in the ACC, but not the hippocampus.

Disclosures: L. Barboza: None. **B. Bessières:** None. **O. Nazarzoda:** None. **C.M. Alberini:** None.

Poster

P823. Episodic and Episodic-Like Memory II

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Program #/Poster #: P823.09

Topic: H.07. Long-Term Memory

Support: NSF GRFP
NIH Training Grant (T32 EY013933)
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NY Stem Cell Foundation Robertson Neuroscience Investigator Award
NIH Director's New Innovator Award (DP2-AG071918)

Title: Flexible use of memory by food-caching birds

Authors: *M. C. APPLEGATE, D. ARONOV;
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Abstract: A hallmark of human episodic memory is “flexibility” - the ability of a single memory to influence different behaviors in pursuit of different goals. It is unknown to what extent memory in other animals is similarly flexible. To address this question, we studied spatial behaviors of a specialist food-caching bird, the black-capped chickadee. These birds naturally pursue different goals at different moments in time as they explore an environment, cache food, and later retrieve caches. We designed a behavioral setup to engage these behaviors and track them automatically. In our apparatus, chickadees took seeds from a motorized feeder and cached them into one of 64 sites by peeling back a silicon flap. Site contents were invisible to the bird unless the flap was lifted. The contents and the bird’s interactions with each site were tracked through a transparent floor of the arena via a camera and real-time video processing. Our behavioral paradigm 1) allows birds to express their natural caching instincts, 2) permits high-throughput, automated behavioral tracking, and 3) is compatible with modern neuroscience techniques, such as awake-tethered recordings. We recorded chickadee behavior in two conditions: one in which they freely cached seeds throughout this arena, and one in which they retrieved previously made caches. We next used probabilistic modeling to disentangle the contributions of memory-guided and non-mnemonic strategies to the behavioral choices made by chickadees in these tasks. We first accounted for birds’ biases in their choice of sites (distribution over space, p_{bias}). We then considered the effect of three types of locations on subsequent site interactions: the previous site checked by the bird, sites already occupied by caches, and sites previously checked by the bird that are currently empty. We asked whether the probability of caching or checking at these locations, or nearby locations, was altered relative to p_{bias}. We found that chickadees use memories of the contents of individual cache sites in a context-dependent manner. During caching, chickadees are 3-fold more likely to avoid sites that already contain food, resulting in an even distribution of caches throughout the environment. During retrieval, they instead show a 2-fold propensity to return to occupied sites and obtain food. These effects are site-specific, long-lasting, and do not diminish as more seeds are cached. Thus, chickadees can use a single memory to achieve at least two unrelated behavioral goals. These results demonstrate memory flexibility in an animal in a tractable spatial paradigm.

Disclosures: M.C. Applegate: None. **D. Aronov:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.01

Topic: H.03. Decision Making

Support: Gatsby Charitable Foundation (562980)
Wellcome Trust (562763)

Title: Pupil dilation as a proxy for implicit statistical learning in freely moving mice and humans

Authors: *A. ONIH, T. GEORGE, S. NIERVWETBERG, A. AKRAMI;
Sainsbury Wellcome Ctr., Univ. Col. London, London, United Kingdom

Abstract: Pupil dilation as a proxy for implicit statistical learning in freely moving mice and humansAdedamola Onih, Tom George, Svenja Nierwetberg, Athena Akrami Sensory events in natural environments are mostly patterned and structured. Different organisms have evolved to extract these structures efficiently and often without any explicit instruction. Previous studies have shown that by learning the statistical features of sensory inputs, humans can make predictions about future events, and when those predictions are violated, they exhibit a surprise response. In humans, multiple oddball paradigms have shown pupil dilation to be a reliable proxy for surprise in response to violations from predictable sensory events.. We developed a novel comparative behavioural paradigm, “X” detection, to investigate how mice and humans implicitly learn and generalise the statistics from their sensory world after a limited number of exposures. In this paradigm, subjects were exposed to task-irrelevant, structured auditory sequences while performing an auditory distractor task. Stimulus set is designed such that mere novelty detection can be distinguished from learning abstract rules. Tracking pupil diameter, we show that in both mice and humans, predictability of (task-irrelevant) auditory events correlates with the pupil size. This establishes pupil diameter as a reliable indicator of rule extraction over several sensory repeats. We use this paradigm to test the capacity of mice to learn auditory sequences of varied complexities, in comparison to human subjects, as well as computational models designed to learn different classes of regularities in unsupervised manners. We therefore establish mouse pupil size and the “X” detection task as a useful model for tracking the implicit extraction of statistics from the sensory world, and thus, a tool for further investigation into the neural correlates of statistical learning.

Disclosures: A. Onih: None. **T. George:** None. **S. Niervwetberg:** None. **A. Akrami:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.02

Topic: H.03. Decision Making

Title: Leveraging unsupervised behavioral segmentation to identify its neuronal correspondence during unconstrained behavior of macaques

Authors: *B. VOLOH[1], D. J. N. MAISSON[1], B. Y. HAYDEN[1], J. ZIMMERMANN[2];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Neurosci., Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Rhesus macaques have been an invaluable animal model in determining the function and electrophysiology of the brain. Typical electrophysiological experiments are performed under highly unconstrained and unnatural conditions - such as "foraging" with eye movements. This raises doubt as to the ecological validity of neural inferences, and thus their external validity. A useful alternative would be to study behavior in freely moving unconstrained conditions. A key obstacle in the study of unconstrained behavior is behavioral segmentation, namely, the determination and annotation of behavioral states. To this end, we studied macaque behavior (N=2) in a large, open-field environment while they performed a foraging task. Pose reconstruction was achieved with a software tool we developed called OpenMonkeyStudio. For this study, we developed a data-driven, unsupervised behavioral segmentation pipeline, which takes in postural keypoints and embeds them in a lower, 2-dimensional space, in order to identify and cluster repeated occurrences of similar poses. Embedding poses resulted in well-formed, semantically meaningful clusters that could be identified by a human, such as "left stride", "right stride", and "sitting". Importantly, the structure of the embedding space was itself meaningful. Transitions tended to occur between nearby, rather than distant, clusters, suggesting a hierarchical organization of behavior. We further identified idiosyncratic sequences of poses (eg "walking" being composed of left and right stride poses) by embedding pose sequences on the basis of their circular edit distance. Finally, we re-embedded new pose data (from one subject) from sessions with simultaneous, large-scale, wireless neural recordings (128 channels spanning the prefrontal expanse, including dACC, DLPFC, OFC, VLPFC, and PM, among others). We found that across the population of all recorded neurons (n=5303), spike rates corresponded to specific postural states. This was true for all levels of cluster granularity of our embedding space, suggesting that neural responses track multiple time-scales of behavior. Taken together, these results provide a first insight into the neural basis underlying structured behavior during unconstrained foraging

Disclosures: B. Voloh: None. **D.J.N. Maisson:** None. **B.Y. Hayden:** None. **J. Zimmermann:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.03

Topic: H.03. Decision Making

Support: 1R01MH125377-01A1

Title: Anterior Cingulate Cortex Tracks the Distribution of Depleting Reward in Freely Moving Rhesus Macaques

Authors: *R. LOPEZ CERVERA, B. VOLOH, D. MAISSON, B. Y. HAYDEN, J. ZIMMERMANN; Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Foraging is a canonical decision-making behavior that has likely shaped functional neuroanatomy. Foragers in patchy environments are able to efficiently maximize their food intake by balancing the exploitation of resource patches with exploration for new patches. Making patch-leaving decisions requires the maintenance and integration of multiple forms of information. We have hypothesized that such decisions involve the generation and maintenance of a discrete continuous and abstract decision variable. The magnitude of this variable, which is presumed to be encoded in the dorsal anterior cingulate cortex, would be roughly akin to 'the current sum of evidence in favor of abandoning the current patch.' All past studies on this topic have been limited either by the use of virtual or chaired tasks on one hand, or the use of animal models with unclear prefrontal homology to humans on the other. To better understand foraging behavior in a more natural context, we developed a novel open field patch-leaving foraging task for rhesus macaques and recorded activity within dACC during task performance. We find that dACC neurons track the patch distribution of depleting reward. Furthermore, the relatively high firing rates that we observed when an animal depleted approximately half of a patch correlated with the relatively lower patch leaving rates for those same patch states. This novel signal may be one of several factors that subserve foraging computations.

Disclosures: R. Lopez Cervera: None. **B. Voloh:** None. **D. Maisson:** None. **B.Y. Hayden:** None. **J. Zimmermann:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Program #/Poster #: P827.04

Topic: H.03. Decision Making

Support: NIDA DA038615
NIDA P30DA048742

Title: Dynamic tracking of social states in freely moving rhesus macaques

Authors: *J. K. MORROW, B. R. VOLOH, D. J. N. MAISSON, J. ZIMMERMAN, B. Y. HAYDEN; Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Primates, including humans, are fundamentally social creatures. Our social interactions take place in a rich, complex world that affords many dimensions of movement as well as opportunities for communication and physical interaction. This core aspect of social life - its embodiedness - is absent from nearly all of social neuroscience, due in part to the simple difficulty of rigorously measuring social behavior in open environments. We have developed a new experimental apparatus for eliciting and observing social interactions in rhesus monkeys, an important model organism for human neuroscience. The apparatus consists of a large (2.45 x 2.45 x 2.75 m) enclosure encircled by 62 machine vision cameras that continuously track the subjects as they freely interact within the space over several hours. We developed a system known as OpenMonkeyStudio that uses a deep neural network to predict the

positions of 13 body landmarks on the head, torso, and limbs to reconstruct 3-dimensional pose information for each monkey in the enclosure. Here, we describe extensions to OpenMonkeyStudio that allow for tracking of two monkeys at the same time. Specifically, we show that we can reliably individuate each animal, classify their individual actions over time, and generate proxemics for the pair (i.e., track the distance, angle, and orientation of one subject relative to the other). Hidden Markov modeling could then be applied to these data to estimate transitions between social states, that is, repeatedly observed, joint behavioral patterns expressed by the pair. In other words, we can determine how the actions of one animal affect the actions of the other, indicative of social engagement (or disengagement). This information has a myriad of uses including inferring dominance hierarchies or tracking how behavioral (e.g., exposing the animals to stressors) or pharmacological (e.g., transient inactivation of specific neural pathways) interventions impact social behavior. These results demonstrate the utility of our experimental design for tracking natural interactions between multiple animals. This paradigm could provide a powerful tool for assessing disorders that include social or affective deficits that are hard to track in traditional laboratory settings.

Disclosures: J.K. Morrow: None. **B.R. Voloh:** None. **D.J.N. Maisson:** None. **J. Zimmerman:** None. **B.Y. Hayden:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Program #/Poster #: P827.05

Topic: H.03. Decision Making

Support: NSF Grant 3002-11918-00089509

Title: Place-specific spatial encoding in the orbitofrontal cortex of freely moving rhesus macaques

Authors: *D. MAISSON, B. VOLOH, J. ZIMMERMANN, B. Y. HAYDEN;
Dept. of Neurosci., Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: There is growing interest in how the prefrontal cortex encodes a map of space. However, spatial coding in the primate prefrontal cortex, particularly in the orbitofrontal cortex (OFC), has remained largely unexplored. Investigating a prefrontal cognitive map has been limited by the ability to track the unrestrained movement of primates through an open field while recording neural activity. We developed a novel system, the Open Monkey Studio, which enables marker-less tracking and pose estimation of freely exploring rhesus macaques (Macaca mulatta). We coupled this new technology with a wireless recording system that makes use of a chronically implanted electrode array and stores neural data on a local data logger. Our recording environment is a cubic cage that is approximately 3 meters long on each dimension. In each session, there are 1-4 interactive computerized feeding stations, which represent "patches" in a foraging sense, and are available for the subject to forage from or ignore as they roam freely around the environment. To investigate spatial coding in the OFC, we tracked the movement of the monkey across time, while recording OFC neural activity, and estimated the animal's center of mass on 2 dimensions (length and width). To selectively investigate spatial coding in OFC, which is canonically a

core reward structure, we built a regression model to remove signature reward responses from the neural activity of each neuron. We then used the center of mass estimates to bin the reward-residualized neural activity into 30cm2 spatial bins. For each bin, we calculated a rate map, and computed the spatial information (bits/spike). To determine if the spatial information was significant, we shuffled the data 1000 times. For each shuffled set, we again computed spatial information. A neuron had significant spatial tuning, absent reward encoding, if its spatial information was greater than that of at least 95% of the shuffled sets. We found that the majority of neurons in OFC (n=194/302, 64.26%) encode spatial information. These results are consistent with the hypothesis that OFC contributes to the encoding of a broader cognitive map.

Disclosures: D. Maisson: None. **B. Voloh:** None. **J. Zimmermann:** None. **B.Y. Hayden:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.06

Topic: H.03. Decision Making

Title: Subject-to-subject and session-to-session variability in behavioural strategy for the International Brain Lab task

Authors: *C. FINDLING[1], P. DAYAN[2], A. POUGET[1], .. INTERNATIONAL BRAIN LAB[1];
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Abstract: Most models of rodent behavior fit responses averaged across sessions and animals. Here, we ask instead whether different mice use different strategies and whether the same mouse uses different strategies on different sessions. Our analysis is based on a large cohort of mice (N=63), each performing 3-4 sessions of the International Brain Laboratory task. On each trial, mice earned liquid reward by turning a wheel to report whether a Gabor patch (of variable contrast) was on the left or right side of a screen. The prior probability that the stimulus appeared on the right switched in blocks between 0.2 or 0.8 in a random and uncued manner, with a nearly flat hazard rate. Here, we investigate different forms of variability in the behavior of the population using a 3 level hierarchical Bayesian model (HBM) which had a session level, nested within a subject level, itself nested within a population level. The session level captured the between-session variability within a subject; the subject level captured the between-subject variability. The HBM allowed L=4 candidate categories of behavioral strategies to which each session of each mouse could be attributed. The first category of optimal Bayesian agents implement the full generative process of the task, and so enjoy an explicit notion of block structure. The second category of stimulus-kernel strategies captures a local form of the bias within a block by low-pass filtering the sides on which stimuli were recently presented. The third action-kernel category is similar to the second but integrates over the sides that the mouse recently chose rather than over stimulus sides. The final fixed belief category maintains a fixed bias that does not change throughout the session. Inference was performed by combining variational Expectation-Maximization for session- and mouse-level parameters with type II maximum likelihood for population-level parameters (Piray et al. 2019). We found substantial between- and within-subject variability. For the former: the model fits favored action-kernel

strategies on at least one session for 71% of mice, optimal Bayesian strategies for 30%, fixed belief strategies for 19%, and stimulus kernel strategies for 13%. For within-subject variability, ~50% of the mice that performed 2 sessions or more were better explained by multiple strategies across sessions. Our results highlight the importance of not averaging across animals and sessions when analyzing rodent behavior. We are currently analyzing an additional, within-session level of strategy switching, and considering the representation of these various systematic differences in neural activity.

Disclosures: C. Findling: None. **P. Dayan:** None. **A. Pouget:** None. **.. International Brain Lab:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.07

Topic: H.03. Decision Making

Support: Gatsby Charitable Foundation (562980)
Wellcome Trust (562763)
EMBO ALTF 819-2020

Title: A novel behavioral paradigm for parametric spatial working memory

Authors: *E. CHONG, L. CALCATERRA, A. AKRAMI;
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Abstract: Spatial working memory (SWM) is the short-term maintenance and update of spatial information. SWM is important for a broad range of cognitive tasks that involve reasoning about physical objects and spatially-organized information, even in abstract non-spatial contexts. What are the neural computations underlying SWM? We trained rats to perform a novel, parametric SWM task (PSWM), where 2D visual stimuli are projected onto the floor of a large behavioral arena, and animals learn to maintain stimulus locations in their working memory over a delay period. Our projection arena exploits the previously-reported tendency of rodents to attend to stimuli close to the ground, and their rapid acquisition of visual tasks involving such stimuli. Our paradigm additionally overcomes several key limitations of existing rodent SWM tasks: target location is continuous as opposed to discrete, and can be systematically controlled. It also spans a large space within animals' field of view, and mimics rodent naturalistic behavior. Animals were successfully trained to perform the task over several weeks, and we obtained a precise behavioral readout of the spatial precision of working memory in continuous spatial coordinates. Future experiments will involve the use of multiple tools to monitor and perturb brain activity during task performance, allowing the detailed investigation of the neural computations underlying PSWM behavior.

Disclosures: E. Chong: None. **L. Calcaterra:** None. **A. Akrami:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.08

Topic: H.03. Decision Making

Support: NIH Grant R01MH108358
HHMI

Title: Confidence-guided waiting as an evidence accumulation process

Authors: *T. BOYD-MEREDITH[1], A. PIET[2], C. D. BRODY[3];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Allen Inst., Seattle, WA; [3]Princeton Neurosci. Inst. and Dept of Mol. Biol., HHMI / Princeton Univ., Princeton, NJ

Abstract: When making decisions, we can improve our choice accuracy by combining multiple pieces of evidence that bear on the decision. In such an evidence accumulation process, choices are accompanied by a decision confidence signal, which estimates the probability of having chosen correctly. Confidence can be used to guide learning and subsequent actions. Investigation of the neural computations responsible for confidence estimates requires an accurate procedure for inferring the confidence of animal subjects. A post-decision wagering paradigm with randomly delayed reward delivery has recently been developed to simultaneously measure binary choices and graded estimates of decision confidence (Lak et al., 2014). In this paradigm, the length of time that an animal is willing to wait for reward before initiating a new trial is taken as a proxy for confidence. However, it is unclear what algorithm the animal uses to translate its decision confidence into a wait time decision. Here, we show that a post-decision drift diffusion to bound model can generate optimal wait time behavior. In this framework, each time step that the animal waits without receiving reward is taken as a piece of evidence favoring the unchosen option over the chosen option. The animal stops waiting for reward and starts a new trial once the balance of evidence crosses a fixed threshold. The decision to wait for reward results from the continued evolution of the latent variable used to determine initial choice. This unified view provides a parsimonious account of multiple decision processes previously studied separately. Moreover, this model can disambiguate patterns of waiting behavior produced by perturbation of the animal's initial confidence from patterns of waiting produced by perturbation of confidence-independent parameters of the wait time model. This improves the power of inactivation experiments to elucidate the role of different brain regions in generating confidence-guided waiting behavior. We trained rats to perform the wait time post decision wager after trials of the poisson clicks task. In the poisson clicks task, subjects must integrate and compare two trains of randomly-timed auditory clicks in order to choose correctly between two reward ports. This behavior is described by an extensively studied accumulation model (Brunton et al., 2013). We used the latent state at the final time point of the choice model as the initial point of a drift diffusion process controlling the wait time decision. Fitting the parameters of the accumulation process offers a concise explanation of rats' wait time distributions and provides a tractable strategy for an animal performing the task.

Disclosures: T. Boyd-Meredith: None. **A. Piet:** None. **C.D. Brody:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Program #/Poster #: P827.09

Topic: H.05. Working Memory

Support: COFAA Fellowships Chuc-Meza & Garcia-Ramirez
SIP-IPN 20211149 & 20211146

Title: Partial dopaminergic denervation of the globus pallidus produces short-memory impairment in rats

Authors: K. BARON-QUIROZ[1], M. GARCIA-RAMIREZ[2], *E. CHUC-MEZA[2];
[1]Unidad Profesional Interdisciplinaria de Biotecnología del IPN, Mexico City, Mexico; [2]Natl. Sch. Biolog Sci. IPN, Mexico city, Mexico

Abstract: Rats with low-level globus pallidus (GP) dopaminergic denervation can develop anxiety without any motor alterations (Avila et al. 2020). Besides, patients with unilateral or bilateral infarcts in the external GP show cognitive deficiencies, including amnesia and attention deficit (Jeon et al. 2002; Kim et al. 2008). In healthy subjects, on the other hand, the activity of the GP is enhanced during working memory tasks entailing the filtering of distractors and the storage of information (McNab & Klingberg, 2008). For these reasons the aim of this study was to evaluate the effect of low-level 6-OHDA-induced unilateral and bilateral GP lesions in male Wistar rats (n=8/group) on recognition memory, motor activity, and the number of TH+ neurons in the SNc. For unilateral- and bilateral-lesioned animals, there was a significant decrease in the number of TH+ neurons (27% and 42%, respectively) and in the object, location, and temporal order discrimination indexes of recognition memory tests. Motor activity was unaffected. Thus, GP dopamine denervation was detrimental to short-memory.

Disclosures: K. Baron-Quiroz: None. **M. Garcia-Ramirez:** None. **E. Chuc-Meza:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

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Program #/Poster #: P827.10

Topic: H.05. Working Memory

Support: National Natural Science Foundation of China 31930052
National Natural Science Foundation of China 31771146
National Natural Science Foundation of China 11734004

Title: Dynamic perturbation during retention alters human sequential working memory

Authors: *J. LI[1], Q. HUANG[2], Q. HAN[3], Y. MI[4], H. LUO[5];
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Sciences, Peking Univ., Beijing, China; [4]Ctr. for Neurointelligence, Sch. of Med., Chongqing Univ., Chongqing, China; [5]Dept. of Psychology, Peking Univ., Beijing, China

Abstract: Temporarily storing a list of items in working memory (WM) for subsequence goal-directed behavior is an important function in many cognitive processes. This ability has been posited to rely on dynamic representations during retention such as neural reactivations or a theta-gamma oscillation code. However, the causal evidence for the role of neural network dynamics in sequential WM is still lacking. We use a temporal-correlated "dynamic perturbation" approach to interfere with the underlying representations during retention and manipulate the relative memory strength of memory items. Six human behavior experiments confirm the validity of this manipulation approach. A continuous attractor model with short-term synaptic plasticity (STP) principles reproduces all the experimental results. The model indicates that the modification of multi-item synaptic efficacies accumulates over time and eventually leads to the changes in recall performance. Besides the manipulation of relative memory strength, this dynamic perturbation also manipulates the memory performance of order information in sequential WM task. Our results support the causal role of temporal dynamic neural network in mediating sequential WM and offer a promising, non-invasive method to manipulate WM.

Disclosures: J. Li: None. **Q. Huang:** None. **Q. Han:** None. **Y. Mi:** None. **H. Luo:** None.

Poster

P827. Learning and Memory During Freely Moving Behavior

Location: Virtual Only

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Program #/Poster #: P827.11

Topic: H.03. Decision Making

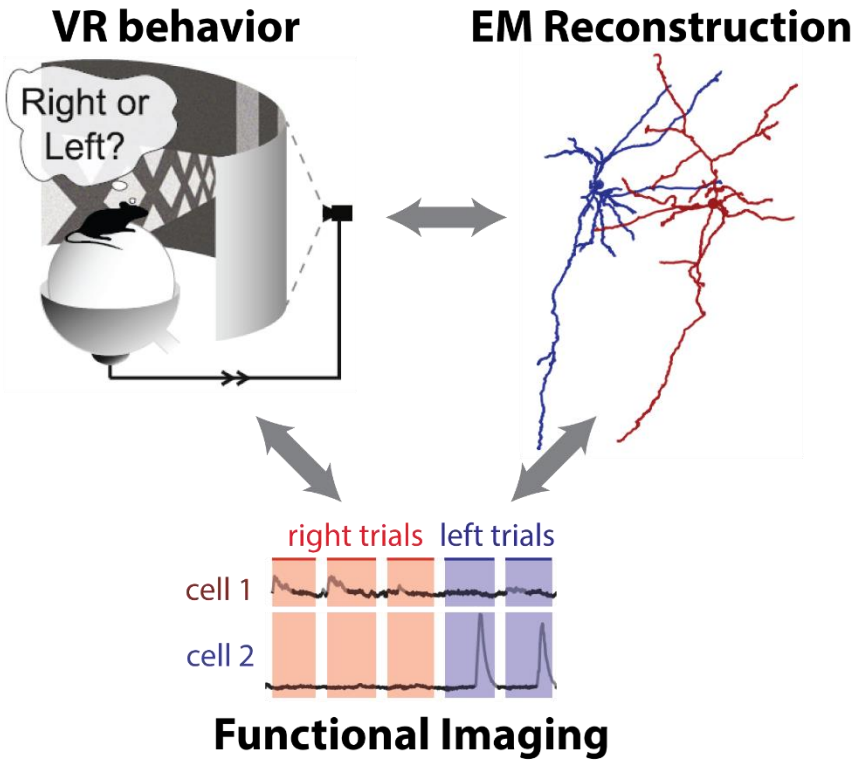
Support: NIH 1R01NS108410-01

Title: Choice-selective synaptic wiring motifs in posterior parietal cortex

Authors: *A. T. KUAN[1], L. N. DRISCOLL[2], G. BONDANELLI[3], J. HAN[4], M. KIM[1], D. G. C. HILDEBRAND[5], B. J. GRAHAM[6], L. A. THOMAS[7], S. PANZERI[8], C. D. HARVEY[1], W.-C. A. LEE[9]; [1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Neurobio., Stanford Univ., Palo Alto, CA; [3]Inst. Italiano di Tecnologia, Genoa, Italy; [4]Northeastern Univ., Seattle, WA; [5]Rockefeller Univ., New York, NY; [6]Harvard Univ., Cambridge, MA; [7]Univ. of California Berkeley, Berkeley, CA; [8]Dept. of Neural Information Processing, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [9]BCH / Harvard Med. Sch., Boston, MA

Abstract: An increasing body of literature suggests that cortical association areas play a crucial role in perceptual decision-making. Recent work in mice has shown that neurons in the posterior parietal cortex (PPC) exhibit activity predictive of behavioral choice. However, it remains unclear how this choice-specific behavior emerges from the underlying circuit connectivity in PPC. To investigate these structure-function relationships, we combined virtual reality behavior, *in vivo* calcium imaging, and large-scale electron microscopy in the same mouse to create a functional connectivity map of PPC neurons.
We used this multimodal dataset to analyze how synaptic connectivity of individual neurons relates to their cell type and choice-selectivity. We show that layer 2/3 excitatory and inhibitory neurons exhibit

choice-selective connectivity motifs, whereby neurons exhibit preferential connectivity to partners with similar choice-selectivity. These findings suggest that interneurons, as well as pyramidal neurons, exhibit choice-specific wiring, display choice-specific activity, and support decision-making computations and behaviors. This conclusion contrasts with the prevailing circuit models of primary visual cortex, where interneuron connectivity is essentially random, and suggests that critical aspects of connectivity may differ between sensory and association areas. To investigate the implications of these measurements, we performed circuit modeling to analyze how choice-specific wiring is constrained by network stability and contributes to computations such as amplification, feature competition, or winner-take-all. Taken together, these results provide an example for how synaptic connectivity motifs give rise to neuronal activity, which can contribute to a general understanding of how cortical circuits support complex behavior.



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Poster

P827. Learning and Memory During Freely Moving Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P827.12

Topic: D.08. Visual Sensory-motor Processing

Support: NEI, NIH

Title: The neural mechanism of the encoding of the familiar face in the primate striatum tail

Authors: *J. KUNIMATSU[1], H. AMITA[2], O. HIKOSAKA[3];
[1]Univ. of Tsukuba, Tsukuba, Japan; [2]Primate Res. Inst., Kyoto Univ., Inuyama, Japan; [3]Lab. Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: We can quickly find a familiar person in the crowd of people. This ability is necessary for our daily life, however, the underlying neuronal mechanism is still unclear. Recently, we found that neurons in the basal ganglia posterior circuit, including the striatum tail (STRt), encode values of visual objects stably based on the long-term memory (Yamamoto et al., 2013; Kunimatsu et al., 2019). Such stable value coding is useful for automatically and quickly finding good objects among many others (Hikosaka et al. Trends Cogn Sci 2013). We hypothesized that the long-term value coding neurons in STRt are involved in the detection of the socially familiar face. To address this question, we first studied whether striatal tail (STRt) neurons respond to face images by the passive-viewing task. In this task, the object was chosen randomly from twelve images, which were presented one at a time at the preferred position for the recorded neuron while the monkey fixed its gaze at the center. The images included three categories: 1) face images of socially familiar persons who take daily care of the monkeys for more than one year (familiar face), 2) face images of unknown persons (unfamiliar face), and 3) no reward associated fractal objects. We recorded 68 visual neurons in STRt, 30 of them (45%) showed a significant response to the face images. On the average, the response was stronger to familiar faces than unfamiliar faces in these neurons ($p < 0.05$). Next, we tested the object value (high-valued or low-valued) on long-term reward experiences for these face-responsive neurons. We found that these neurons also encoded the values of many fractal objects. Furthermore, the strength of neuronal modulation of social familiarity bias (familiar or unfamiliar) and object value bias (high-valued or low-valued) are positively correlated ($r = 0.43$, $p < 0.05$). These results suggested that the social familiarity and object value information are mediated by a common neuronal mechanism. The STRt may contribute to the quick detection of real-life familiar faces.

Disclosures: J. Kunimatsu: None. **H. Amita:** None. **O. Hikosaka:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

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Program #/Poster #: P840.01

Topic: H.07. Long-Term Memory

Support: R01-EY022229
ONR N00014-16-1-2832
ONR N00014-17-1-2304

Title: Network interactions during long-term memory guided versus stimulus-guided attention in humans

Authors: *K. ISENBURG[1], T. M. MORIN[1], M. L. ROSEN[2], D. C. SOMERS[1], C. E. STERN[1];
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Abstract: Network Interactions during Long Term Memory-Guided versus Stimulus-Guided Attention in Humans
Isenburg K, Morin T.M., Rosen M.L., Somers D.C., Stern C.E.
Despite the remarkable capacity of human visual processing, we are limited in what we can pay attention to at a given moment. Recent work has identified differences between long term memory-guided attention (LTM-guided attention) and attention guided by external stimuli (STIM-guided attention), shedding light on large-scale brain network contribution to these two processes (Rosen et al., 2018). Given previous evidence of the Dorsal Attention Network (DAN) in the processing of external stimuli, and the Default Mode Network (DMN) in self-referential processing and memory retrieval, we examined whether these two networks would contribute differentially to STIM-guided vs LTM-guided attention. We hypothesized that the Cognitive Control Network (CCN), with posterior regions previously implicated in LTM-guided attention, would adapt connectivity with DMN and DAN based on LTM-guided vs STIM-guided attention. This analysis uses data previously collected from a neuroimaging study utilizing task-based functional Magnetic Resonance Imaging (fMRI) to compare connectivity differences between LTM-guided and STIM-guided attention in a block design (Rosen et al., 2018). 24 healthy controls (13 male) were enrolled and attended one training and one fMRI session, consisting of 12 scans. Brain activity was analyzed using a generalized Psychophysiological Interaction (gPPI) model implemented in Conn Toolbox. Connectivity results were analyzed based on the Schaefer 400 parcellation of the Yeo et. al (2011) 7-network brain atlas. Parcels of the DMN, DAN, and CCN were used to generate a connectivity matrix between all pairs (189 nodes) contrasting connectivity during LTM-guided vs. STIM-guided attention. Threshold Free Cluster Enhancement (TFCE) was employed to identify clusters where connectivity significantly differed across task conditions. Results showed 11 significant clusters of connections between Schaefer nodes. Preliminary findings showed stronger connectivity between the nodes of the posterior cingulate/medial prefrontal DMN with posterior nodes of the DAN and prefrontal nodes of the CCN during LTM-Guided attention. Additionally, connectivity decreased within the DMN, specifically between posterior cingulate nodes and prefrontal nodes. These results suggest that LTM-guided attention is supported by the postero-medial subdivision of the DMN (Karenback et al., 2018), gating network integration as they split off from the larger DMN and couple with nodes of the DAN and CCN.

Disclosures: K. Isenburg: None. **T.M. Morin:** None. **M.L. Rosen:** None. **D.C. Somers:** None. **C.E. Stern:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

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Program #/Poster #: P840.02

Topic: H.07. Long-Term Memory

Support: National Health and Medical Research Council of Australia grant number APP1091593
National Health and Medical Research Council of Australia grant number APP1117724
Australian Research Council grant number DP170101815

Title: Anatomical connectivity between cortical brain areas and the anterior-posterior axis of the human hippocampus: new insights using quantitative fibre tracking.

Authors: *M. A. DALTON, A. D'SOUZA, J. LV, F. CALAMANTE;
Univ. of Sydney, Sydney, Australia

Abstract: Background. The hippocampus is central to a broad range of cognitive functions including episodic memory. To date, the anatomical connectivity of the human hippocampus is largely inferred from the results of studies conducted in the non-human primate brain. We know much less about how different regions along the anterior-posterior axis of the human hippocampus anatomically connect with cortical regions to support key functions such as memory. The aim of this study was to address this gap by assessing where along the anterior-posterior axis of human hippocampus different cortical brain areas preferentially connect. **Methods.** We combined high quality data from the Human Connectome Project (HCP) and cutting-edge quantitative fibre-tracking methods. Ten subjects were selected from the HCP 100 unrelated subject database. We implemented a Diffusion Weighted Imaging (DWI) pipeline specifically tailored to study hippocampal connectivity using MRtrix3. We combined our tailored pipeline with Track Density Imaging (TDI) to create 'endpoint density maps' which allowed us to quantitatively assess and visualise, for the first time in the human brain, where within the hippocampus different cortical brain areas preferentially 'connect'. **Results.** Patterns of anatomical connectivity generally aligned with predictions based on observations from the non-human primate literature. The results of group level analyses revealed that the hippocampus displayed preferential connectivity with discrete cortical areas in temporal, medial parietal, dorsal and ventral stream visual and early visual cortices. Strikingly, our results showed that each of these cortical areas displayed preferential connectivity with specific regions along the anterior-posterior and medial-lateral axes of the hippocampus. In parallel, circumscribed regions within the hippocampus were highly connected with multiple cortical areas. Intriguingly, we identified two 'hubs' of anatomical connectivity in the medial hippocampus; a posterior medial hub preferentially linked with visuospatial processing areas in parietal and early visual cortices and an anterior medial hub more broadly linked with temporopolar, inferotemporal, parietal and early visual areas. **Conclusions.** This study represents one of the most comprehensive *in-vivo* characterisations of structural connectivity between cortical brain areas and the human hippocampus to date. Our results contribute to ongoing efforts to characterise anatomical connectivity of the human hippocampus with implications for understanding functional differentiation along the long axis of the hippocampus.

Disclosures: M.A. Dalton: None. **A. D'Souza:** None. **J. Lv:** None. **F. Calamante:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

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Program #/Poster #: P840.03

Topic: H.07. Long-Term Memory

Support: Volkswagen Foundation BMBF 031L0197B
German Research Council MO930/4-2
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Swiss National Science Foundation P300P1_161178

Title: Single-neuron mechanisms of neural adaptation in the human temporal lobe

Authors: *T. P. REBER[1,2], S. MACKAY[2], M. BAUSCH[2], M. S. KEHL[2], V. BORGER[3], R. SURGES[2], F. MORMANN[2];
[1]Fac. of Psychology, UniDistance Suisse, Brig, Switzerland; [2]Dept. of Epileptology, Univ. of Bonn Med. Ctr., Bonn, Germany; [3]Neurosurg., Univ. of Bonn, Bonn, Germany

Abstract: A central function of the human brain is its ability to adapt to new situations based on past experience. Adaptation is reflected behaviorally by shorter reaction times to repeating or similar stimuli, and neurophysiologically by reduced neural activity in bulk-tissue measurements with fMRI or EEG. Several potential single-neuron mechanisms have been hypothesized to cause this reduction of activity at the macroscopic level. We here explore these mechanisms using an adaptation paradigm with visual stimuli bearing abstract semantic similarity. We recorded intracranial EEG (iEEG) simultaneously with spiking activity of single neurons in the medial temporal lobes of 25 neurosurgical patients. Recording from 4917 single neurons, we demonstrate that the reduced event-related potentials in the macroscopic iEEG signal is associated with a sharpening of tuning curves of single neurons in the amygdala as well as an overall reduction of single-neuron activity in the hippocampus, entorhinal cortex, and parahippocampal cortex. Together, these results identify the neuronal mechanism underlying neural adaptation in the human medial temporal lobe.

Disclosures: T.P. Reber: None. **S. Mackay:** None. **M. Bausch:** None. **M.S. Kehl:** None. **V. Borger:** None. **R. Surges:** None. **F. Mormann:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

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Program #/Poster #: P840.04

Topic: H.05. Working Memory

Support: Japan Science and Technology AgencyCenter of Innovation Program JPMJCE1311
NIH Grant R01EY019466
NIH Grant R01EY027841
United States-Israel Binational Science Foundation Grant BSF 2016058

Title: Neurofeedback-supported mental imagery training selectively boosts the capacity of visual working memory and attention and reveals a causal role of contralateral delay activity and visual working memory capacity

Authors: M. MACHIZAWA[1,2], R. MIZUOCHI[1], S. YAMAWAKI[1], T. WATANABE[2];
[1]Ctr. for Brain, Mind and KANSEI Sci. Res., Hiroshima Univ., Hiroshima, Japan; [2]Dept. of Cognitive, Linguistic & Psychological Sci., Brown Univ., Providence, RI

Abstract: Brain training programs or intensive behavioral training techniques have been touted to improve our cognition. However, most of such approaches had been shown not to generalize and robustly enhanced our higher cognitive function, especially visual working memory (VWM) that is pivotal for our daily lives. Social demands are rising to break through the limited applicability of these approaches to improve our higher cognitive functions. Neurofeedback (NF) is one of the established methods to quantify and visualize our mental operations as a focused brain training. Here we propose a robust and novel neurofeedback training method that can improve the hardly-improved brain functions, attention and VWM. We have trained subjects with the contralateral delay activity (CDA), which is a robust neural substrate that can quantify the amount of our mental representation (Vogel & Machizawa, 2004) that also reflects the control of our selective attention (Vogel, McCollough & Machizawa, 2005). Twenty participants underwent a CDA NF training for five days, randomly assigned to the left- or right-lateralized training group (LHG and RHG, respectively), and blinded for the target neural marker. Each trial consisted of a baseline resting period followed by a mental imagery induction phase and feedback. Participants were asked to create mental imagery of their choice and try to improve the NF score. Their CDA amplitude relative to the baseline was computed and the feedback score was provided on a real-time basis. Their causal impact of the CDA NF was assessed by a test battery of attentional network and VWM capacity tasks at pre- and post-training days. The results revealed that the CDA NF equally improved their selective attention ability for both groups. Notably, the LHG but not RHG robustly improved VWM capacity with a high effect-size (Cohen's *d*: 0.94). The pooled outcome revealed left-lateralized CDA, but not right-lateralized CDA, correlated with the VWM improvement. Moreover, the individual variations in the behavioral and CDA changes revealed the causal role of the CDA for VWM capacity. Together with the evidence of the left-lateralized neuroanatomical relation of the capacity of VWM, our finding may elucidate a critical role of the functional neuroanatomy underlying VWM that may be applied for the prevention of dementia or attention deficiency.

Disclosures: M. Machizawa: None. **R. Mizuochi:** None. **S. Yamawaki:** None. **T. Watanabe:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P840.05

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Single-neuron firing properties in the human amygdala predict subjective decisions on the delay discounting task

Authors: *M. OMIDBEIGI[1], J. GILL[4], Z. AGHAJAN[2], E. A. MANKIN[5], G. KALENDER[2], I. FRIED[6], N. A. SUTHANA[3], A. BARI[1];
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Abstract: INTRODUCTION: The amygdala has long been described to be involved in emotion, especially fear-related processes. However, recent research has demonstrated its role in various decision-making in both humans and animals. A frequently used experimental paradigm to study human decision-making is the delay discounting task (DDT). DDT measures a subject's preference for larger hypothetical monetary rewards at variable delays compared to smaller immediate rewards. While the phenomenology of delay discounting and its relation to mental health has been studied in detail, little is known about its neural correlates in thedecision-making process. Here we hypothesized that the activity of the human amygdala is predictive of subject choice on the DDT. **METHODS:** We explored single neuronal activity from the amygdala in nine treatment-refractory epilepsy patients that were implanted with depth electrodes for seizure localization. We recorded from 12 amygdalas (5 left, 7 right) whilesubjects performed the DDT. In DDT, participants repeatedly chose between a small immediate reward (less than $10) and a larger delayed ($10 after either 2, 30, 180, 365 days) reward to estimate the discount rate for a reward of $10. Trials were compared between those in which the participant chose an immediate reward against trials in which subjects chose the delayed reward. We used the Wilcoxon rank-sum test in order to compare trials firing rate. **RESULTS:** We recorded the activity of 66 amygdala neurons from 9 patients. Neuronal discharge rates were examined During the time between stimulus onset and response time. During the DDT, 36 of 66 units (54.5%) differentiated immediate trials from delay trials by significant changes in firing rate 200-1000ms before the response. In population response of amygdala neuronal activity, we observed a significant (P value<.001, Wilcoxon rank-sum test) difference between immediate and delay trials. **CONCLUSION:** Our results uncover neural correlates of subjects' decisions between immediate and delayed reward during decision-making and suggest that amygdala neural firing rates can predict that decision.

Disclosures: M. Omidbeigi: None. **J. Gill:** None. **Z. Aghajan:** None. **E.A. Mankin:** None. **G. Kalender:** None. **I. Fried:** None. **N.A. Suthana:** None. **A. Bari:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P840.06

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R21-MH113917

Title: Alpha transcranial alternating current stimulation selectively modulates reward-dependent corticostriatal connectivity

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Abstract: Receipt of reward evokes pleasure, alters pupillary responses, and increases activation within the striatum. Although much of the existing work on human reward processing has been limited to

correlative approaches such as neuroimaging, understanding how to manipulate reward processing with noninvasive brain stimulation could advance theories of reward processing and decision making and also have significant translational impact for disorders characterized by aberrant reward processing. Unfortunately, the striatum is buried deep inside the brain, making it inaccessible to approaches that manipulate function via noninvasive brain stimulation. We approached this problem by applying 10 Hz transcranial alternating current stimulation (α-tACS) to the ventrolateral prefrontal cortex (VLPFC) -- an area with dense projections to the striatum -- and a control site (temporal parietal junction). Stimulation was applied while participants underwent functional magnetic resonance imaging and received monetary reward and punishment. We hypothesized that alpha-tACS applied to VLPFC would alter reward processing, as indexed by pupillary responses and reward-dependent corticostriatal connectivity. We found that stimulation over VLPFC reduced the extent to which the receipt of reward constricted pupil size. VLPFC stimulation was also associated with enhanced VLPFC responses to reward and suppressed responses to punishment. In addition, we also found that VLPFC stimulation enhanced corticostriatal connectivity during the receipt of reward. These results suggest that tACS applied to prefrontal regions that are connected to the striatum can modulate reward-dependent corticostriatal connectivity. Understanding how tACS can be used to modulate reward-dependent corticostriatal connectivity may have important implications for psychopathologies associated with aberrant reward processing.

Disclosures: D.V. Smith: None. **Y. Liu:** None. **B. Krekelberg:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P840.07

Topic: H.05. Working Memory

Support: NIH Grant R01MH112357

Title: The flow of information transformation across cortical networks during story listening

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Abstract: When listening to a spoken narrative, the listener's brain constantly synthesizes low-level input into higher-level representations along a cortical hierarchy with increasing temporal receptive windows. For example, the early auditory cortex processes rapidly-evolving acoustic features, early language areas synthesize the sounds into words, higher-order language areas synthesize the spoken words into sentences, while the default mode network synthesizes the spoken sentences to extract slow-evolving semantic features. This hierarchical processing architecture indirectly implies a temporal sequence of information transformation with longer temporal lags between regions farther apart in the cortical hierarchy. The current study directly examined the temporal lags between activities in different brain regions along the processing timescales hierarchy while subjects listened to a naturalistic spoken narrative.
We aggregated eight fMRI datasets acquired from 126 participants while they listened to spoken stories

and computed the inter-subject functional connectivity across areas along the processing hierarchy at varying lags (i.e. cross-correlation). For each seed-target pair, the lag with the peak correlation value was extracted as an estimate of the temporal lag between seed-target pairs. Regardless of the choice of the seed, we found the same order of peaks across the processing hierarchy, where early auditory peaked first, followed by ventral language areas, dorsal language areas, attention network, and lastly the default mode networks. This lag gradient was consistently found across intact stories but absent in resting-state and scrambled-story data, indicating a stimulus-driven flow of information transformation.
By simulating brain responses to narrative-like nested structure, we demonstrated that activation accumulation at varying granularity (e.g. word, sentence, and paragraph) can explain the lag gradient across networks. In addition, our simulation showed that the structural properties of natural narratives can account for the scale-free dynamics observed in the brain activity and the stronger low-frequency fluctuations in networks with longer temporal receptive windows.
In conclusion, this study revealed a novel lag gradient along the cortical hierarchy during story listening and illustrated how information is synthesized at different timescales along the processing hierarchy.

Disclosures: C.H.C. Chang: None. **S.A. Nastase:** None. **U. Hasson:** None.

Poster

P840. Human Medial Temporal Lobe: Cortical Circuitry and Networks

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Program #/Poster #: P840.08

Topic: H.05. Working Memory

Support: NIH Grant ZIA-NS003144
NIH Grant 1R01MH117132
NINDS Competitive Postdoctoral Fellowship Award

Title: The medial temporal lobe supports visual short-term memory precision

Authors: *W. XIE[1], M. CAPPIELLO[2], J. H. WITTIG, JR[1], S. INATI[3], M. A. YASSA[4], E. ESTER[5], W. ZHANG[2], K. A. ZAGHLOUL[1];
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Abstract: Precision of information retained in short-term memory (STM) underlies our ability to pinpoint the exact details of a stimulus that we recently encountered. Imprecise STM has been associated with more variable neural representations and more variable recall behavior. However, the neural mechanisms supporting STM precision are yet fully understood. Here, we use converging evidence from multiple experimental modalities to test the hypothesis that STM precision relies on circuitry of the medial temporal lobe (MTL), a region commonly associated with the ability to distinguish similar information contents in long-term memory. First, using previously established neuroimaging methods, we find that MTL structures involved in discriminating the contents of long-term memory are also sensitive to task

demands on STM precision. Second, using intracranial electroencephalography (iEEG), we find that delay-period MTL activity retains precise item-specific information that is predictive of STM recall fidelity. Finally, we find that perturbing the MTL through electrical stimulation or surgical removal reduces STM precision. Collectively, these data provide correlational and causal evidence that the MTL makes an essential contribution to STM precision.

Disclosures: W. Xie: None. **M. Cappiello:** None. **J.H. Wittig:** None. **S. Inati:** None. **M.A. Yassa:** None. **E. Ester:** None. **W. Zhang:** None. **K.A. Zaghloul:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

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Program #/Poster #: P849.01

Topic: H.08. Learning and Memory

Support: NIA R00AG056596
NIA R21AG068444
Whitehall #2020-05-06
AFAR #A21105

Title: Epigenetic mechanisms underlying reconsolidation-based memory updating

Authors: *C. W. SMIES, L. BELLFY, D. S. WRIGHT, M. W. URBAN, J. L. KWAPIS;
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Abstract: Memories are plastic records of experience that require maintenance in the form of updating to remain meaningful. The molecular mechanisms underlying memory formation have been heavily studied, whereas the mechanisms underlying memory updating have yet to be fully investigated. One key mechanism necessary for successful memory formation is histone acetylation, the addition of acetyl groups to histone tails, which typically enables gene expression necessary for memory formation. Enhancing histone acetylation by blocking histone deacetylase 3 (HDAC3, an enzyme that reduces histone acetylation) during memory consolidation enhances both gene expression and long-term memory formation in young and old mice (McQuown et al., 2011 & Kwapis et al., 2018). Recent work has suggested that histone acetylation is also important for reconsolidation-dependent updating, as broadly blocking histone acetylation disrupts both consolidation and reconsolidation of fear memories (Maddox et al., 2013), although the specific role of HDAC3 in reconsolidation-dependent updating is currently unclear. Here, we tested whether the HDAC3-specific inhibitor RGFP966 would improve reconsolidation-dependent memory updating in young and old male C57BL/6J mice using the novel Objects in Updated Locations (OUL) paradigm (Wright et al., 2020). In OUL, mice are trained on the locations of two identical objects. Next, this memory is updated by moving one object to a novel location. Finally, memory for both the original and updated locations is assessed during a test session, where memory is indexed by the time spent investigating the three familiar locations in relation to a novel location. Here, we report that systemically inhibiting HDAC3 immediately following memory updating ameliorates age-induced deficits in memory updating in the OUL task. In contrast, young mice that

receive RGFP966 immediately following the update session show intact memory for the updated information but decreased memory for the initial training information. Together, these data suggest that HDAC3 inhibition can enhance memory updating, but this enhancement may come at the expense of the original memory. In old animals that normally fail to update, HDAC3 inhibition enhances the updated information without affecting the original memory. In young animals that already show robust memory updating, HDAC3 seems to strengthen the updated information so that it outcompetes the original memory. Thus, the updated and original memories are tightly linked and may compete for expression.

Disclosures: C.W. Smies: None. **L. Bellfy:** None. **D.S. Wright:** None. **M.W. Urban:** None. **J.L. Kwapis:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

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Program #/Poster #: P849.02

Topic: H.08. Learning and Memory

Support: NIA R00AG056596
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Whitehall #2020-05-06
AFAR #A21105

Title: The role of circadian gene Per1 in gating contextual memory performance within the retrosplenial cortex

Authors: *C. A. BRUNSWICK, K. K. BODINAYAKE, D. S. WRIGHT, E. M. STUART, C. F. LO, A. C. HEIMANN, S. S. LAKHIA, J. L. KWAPIS;
Dept. of Biol., Penn State Univ., University Park, PA

Abstract: The link between the circadian system and memory performance is well-characterized and widely accepted. Circadian rhythms are endogenous cycles governed predominately by complex transcriptional patterns of circadian genes within the suprachiasmatic nucleus (SCN). Relatively little research has investigated the roles these genes play outside of the SCN. However, one such circadian gene—Period 1 (*Per1*)—has recently been implicated in gating memory formation independent of its role within the SCN. We investigated how *Per1* expression relates to memory performance in a memory-relevant cortical structure, the retrosplenial cortex (RSC). We sought to elucidate how *Per1* expression within the RSC is affected by a memory task, given the RSC's role in memory formation. First, male C57BL/6J mice were trained, during the day, in contextual fear conditioning and were then sacrificed at various timepoints following training (immediately, 30 min, 1 hr, or 2 hr post-training). We then performed qPCR on RSC tissue from these mice and determined that *Per1* expression was modulated by learning and peaked one hour after a learning event. Given *Per1*'s well-documented role in maintaining circadian rhythms, we next investigated how learning-induced expression of *Per1* changes across the circadian cycle and the link between *Per1* expression and memory performance. Two cohorts of male C57BL/6J mice were trained in a spatial memory task (object location memory, OLM) at six timepoints

spanning the circadian cycle (Zeitgeber Times: ZT1, ZT5, ZT9, ZT13, ZT17, ZT21). The first cohort of animals was used to investigate how performance in OLM varies throughout the circadian day. A second cohort was trained in the OLM task simultaneously and then sacrificed an hour later to analyze *Per1* expression. We found a significant effect of circadian timepoint on memory performance, with better memory for OLM observed during the day than at night. Learning-induced *Per1* expression within the RSC also varied with timepoint and peaked during the day. Notably, learning did not drive this same pattern of *Per1* expression within the SCN. These results confirm the role of *Per1* in modulating memory performance independent of the SCN's governance of the circadian system and demonstrate, for the first time, that *Per1* expression is induced by learning within the RSC in a circadian-dependent fashion. Furthermore, this induction of *Per1* expression by learning oscillates in tandem with memory performance across the circadian day/night cycle. Future experiments will directly manipulate expression of *Per1* in the RSC to determine how this impacts memory performance.

Disclosures: C.A. Brunswick: None. **K.K. Bodinayake:** None. **D.S. Wright:** None. **E.M. Stuart:** None. **C.F. Lo:** None. **A.C. Heimann:** None. **S.S. Lakhia:** None. **J.L. Kwapis:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

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Program #/Poster #: P849.03

Topic: H.08. Learning and Memory

Support: NIA R00AG056596
NIA R21AG068444
Whitehall #2020-05-06
AFAR #A21105
T32 AG049676

Title: Hippocampal Per1 and memory allocation both oscillate in tandem with memory performance

Authors: *L. BELLFY[1], C. W. SMIES[1], K. K. BODINAYAKE[1], A. R. BERNHARDT[1], E. M. STUART[1], D. S. WRIGHT[1], C.-Y. LO[1], J. L. KWAPIS[2];
[1]Dept. of Biol., Pennsylvania State Univ., University Park, PA; [2]Dept. of Biology, Ctr. for Mol. Investigation of Neurolog. Disord, Penn State Univ., University Park, PA

Abstract: Circadian rhythms influence many biological processes, including long-term memory formation. In mice, performance on behavioral paradigms varies dramatically depending on the time of day animals are tested, with better memory performance typically observed during the day compared to night. We used a dorsal hippocampus (DH)-dependent learning paradigm called Object Location Memory (OLM) to elucidate the molecular relationship between the circadian rhythm and memory. In this paradigm, young mice (around 3 months old) learn the location of two identical objects during a training session. During the test session 24 hours later, one of the objects is moved to a novel location. Memory for the training session is determined by the time the mouse spends investigating the object in the novel location. An outstanding question is how the molecular mechanisms of long-term memory are altered

across the day/night cycle. One mechanism that may regulate memory across the 24 hour day is the circadian gene *Period1* (*Per1*), which modulates memory formation directly in the DH independent of its role in the circadian clock in the brain's central pacemaker, the suprachiasmatic nucleus. Here, we tested whether *Per1* functions in the DH to regulate memory across the day/night cycle. First, we measured memory performance in OLM across the diurnal cycle. We found that mice show improved learning during the day compared to night, with peak and trough learning occurring at ZT5 and ZT17, respectively. Next, we assessed hippocampal *Per1* expression across the 24h day. We found that learning drove larger increases in hippocampal *Per1* during the day than at night. As *Per1* expression oscillated in tandem with memory performance, *Per1* may exert circadian control over hippocampal memory formation. Finally, we tested whether *Per1* may modulate hippocampal memory performance by regulating memory allocation, the process of determining which individual neurons across the brain encode a given memory. As *Per1* regulates the activity of the transcription factor CREB, a key mechanism controlling memory allocation, it is well-positioned to control memory allocation across the day/night cycle. Therefore, we monitored memory allocation across the diurnal cycle using *Arc* fluorescence in situ hybridization (*Arc* FISH) and found that a higher proportion of neurons are recruited to memory during the day (when both *Per1* levels and memory peak) than at night (when *Per1* and memory trough). *Per1* may therefore regulate hippocampal memory formation across the circadian day by controlling memory allocation. In conclusion, *Per1* may exert local control in the DH over memory formation by regulating memory allocation.

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Poster

P849. Learning and Memory: Molecular Mechanisms III

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Program #/Poster #: P849.04

Topic: H.08. Learning and Memory

Support: NIH Grant AG062398

Title: Phosphorylation is a critical post-translational modification of 4EBP2 for memory dependent on sleep

Authors: N. BURKERT, I. SUCCI, L. GIVVINES, O. SKWIERAWSKI, E. WASH, ***J. C. TUDOR**; St. Joseph's Univ., Philadelphia, PA

Abstract: Sleep is critical for learning and memory formation. Five hours of sleep deprivation has been shown to impair memory in male mice by attenuating protein synthesis in the hippocampus. The mammalian target of rapamycin (mTOR) signaling pathway is a key regulatory pathway that is also affected by sleep deprivation. Eukaryotic translation initiation factor 4E binding protein 2 (4EBP2) is critical in this pathway for protein synthesis. To examine the role of 4EBP2 in sleep-dependent memory, we developed mutant 4EBP2 adeno-associated viruses (AAVs) with a CaMKII alpha promoter fragment to selectively express in excitatory neurons in the hippocampus. Point mutations to alanine residues at the

phosphorylation sites rendered the 4EBP2 protein phosphodefective, while point mutations to aspartate residues at the phosphorylation sites resulted in phosphomimetic 4EBP2. We found that mice infected with the phosphomimetic 4EBP2 AAV in the hippocampus were resistant to the memory impairments associated with sleep deprivation, while well-rested mice infected with the phosphodefective 4EBP2 AAV in the hippocampus had similar memory deficits to those associated with sleep deprivation. Further, phosphomimetic 4EBP2 prevented the deficits in protein synthesis in the hippocampus caused by sleep deprivation, while phosphodefective 4EBP2 lowered the amount of protein synthesis. Our findings support the role of phosphorylation as a critical post-translational modification of 4EBP2 for sleep-dependent memory formation. Work is continuing to examine whether this signaling pathway is also affected by sleep deprivation in female mice or if female hormones are protective to this effect.

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Poster

P849. Learning and Memory: Molecular Mechanisms III

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Guangdong Project No. 2019QN01Y202
Science and Technology Program of Guangzhou No. 202007030001

Title: Plexin-a1 expression in the inhibitory neurons of infralimbic cortex regulates the specificity of fear memory

Authors: X. CHENG[1,2,3], Y. ZHAO[1,2,3], S. ZHENG[4], P. ZHAO[1,2,3], J.-L. ZOU[5], W.-J. LIN[6,3], W. WU[7], X. YE[1,2,3];
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Abstract: Maintaining appropriate levels of fear memory specificity is crucial for individual's survival and mental health, whereas overgeneralized fear commonly occurs in neuropsychiatric disorders, including posttraumatic stress disorder and generalized anxiety disorder. However, the molecular mechanisms regulating fear memory specificity remain poorly understood. The medial prefrontal cortex

(mPFC) is considered as a key brain region in fear memory regulation. Previous transcriptomic studies have identified that plexin-A1, a transmembrane receptor critical for axon development, was downregulated in the mPFC after fear memory training. In this study, we identified that learning-induced downregulation of the mRNA and protein levels of plexin-A1 specifically occurred in the inhibitory but not excitatory neurons in the infralimbic cortex (IL) of mPFC. Further studies of plexin-A1 by virus-mediated over-expression of functional mutants selectively in the IL inhibitory neurons revealed the critical roles of plexin-A1 for regulating memory specificity and anxiety. Moreover, our findings revealed that plexin-A1 regulated the distribution of glutamic acid decarboxylase 67, a GABA synthetase, which in turn modulated the activity of IL and its downstream brain regions. Collectively, our findings elucidate the molecular modifier of IL inhibitory neurons in regulating memory specificity and anxiety, and provide candidates for developing therapeutic strategies for the prevention or treatment of a series of fear generalization-related neuropsychiatric disorders.

Disclosures: X. Cheng: None. **Y. Zhao:** None. **S. Zheng:** None. **P. Zhao:** None. **J. Zou:** None. **W. Lin:** None. **W. Wu:** None. **X. Ye:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P849.06

Topic: H.08. Learning and Memory

Title: Bdnf and egr1 play doubly dissociable role in the consolidation and reconsolidation of first- and second-order fear memories in the basolateral amygdala complex

Authors: *A. SHVETCOV, R. F. WESTBROOK, N. M. HOLMES;
Univ. of New South Wales, Sydney, Australia

Abstract: We used rats to examine the roles of BDNF and EGR1 in consolidation and reconsolidation of first- and second-order fear memories in the basolateral amygdala complex (BLA). Rats were exposed to pairings of a light and foot shock to produce first-order conditioned fear of the light. They were then exposed to pairings of a tone and the conditioned light to produce second-order fear of the tone. The initial experiments examined the effect of infusing a BDNF antisense oligonucleotide (ASO) into the BLA on consolidation and reconsolidation of the first- and second-order fear memories. The BLA BDNF ASO infusion disrupted consolidation of the first-order (visual) fear memory when administered prior to pairings of the light and shock (Exp. 1); and disrupted consolidation of the second-order (auditory) fear memory when administered prior to pairings of the tone and the already conditioned light (Exp. 2). This infusion had no effect on reconsolidation of the first-order memory when administered prior to the tone-light pairings (Exp. 2) and no effect on reconsolidation of the second-order memory when administered prior to a brief re-exposure to the already conditioned tone (Exp. 3). The next experiments examined the effect of infusing an EGR1 ASO into the BLA on consolidation and reconsolidation of first- and second-order fear memories. The BLA EGR1 ASO infusion spared consolidation of the first-order (visual) fear memory when administered prior to light-shock pairings (Exp. 4). In contrast, this infusion disrupted retrieval of the first-order memory when administered before tone-light pairings; and thereby, acquisition

of the second-order fear memory (Exp.5). It also disrupted reconsolidation of the first-order fear memory when administered before the tone-light pairings (Exp. 5), and disrupted reconsolidation of the second-order fear memory when administered prior to a brief re-exposure to the conditioned tone (Exp. 6). Taken together, these results show that ERG1 and BDNF have doubly dissociable roles in the consolidation and reconsolidation of first- and second-order fear memories in the BLA. BDNF, but not ERG1, is critical for consolidation of both types of memory but is not needed for *re*consolidation of either. In contrast, EGR1 is critical for *re*consolidation of both types of memory but is not needed for consolidation of either.

Disclosures: A. Shvetcov: None. **R.F. Westbrook:** None. **N.M. Holmes:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P849.07

Topic: H.08. Learning and Memory

Support: Ministry of Science & Technology, Israel

Title: Activation of Rac1 GTPase in the basolateral amygdala leads to long-term fear memory impairment and neuronal morphological changes

Authors: *J. F. COSTA, M. DINES, R. LAMPRECHT;
Sagol Dept. of Neurobio., Univ. of Haifa, Haifa, Israel

Abstract: Evidence indicates that long-term memory-related processes such as consolidation, extinction, and forgetting involve changes in synaptic efficacy produced by alterations in neuronal transmission and morphology. Rac1 GTPase activity is regulated by synaptic activation and it can affect neuronal morphology by controlling actin-regulatory proteins. In this study, we have analyzed the role of Rac1 GTPase in the regulation of neuronal morphology and memory formation using a photoactivatable form of Rac1 (PA-Rac1). PA-Rac1 was expressed in mice basolateral amygdala (BLA) and photoactivated during fear conditioning. Mice in the control group were trained for fear conditioning but PA-Rac1 was not activated. Two days after fear conditioning, animals were tested for fear memory and their brains were removed immediately afterward and subjected to the Sca*l*eS clearing method to observe possible changes in neuronal morphology. We observed that activation of PA-Rac1 during fear conditioning impaired long-term fear memory. We also found significant changes in neuronal morphology in the PA-Rac1 activated neurons in the BLA two days after fear conditioning. We detected a small increase in the cell body sphericity but not its area or volume. Moreover, dendritic shafts presented a significant reduction in volume, area, mean diameter, and length, mostly in the dendrites that are proximal to the soma. We also observed alterations in terms of neuronal complexity such as an increase in dendritic branch points with a consequent increase of dendritic segments. Furthermore, we detected an increase in spine density in specific dendritic branches. These findings suggest that such alterations in neuronal morphology are involved in attenuating fear memory formation in the BLA.

Disclosures: J.F. Costa: None. **M. Dines:** None. **R. Lamprecht:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P849.08

Topic: H.12. Aging and Development

Title: Evidence for tonically active presynaptic alpha-2 adrenoceptors and their modulation of NMDA receptor mediated release of catecholamines in rat brain slices

Authors: *Y. M. ALJOHANI, G. DEZFULI, K. J. KELLAR;
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Abstract: Maintaining optimal levels of catecholamine neurotransmission in the central nervous system is vitally important. These neurotransmitters modulate several crucial physiological processes, including aspects of arousal/attention, focus, neuroendocrine functions, and the sleep-wake cycle; in addition, they play complex roles in regulating cognition and affect. Previously, we demonstrated that in brain slices from aged Fischer 344 rats, there is an age-related decrease in glutamate-stimulated norepinephrine (NE) release in the cerebral cortex and hippocampus (Dezfuli et al., 2019) and a regionally specific decline in glutamate-stimulated dopamine (DA) release, with a deficit in the striatum but no significant reduction in the olfactory tubercle (Aljohani et al., 2021). We have begun to explore the modulation of this glutamate-stimulated release of neurotransmitters and now report that stimulation of alpha-2 adrenergic receptors with clonidine decreases the glutamate-stimulated NE release in a dose-dependent manner; while in contrast, blockade of these receptors with phentolamine, an alpha-1 and alpha-2 adrenergic receptor blocker or with idazoxan, a selective alpha-2 receptor blocker, markedly potentiates glutamate-stimulated NE release in cortical brain slices. These findings strongly indicate that alpha-2 adrenergic receptors modulate NE release in the cerebral cortex and that they are tonically active. Furthermore, these studies are consistent with a presynaptic location of alpha-2 receptors on NE axons, positioned to modulate the glutamate-stimulated release of NE and related behaviors (e.g., cognition and/or affective disorders). Results from the dopamine studies are ongoing and will be reported.

Disclosures: Y.M. Aljohani: None. **G. Dezfuli:** None. **K.J. Kellar:** None.

Poster

P849. Learning and Memory: Molecular Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P849.09

Topic: H.05. Working Memory

Title: The role of ciliary melanin concentrating hormone receptor 1 in cognitive functions in mice

Authors: *W. ALHASSEN[1], B. ROBBINS[1], H. NGUYEN[1], A. ALACHKAR[2];
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Abstract: Primary cilia are microtubule-based sensory organelles that project from the surfaces of most cells and play crucial roles in cell signaling and communication through detecting and transducing external stimuli, and regulating the proper cell differentiation and migration. Primary cilia are involved in pathways such as the Sonic hedgehog, WNT, and cAMP mediated pathways. Alterations of neuronal primary cilia can cause abnormal neurogenesis and neural differentiation, leading to ciliopathies that may cause brain abnormalities, resulting in higher susceptibility to psychiatric disorders. MCHR1 is one of the few GPCRs that are selectively expressed on neuronal primary cilia. We have previously shown that MCHR1 mRNA levels are significantly lower in the PFC of subjects with schizophrenia and found that the disruption of the MCH system in mice led tobehavioral abnormalities including social and cognitive deficits. Thus we aim to establish the role that ciliary MCHR1 play in cognitive function by selectively removing MCHR1 by deleting IFT88 from neurons that express MCHR1. Animals that have loxP sites that flank the exons 4-6 of the intraflagellar transport 88 gene (IFT88) will be bred with our MCHR1CreER mice, which will result in the deletion of exon 4-6 in the tissues upon activation of the estrogen receptor expressed on Cre. Upon a tamoxifen injection i.p, tamoxifen-bound Cre-ER dissociates from HSP90, translocates into the nucleus, and carries out site-specific recombination between flanking loxP sites. Tamoxifen will be injected at 7 weeks old mice and at 8 weeks old were tested in cognitive behavioral assays. Animals where ciliary MCHR1 is removed displayed impaired working memory, recognition memory, spatial memory. In this study we show that the MCHR1 that localize specifically to cilia may be responsible for cognitive deficits seen in mice.

Disclosures: W. Alhassen: None. **B. Robbins:** None. **H. Nguyen:** None. **A. Alachkar:** None.

Poster

P883. Language: Acquisition and Usage

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P883.01

Topic: H.11. Language

Title: Why our brain makes pauses when we speak: analyzing pauses in English (L1/L2), Spanish (L1/L2) and heritage Spanish

Authors: *N. ENRIQUEZ;
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Abstract: Why our brain make pauses when we speak: Analyzing pauses in English (L1/L2), Spanish (L1/L2) and heritage Spanish We present a study on processing problem indicators in oral production in both Spanish and English in a simulated complaint task. Subjects are native English, native Spanish and heritage Spanish speakers. The aim was to describe the role of speech pauses as problem processing indicators in oral production as a communication strategy and their differences between groups of speakers and the language used in the simulation. Hypotheses: i) pauses are different quantitative and qualitatively depending on the speaker's competence; ii) results for heritage speakers will

be closer to L1 group than to L2; iii) cognitive load will be higher using a second language and iv) not only traditional parts of the brain involved in speaking (Wernicke, Broca) are going to be activated during a pause. In order to test these hypotheses, we gathered two different corpora. Recla/SP (10050 tokens) which consists of a sample of 30 dialogues in Spanish (10 native, 10 heritage and 10 non-native) and Recla/EN (9270 tokens) which contains 30 dialogues in English (10 native, 10 heritage and 10 non-native). We report preliminary findings on EEG data (32 channels, 500 Hz) during oral production. The bandpower in EEG data during 36 speech pauses was compared to baseline, where the subjects relaxed and looked at a blank paper in front of them for 1 min. The data was preprocessed by using the H-inf filter to remove eye-related artifacts, band-pass filtering the signal between 0.3 and 50 Hz, using the PREP pipeline for robust re-referencing, and ASR for removal of artefactual power bursts. At the onset of the speech pauses we found statistically significant ($p<0.01$) modulation in the left frontal areas for the delta band (1-4Hz), and activation of central-left regions in the alpha (8-12 Hz) and gamma (30-50 Hz) bands. The pattern was found both in English and Spanish speech production, with pre-frontal bandpower deactivation in the English task. Data confirms the role of pauses as indicators of the difficulty of the task itself and the linguistic difficulty in carrying it out in L2, hypothesis (i), (ii) and (iii). The study also reveals significant differences between native, heritage and non-native speakers, hypotheses (i) and (ii). In native speakers, pauses are indicators of difficulty in management decisions, while in non-native speakers indicate difficulties with syntax and verb inflection. As was stated in (ii) results for heritage are closer to L2. The cortico-basal ganglia-thalamo-cortical loop is highly involved in speaking, as well as, in pauses showing activation in L1 and L2 in all groups (iv).

Disclosures: N. Enriquez: None.

Poster

P883. Language: Acquisition and Usage

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Program #/Poster #: P883.02

Topic: H.11. Language

Support: USDA/Agricultural Research Service Project 6026-51000-012-06S

Title: Effect of diet on the development of language-specific perception of phonemes in the infant's brain. An event-related potentials study

Authors: *G. C. ALATORRE-CRUZ[1,3], A. ANDRES[4], G. YUYUAN[5], H. DOWNS[5], D. R. HAGOOD[5], D. K. WILLIAMS[2,5], L. J. LARSON-PRIOR[6,3];
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Abstract: Phonemic identification occurs early in cortical development. Infants can discriminate most tones at three months old and phonemic features by 5 - 6 months. Given that nutrition is fundamental to brain development, dietary intake may affect this early linguistic processing stage. A positive effect of breastfeeding has been reported for language encoding in infancy. However, no studies have addressed

the impact of other dietary choices on phonemic discrimination across early development. In this longitudinal study, 2-month-old infants were stabilized on one of three diets: breast milk (BF, 633 infants, 330 female), cow milk formula (MF,581 infants, 293 female), or soy-milk formula (SF, 607 infants, 273 female). Infants were assessed for their ability to discriminate phonemic sound differences at 3, 6, 9, 12, and 24 months. Infants were instrumented for brain electrophysiology (128 sensors, EGI) and tested with an oddball paradigm composed of frequent (/pa/ 80 %) and deviant (/ba/ 20%) auditory stimuli. The amplitude and latency of the mismatch negativity component (i.e., MMN, 300 - 500 ms) were compared between dietary groups in each age group. The differences between dietary groups were observed at 6, 12, and 24-months old. At 6-months old, the MMN amplitude was higher in the BF than MF and SF infants, while MMN latency was shorter for MF than the other two groups. Dietary groups also differed at 12-months old, the SF infants showed shorter MMN latency than BF and MF groups in the frontal left region, while at 24 months old, MF infants displayed longer MMN latency than the SF group. Given that the distinction between phonetic and phonemic features has been characterized as an increase in latency and amplitude of the MMN component, our results suggest that BF infants develop phonemic discrimination earlier than MF and SF infants. SF infants seem to have the slowest development of phonetic discrimination. Therefore, our results suggest that phonemic discrimination is differentially modulated by infant diet.

Disclosures: G.C. Alatorre-Cruz: None. **A. Andres:** None. **G. Yuyuan:** None. **H. Downs:** None. **D.R. Hagood:** None. **D.K. Williams:** None. **L.J. Larson-Prior:** None.

Poster

P883. Language: Acquisition and Usage

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P883.03

Topic: H.11. Language

Title: Neural basis of Sign Language Proficiency Revealed by the Naturalistic fMRI Paradigm and Inter-subject Correlation Analysis

Authors: *Y. LIN[1], Y.-S. CHIU[3], W.-J. KUO[1,2];
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Abstract: In this study, we used a naturalistic viewing paradigm together with fMRI to investigate neural basis of signlanguage proficiency of the hearing bilinguals with Mandarin as L1 and Taiwan sign language (TSL) as L2. 15 professional TSL interpreters and 15 TSL learners were recruited as participants. For naturalistic viewing in TSL, a story to describe local culture and events was translated into TSL by an expert and the connected TSL expression was videotaped. The participants were presented with the tape during MR scanning. The brain images were preprocessed with the standard procedure and analyzed with the inter-subject correlation (ISC) analysis to detect brain areas were showed correlated, synchronized BOLD activities during TSL comprehension. The ISC results of the two groups were further compared to reveal the sign language proficiency. By doing so, we found that the neural networks which work with reliable stability to encode TSL across individuals of the two groups was widely

distributed, including the ventral and dorsal visual pathways, bilateral inferior parietal cortex, bilateral premotor cortex, and left middle frontal gyrus. We further examined the ISC difference between two groups and found that the interpreter group showed brain regions with higher stability in the bilateral temporal cortex, the left inferior parietal cortex, and the left middle frontal gyrus. On the other hand, the learner group showed higher stability of their correlated brain activities in the visual dorsal processing stream and some sensorimotor regions. In sum, our results revealed that sign language proficiency in normal hearing participants was encoded in a widely distributed set of cortical networks which migrated from primary visuomotor brain areas and settled in brain areas which feature in processing human language and social/biological motion.

Disclosures: Y. Lin: None. **Y. Chiu:** None. **W. Kuo:** None.

Poster

P883. Language: Acquisition and Usage

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Program #/Poster #: P883.04

Topic: H.11. Language

Support: ERC Consolidator Grant 773202

Title: Changes in the localization of functional activation to repetition sequences in infants across fNIRS studies

Authors: *J. GEMIGNANI[1], J. GERVAIN[1,2];
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Abstract: Infants' ability to perceive repetition-based regularities plays a central role in language acquisition and has been long investigated, especially with functional near-infrared spectroscopy (fNIRS). However, exactly which brain areas are involved in processing repetitions and how this changes with development has received little attention. In this work, we explored how the pattern of functional activations elicited by different regularities changes across studies and age groups. We examined seven fNIRS studies conducted in three different labs; the final sample comprised data from 150 infants (72 M, 78 F; 91 newborns, 59 six month-olds). Stimuli included trisyllabic auditory sequences in the form of AAB or ABB as well as random sequences. fNIRS was measured with 24 channels distributed bilaterally to sample the fronto-temporal-parietal regions. Data analysis included pre-processing and block-averaging; then, for each study, cluster-based permutation tests were performed to compare changes in oxygenated hemoglobin (HbO) concentrations between conditions and identify clusters of active channels; in particular, paired t-tests compared (i) repetition sequences to a zero baseline (R>0), (ii) random sequences to a zero baseline (N>0) and (ii) repetition to random sequences. They were carried out within the time course of the hemodynamic response, for each channel; then, temporally and spatially adjacent pairs with a significant *t* value were grouped to form cluster candidates; clusters' significance was finally assessed with a permutation analysis, by comparing their *t* value to the null distribution of *t* values obtained by randomly relabeling data and carrying out the same paired t-test (1000 times). We found that newborns display a bilateral pattern of activation for the condition R>0, while no significant

activation was found in the left hemisphere for the N>0 comparison; by contrast, we found the clusters of the six months olds to be bilaterally distributed both for the R>0 and the N>0 comparison. Changes in the functional connectivity underlying these patterns are also being explored. Our results suggest that a permutation-based analysis provide a way to derive regions of interest from the data and assess their changes across dimensions of interest, e.g. age.

Disclosures: J. Gemignani: None. **J. Gervain:** None.

Poster

P883. Language: Acquisition and Usage

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Program #/Poster #: P883.05

Topic: H.11. Language

Support: NIH Grant P41 EB018783

Title: Relationship between "tip-of-the-tongue" word retrieval errors and EEG spectral features

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Abstract: *Background:* Temporary word retrieval failures that occur when a person cannot recall a specific word, but can recall information about the word (e.g., number of syllables) are known as "tip-of-the-tongue" (TOT) errors. TOT errors are common, especially in older adults. TOT errors are thought to involve inaccurate phonological retrieval after lexical selection has occurred, which may be similar to the underlying cause of word retrieval errors that some persons with aphasia (PWA) experience. Previous work has demonstrated that word retrieval in PWA can be predicted using EEG spectral features. The aim of the current study was to investigate the predictive relationship between word retrieval errors and EEG spectral features in healthy adults using a Famous People naming task (Middleton & Schwartz, *J Speech Lang Hear Res*, 2013).
Method: Eighteen healthy adults (mean age = 57 yrs; 3m/15f) participated in this study, which included a behavioral screening session and 4 EEG sessions. Data were collected with informed consent and PSU IRB approval. Participants who advanced beyond screening produced error responses for at least 10% of the items and were able to recognize at least 250 pictures from a set of 704. In EEG sessions, the subject-specific stimuli set (pictures recognized in the screening) presented in the first 2 sessions was repeated in the last 2 sessions. Stimuli were displayed for a maximum of 5s/picture, during which the participant verbally named the person in the picture while a microphone recorded their responses. Scalp EEG (32 channels) was acquired at 1000 Hz (BrainAmp DC (Brain Vision, LLC)) referenced to FCz. NCAN BCI2000 software was used to present the stimuli, and to acquire and synchronize EEG data with the spoken response. All trial responses were scored by two researchers independently on an 8-point rating scale that encoded responses as correct, nil, or various errors.
Analysis & Results: EEG data were notch filtered (55-65Hz), common-average referenced and epoched (-

2s to 2s) relative to the speech onset. Noisy epochs were rejected using trial statistics. Automated speech onset detection was performed to detect onset of spoken response. Multi-taper spectral analysis (0.5-45Hz) was performed. Response analysis, normalized to total number of stimuli per person, showed a significant increase in number of correct responses in the first stimuli exposure vs. second exposure ($p < .05$). A mean speech response time of 2.3s+/-0.2s was observed; significantly lower for correct responses (2.2s+/-0.17s) vs. incorrect (2.6s+/-0.32s); $p < .01$. Preliminary results of EEG analyses are promising and spectral differences between error types will be discussed.

Disclosures: E.A. Riley: None. **C. Sandberg:** None. **D.J. McFarland:** None. **D. Gupta:** None.

Poster

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Topic: H.11. Language

Support: NSF IIS Grant 1912373
BMBF CRCNS Grant 01GQ1906

Title: Representations of Linguistic Information at Different Timescales in the Human Brain During Reading and Listening

Authors: *C. CHEN, T. DUPRE LA TOUR, J. L. GALLANT, D. KLEIN, F. DENIZ;
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Abstract: Natural language contains information at different timescales. For example, syntactic structure occurs at relatively short timescales, while discourse structure occurs at longer timescales. Some evidence from functional neuroimaging experiments suggests that different brain regions may be specialized for processing linguistic information at these different timescales. However, previous neuroimaging studies have not directly compared how linguistic information at different timescales is represented across stimulus modalities.
Here, we study the representation of linguistic information at different timescales and modalities in the brain. We examined fMRI data collected in two previous studies from our lab, in which subjects listened to and read the same set of natural language narratives (Huth 2016, Deniz 2019). We used voxelwise encoding models to determine the selectivity of each voxel to linguistic information at each timescale and modality. First, we transformed the stimuli into timescale-specific feature spaces. To do this, we projected each stimulus word into an embedding space that encodes the meaning of words as vectors. We then applied linear filters to the resulting embedding to decompose the embedding into timescale-specific feature spaces. These feature spaces range from high-frequency components that capture quickly-changing information such as syntactic structure, to low-frequency components that capture slowly-changing information such as discourse structure. Then, for each subject and modality, we used regularized regression to estimate a mapping from each timescale-specific feature space to brain responses in each voxel. We used the estimated mapping to predict brain responses to a held-out narrative, and we used the prediction performance on the held-out narrative to determine the selectivity of

each voxel to linguistic information at each timescale and modality.
We find that short-timescale models predict well in different primary and secondary sensory regions for reading (visual cortex) and listening (auditory cortex). In contrast, long-timescale models predict well in amodal regions distributed across prefrontal, temporal, and parietal cortices for both modalities. For both modalities, voxelwise timescale-selectivity follows a spatially smooth gradient from modality-specific representations of short-timescale information in sensory regions, to modality-general representations of long-timescale information in higher-level cortical regions.

Disclosures: C. Chen: None. **T. Dupre la Tour:** None. **J.L. Gallant:** None. **D. Klein:** None. **F. Deniz:** None.

Poster

P883. Language: Acquisition and Usage

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P883.07

Topic: H.11. Language

Support: NIH: R01EY025978

Title: Specificity in sound-to-meaning correspondences in spoken language

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Abstract: The relationship between the sound of a word and its meaning has long been assumed to be primarily arbitrary; thus, the sounds of language are assumed to bear no necessary resemblance to properties of their referents. Despite this arbitrariness assumption, mounting evidence suggests that non-arbitrary , or sound-symbolic correspondences, exist in natural languages and that language users recognize and use these associations to infer word meaning. Few studies, however, have systematically addressed the range of possible meanings that may be involved in sound-symbolic correspondence and the degree to which sound-symbolic mappings are specific to particular meanings (e.g., pointy) or rather rely on mappings to common abstract domains (e.g., arousal). The current study assessed the relative specificity of sound-symbolic mappings by examining the features of speech sounds associated with fourteen adjectives representing the categorical opposites across each of seven different meaning domains, including the perceptual attributes of shape (round, pointy), size (big, small), luminosity (bright, dark); weight (light, heavy), and texture (soft, hard); and the affective attributes of arousal (calming, exciting) and valence (good, bad). Native English-speaking listeners were presented with 537 (consonant-vowel-consonant-vowel) pseudowords that sampled from the acoustic-phonetic feature space of American English and rated each item from 1 to 7 on each of the fourteen different adjectival scales (e.g., 1= not round, 7 = very round). Average ratings were analyzed as a function of both consonant (manner, voicing, and place of articulation) and vowel (roundedness, height) features for each scale. The results revealed some commonalities across meanings such that similar clusters of speech sound types were associated across particular word meanings. For example, voiced consonants and rounded vowels were both

associated with higher ratings of bigness and heaviness. Some feature-to-meaning mappings were found to be scale-specific, with constellations of different features associated with each meaning. For example, while some phonetic features associated with ratings of pointedness were similar to those of heaviness (e.g., stops), other features differed across the two scales (e.g., vowel roundedness). Further, features associated with perceptual attributes did not map uniformly onto either the arousal or valence dimensions. These findings suggest that sound-symbolic correspondences vary across meaning domains and may reflect the instantiation of meaning-specific, cross-modal associations within natural languages.

Disclosures: K. Matthews: None. **A. Hoffman:** None. **S.A. Lacey:** None. **L. Nygaard:** None. **K. Sathian:** None.

Poster

P883. Language: Acquisition and Usage

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P883.08

Topic: H.11. Language

Support: JSPS KAKENHI 19H00532

Title: Neural substrates for socio-emotional processing via mood-indicating linguistic morphemes: An fMRI study

Authors: *S. KIYAMA[1], Y.-W. SUNG[2], K. XIONG[1], M. MAKUUCHI[3], S. OGAWA[4];
[1]Tohoku Univ., Sendai, Japan; [2]Kansei Fukushi Res. Inst, Tohoku Fukushi Univ., Sendai-Shi, Japan; [3]Natl. Rehabil. Ctr. for Persons with Disabilities, Tokorozawa, Japan; [4]Kansei Fukushi Res. Inst., Touhoku Fukushi Univ., Sendai-shi, Japan

Abstract: Language plays a role in expressing the socio-emotional states of language users, as well as propositional contents. Through language, users perceive another user's emotions and experience their own. However, it is difficult to distinguish how the emotional and propositional aspects of language are regulated, since the emotions are typically expressed with prosody or nonverbal behavior, concurrently with the proposition. We focus on Japanese sentence-final particles (SFPs), as they are function words with no proposition, and users can freely attach SFPs to the sentence to indicate their mood. To examine neural bases for socio-emotional processing with language, we conducted an fMRI study with a mood regulation task in conversation. In the experiment, native Japanese speakers read hypothetical dialogs with either the self-oriented SFP "-yo" or the other-oriented "-ne," in either a self- or other-oriented proposition in the context. We compared the BOLD signals while participants processed the two types of SFP, depending on the two types of context. We estimated the appropriate participant number to be 30 based on a power analysis to obtain a medium effect size ($0.7\ {}_p\eta^2$) in a repeated measures 2 x 2 ANOVA. We then obtained 32 participants' data (21 male, average age was 21.6±1.5), and confirmed no significant sex differences in the following results (FDR corrected $p < .05$, Fig.1). Subsequently, stronger activity was induced for processing the self-oriented "-yo" than the other-oriented "-ne" when the moods of the SFP and context were inconsistent rather than consistent, in the right supplementary motor area, the left anterior dorsal cingulate, the left inferior frontal gyrus pars triangularis, and the right insular lobe.

Contrarily, the left middle temporal gyrus was more strongly activated when the moods of the SFP and context were consistent. Further, the left temporal pole yielded a stronger activation in other-oriented contexts for both SFPs. It suggests that socio-emotional regulation via language requires a wide network of language, motor, social cognition, and emotion areas.

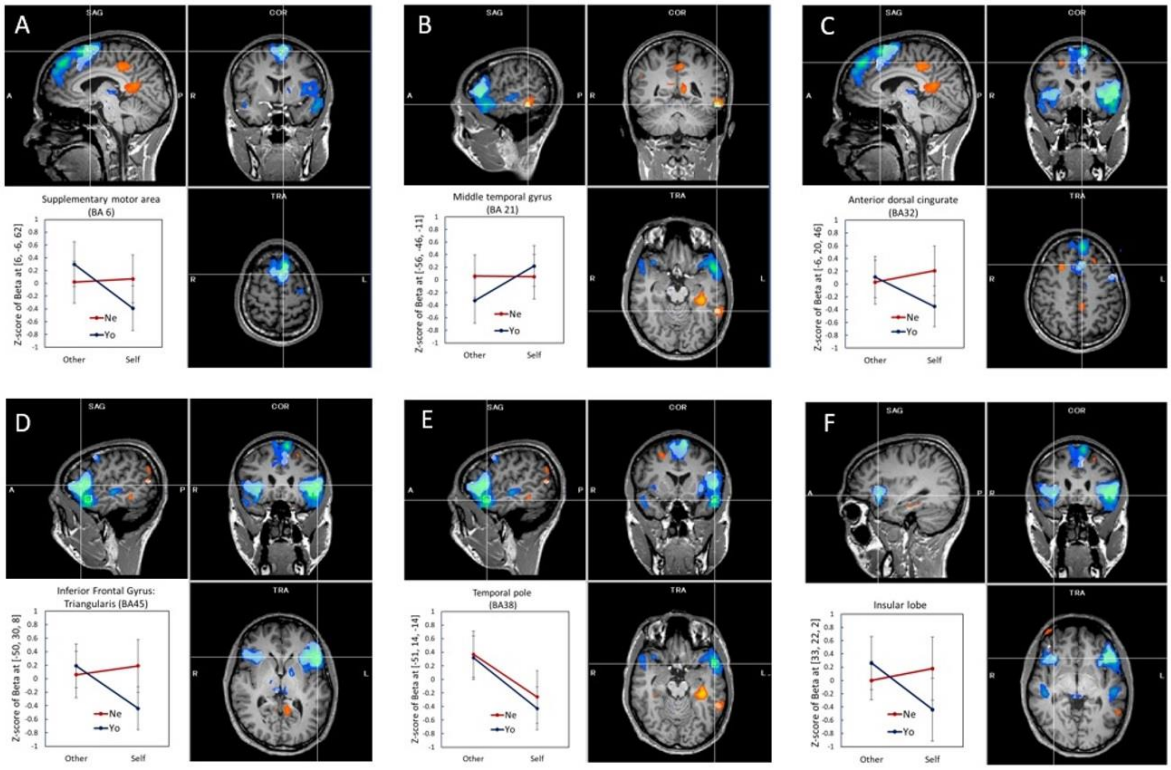


Fig. 1. Overlap fMRI activation of contrasts during processing Japanese mood-indicating sentence-final particle (SFP) '-yo' and the interaction of the two types of SFP ('-yo', '-ne') and Context (other-oriented, self-oriented) by native Japanese speakers (N = 32). All p < 0.05 (FDR corrected). Error bars indicate 95% confidence intervals. Numbers in brackets indicate coordinates of the peak voxel in Talairach space.

Disclosures: S. Kiyama: None. **Y. Sung:** None. **K. Xiong:** None. **M. Makuuchi:** None. **S. Ogawa:** None.

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.01

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Using tract-tracing studies in non-human primates to delineate the anatomic connections that underlie resting-state functional connectivity changes after amygdala neurofeedback in humans

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Abstract: Functional magnetic resonance imaging (fMRI)-based neurofeedback is an emerging therapeutic tool for neurological and psychiatric conditions. Resting-state functional connectivity (rsFC) studies in clinical samples suggest fMRI neurofeedback induces neural plasticity. rsFC is highly correlated with structural connections which might be used to select neurofeedback target candidates. However, *in vivo* diffusion imaging, the current technique to determine structural connections in humans, is error-prone. This study aimed to evaluate whether non-human primate (NHP) anatomic connections determined using the gold-standard method of tract-tracing can be used to explain rsFC the connections that underlie changes due to neurofeedback training. Specifically, we focused on protocols targeting self-regulation of the blood-oxygen-level-dependent (BOLD) signal in the left amygdala. In the first set of analyses, we collected meta-data from three studies reporting rsFC regions-of-interest (ROIs) changes associated with amygdala self-regulation. We registered these ROIs to the human Regional Mapping (RM) parcellation. This parcellation allows direct comparisons between homologous regions of the NHP and human brains. We used the Cocomac tract-tracing database to determine the connectivity strength of amygdalar projections to each RM parcel. The real connectivity strength of each rsFC ROI was calculated and compared with 10^4 ROIs randomly sampled from the human template. Confidence Interval analyses show that more than 60% of intra-hemispheric rsFC associated with neurofeedback training are explained by connections of moderate strength in the NHP data. In the second set of analyses, we placed an anterograde tracer injection in the left amygdala of a macaque monkey. Under darkfield microscopy, we evaluated the NHP regions homologous to the areas with amygdala-cortical rsFC changes after neurofeedback in humans. We identified dense axonal projections in four out of eight intra-hemispheric locations, suggesting a monosynaptic anatomic link to the rsFC changes. In sum, the results show that the precision of NHP neuroanatomy can help understand connections that underlie rsFC changes due to neurofeedback training in humans. This approach can help identify new neurofeedback targets to specific symptoms and conditions.

Disclosures: L. Trambaiolli: None. **C. Biazoli:** None. **S.N. Haber:** None.

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

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Program #/Poster #: P901.02

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Bill Gatton College of Pharmacy faculty startup grant

Title: Nmda antagonism disrupts gamma frequency auditory steady state response (assr) as well as harmonics in female sd rats

Authors: *M. RAZA[1], D. V. SIVARAO[2];
[1]Dept. of Pharmaceut. Sci., Bill Gatton Col. of Pharm., Johnson City, TN; [2]Dept. of Pharmaceut. Sci., Bill Gatton Col. of Pharm., Johnson city, TN

Abstract: **Background**. Schizophrenia patients show dysfunction in processing sensory inputs including a reduction in cortical entrainment to steady-state auditory click stimuli delivered ~ 40 Hz, called the auditory steady-state response (ASSR). Deficits in 40 Hz ASSR are attributed to a reduction in NMDA-mediated neurotransmission within the cortical neural networks. Indeed, acute administration of NMDA antagonists to healthy human subjects or laboratory animals can reproduce many sensory and cognitive deficits seen in schizophrenia patients, including a reduction in 40 Hz ASSR. Click sounds are spectrally complex and carry not only the driving frequency (f_0) but also its integer multiples ($n*f_0$), called harmonics. Harmonics play a pivotal role in sound recognition, a domain in which schizophrenia patients perform poorly relative to controls. Spencer et al. reported that evoked power and phase-locking factor (PLF) to a 20 Hz driving frequency were intact in first-episode psychosis patients but its 40 Hz harmonic was disrupted (Biol. Psychiatry 2008). In the current study, we tested the hypothesis that the NMDA antagonist MK801, would attenuate 40 Hz ASSR, but will only affect harmonics of a 20 Hz click train. **Methods**. Female Sprague-Dawley rats were implanted with epidural (vertex/cerebellum) EEG recording electrodes. Rats were administered vehicle, 0.025, 0.05, and 0.1 mg/kg MK-801 (sc), using a Latin square design; at least 3 days were allowed between treatments. Auditory click trains were presented at 10, 20, 40, 80, and 160 Hz (65dB), 60 minutes post-treatment; 75 trials were recorded. Time-frequency analysis was performed using Windows-based software (EMSE Data Editor, Cortech Solutions). **Results**. MK-801 dose-dependently reduced the PLF for 40, 80, and 160 Hz ASSR only. Evoked power was reduced at 40 and 80 Hz only; dose-dependent increases in power were noted at 160 Hz ASSR. Lastly, while PLF for 20 Hz ASSR was unaffected, dose-dependent reductions in 40 and 80 Hz harmonics were noted. For evoked power, only the second harmonic (ie., 40 Hz) showed a significant decrement. **Conclusion**. NMDA antagonism not only attenuated gamma frequency ASSR but also disrupted the harmonics of 20 Hz ASSR. These findings are reminiscent of observations made in first-episode psychosis patients as well as in chronic schizophrenia (Tsuchimoto et al., Schiz Res., 2011), highlighting the potential of this acute pharmacological model for translational research.

Disclosures: M. Raza: None. **D.V. Sivarao:** None.

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

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Program #/Poster #: P901.03

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Title: Brain age prediction in gray matter volume, cortical thickness and white matter integrity across different durations of illness in schizophrenia using machine learning approach

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Abstract: Brain age prediction is a novel approach to assessing accelerated aging of the brain in different diseases. However, most brain-age studies combined the average brain age gap of individuals with schizophrenia with different durations of illness for comparison with healthy controls. Therefore, this study investigated whether the declined brain structures as reflected by the brain age gap may be present in schizophrenia in terms of gray matter volume, cortical thickness, and white matter integrity across different durations of illness. We recruited 194 individuals with schizophrenia and 330 healthy controls. We extracted gray matter volume, cortical thickness, and white matter integrity from healthy controls and used these features to train three brain-age prediction models using Gaussian process regression, respectively. Three models were applied to predict brain age in individuals with schizophrenia and calculated the brain age gap. Compared with healthy controls, the gray matter volume and cortical thickness models revealed that individuals with schizophrenia had a larger brain age gap across different durations of illness. In addition, gray matter volume and white matter integrity progressively deteriorated in individuals with schizophrenia from approximately 19 and 20 years, respectively, after disease onset, whereas the rate of cortical thickness decline was relatively consistent over the whole disease course. Our findings suggested that schizophrenia differentially affected the decline of different brain structures during the disease course. Moreover, the different trends of decline in thickness and volume-based measures suggest a differential decline in dimensions of brain structure throughout the course of schizophrenia

Disclosures: J. Zhu: None. **S. Tsai:** None. **A. Yang:** None.

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.04

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: RESEARCH–CREATE–INNOVATE (project code:T1EDK-02890)

Title: Smartwatch digital phenotypes relate to positive and negative psychotic symptom variation in a longitudinal monitoring study (e-Prevention) of patients with psychosis

Authors: E. KALISPERAKIS[1], T. KARANTINOS[1], T. KARANTINOS[1], P. FILNTISIS[2], M. LAZARIDI[1], A. ZLATINTSI[2], N. EFTHYMIOU[2], A. MANTAS[1], L. MANTONAKIS[1], V.

GARYFALLI[1], P. TSANAKAS[2], P. MARAGOS[2], *N. SMYRNIS[1];
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Abstract: Monitoring and relapse prevention in psychotic disorders is critical but at the same time challenging due to the difficulty in observing patients outside the clinic and the lack of well-established objective measures of human behavior. One of the proposed solutions to this are digital phenotyping techniques such as recording passive data from sensors in smartphones and wearables. During the ongoing e-Prevention project we record digital phenotypes using a specially modified commercial smartwatch including: a) motion via accelerometer (linear acceleration) and gyroscope (angular velocity); b) heart activity via photoplethysmography including heart rate (HR) (beats per minute) and inter-pulse (PP) intervals measuring heart rate variability (HRV) c) measures extracted from specialized smartwatch algorithms including time spent sleeping and awake as well as steps covered during wakefulness. 35 patients suffering from psychotic disorders (20 with schizophrenia and 15 with bipolar disorder) were monitored for a period of up to 14 months. During the same period patients were assessed monthly for psychopathology using the PANSS scale. Linear mixed model analysis was used to assess the relation of mean and variance of each digital phenotype for each subject and each month to psychopathology. Positive psychopathology was positively correlated with mean HR in both wakefulness and sleep (t_{150}=3.27, p=0.001 and t_{208}=2.86, p=0.005 respectively). Negative psychopathology was negatively correlated to the mean HRV (t_{183}=-2.69, p=0.008) and positively correlated to the variance of HRV (t_{225}=2.81, p=0.005) during wakefulness and positively correlated to time spent sleeping (t_{91}=2.74, p=0.007). The results indicate that digital phenotypes and especially measures of heart rate activity, are sensitive to changes in psychopathology over time and could be possibly used as input variables in expert systems that could aid the clinician in the monitoring of these patients and to the timely prediction of symptom relapse.

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Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.05

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Functional connectivity-based stratification biomarker for major depressive disorder with replicability and predictivity of antidepressant responses

Authors: *Y. KASHIWAGI[1,2], T. TOKUDA[2], Y. TAKAHARA[1,2], Y. SAKAI[2], J. YOSHIMOTO[2,3], A. YAMASHITA[2,4,5], T. YOSHIOKA[2], S. MOMOSAKI[1], K. OGAWA[1], M. KAWATO[2,6], O. YAMASHITA[2,6];
[1]SHIONOGI & CO., LTD., Osaka, Japan; [2]Advanced Telecommunications Res. Inst. Intl., Kyoto, Japan; [3]Nara Inst. of Sci. and Technol., Nara, Japan; [4]Boston Univ. Sch. of Med., Boston, MA; [5]VA Boston Healthcare Syst., Boston, MA; [6]RIKEN, Tokyo, Japan

Abstract: Major depressive disorder (MDD) is highly heterogeneous in terms of symptom presentations, disease trajectories, treatment responses, and underlying biological mechanisms. Identification of biologically homogeneous subtypes of MDD is expected to promote the development of precise diagnoses and effective treatments. Several studies have shown to identify clinically useful subtypes of MDD by data-driven approaches based on clinical features and/or biological substrates, but almost all those stratifications have not sufficiently been replicated in an independent validation cohort. To develop the functional connectivity (FC)-based biomarker for MDD stratification with replicability, we applied the hierarchical supervised/unsupervised approach. In our group, some generalizable diagnostic markers which distinguish healthy controls and MDD patients have been developed based on whole brain FCs by supervised learning algorithms. In this study, the FCs with larger contribution on those diagnostic markers were applied to an unsupervised clustering method for identification of MDD subtypes. Two independent multi-site datasets of resting-state fMRI data were analyzed in this study: One dataset consisted of 138 MDD patients collected from 3 sites, and the other consisted of 181 MDD patients collected from different 4 sites. As an unsupervised method, multiple co-clustering algorithm was individually applied to these 2 datasets. This algorithm is powerful in clustering with high-dimensional data and can identify clustering patterns of subjects based on FCs in specific brain areas. We could confirm the high similarity of the clustering solutions between datasets, which indicates that the approach enables replicable subtyping. To examine clinical usefulness of the subtyping, we applied the multiple co-clustering to all MDD patients (N = 319) and analyzed treatment responsiveness of each subtype with MDD patients who have longitudinal clinical data (before and after 6 week-treatment of antidepressant, N = 96). As a result, we found some characteristic subtypes with high or low responsiveness to antidepressant treatment. These subtypes were defined by distinct patterns of FCs between the thalamus and pre/post central gyrus. We have shown the usefulness of the hierarchical supervised/unsupervised approach and multiple co-clustering method for replicable subtyping, and the subtyping based on the thalamic connectivity with sensorimotor area may be useful for prediction of antidepressant treatment outcomes. In the future study, we are planning prospective clinical researches to validate the clinical characteristics of the MDD subtypes.

Disclosures: Y. Kashiwagi: A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD. **T. Tokuda:** A. Employment/Salary (full or part-time):; Advanced Telecommunications Research Institute International. **Y. Takahara:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD. **Y. Sakai:** A. Employment/Salary (full or part-time):; Advanced Telecommunications Research Institute International. **J. Yoshimoto:** A. Employment/Salary (full or part-time):; Nara Institute of Science and Technology. **A. Yamashita:** None. **T. Yoshioka:** A. Employment/Salary (full or part-time):; Advanced Telecommunications Research Institute International. **S. Momosaki:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD. **K. Ogawa:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD. **M. Kawato:** A. Employment/Salary (full or part-time):; Advanced Telecommunications Research Institute International. **O. Yamashita:** A. Employment/Salary (full or part-time):; Advanced Telecommunications Research Institute International.

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.06

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 5R01MH115045
5R01MH115045
5R01MH118298
5R21MH099448

Title: Discovery of positive modulators of the T-type calcium channel Cav3.3 to treat the sleep spindle deficits observed in schizophrenia patients

Authors: *S. P. MORAN, A. GHOSHAL, J. R. COLEMAN, Jr, M. FITZGERALD, D. BAEZ-NIETO, E. YU, L. YANG, J. GALE, L. A. WANG, N. KURA, N. G. SHUART, Y.-L. ZHANG, M. WEIWER, F. F. WAGNER, J. Q. PAN;
Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Schizophrenia is a debilitating disorder that lacks effective treatments for the negative symptoms (e.g., social withdrawal) and cognitive disruptions (e.g., working memory deficits) in patients. Recently, large scale human genetics studies including genome wide association studies (GWAS) and exome sequencing studies have identified many replicable genomic loci for schizophrenia risk. Cacna1I, was identified as one of these schizophrenia risk genes and it encodes the functional core, α1 subunit, of $Ca_V3.3$ voltage-gated calcium channels. $Ca_V3.3$ channels are expressed in a subset of neurons including GABAergic neurons of the thalamic reticular nucleus (TRN) where they regulate neuronal excitability. The TRN has emerged as a crucial brain nucleus in the generation of sleep spindles, sleep dependent memory, focused attention, and cognitive flexibility, all of which are impaired in patients with schizophrenia. Our group and others have demonstrated that loss of $Ca_V3.3$ dramatically alters TRN neuronal firing in mice, and this altered firing corresponds with reduced sleep spindles occurrences, a phenotype also found in schizophrenia patients. Based on these genetic and biological evidence, we hypothesize that $Ca_V3.3$ potentiators could benefit patients with schizophrenia by rescuing sleep spindle deficits and improving sleep dependent cognitive function. However, there is a lack of selective and potent $Ca_V3.3$ small molecule potentiators. We therefore set out to identify highly selective, potent and brain penetrant Cav3.3 potentiators. We first established a novel primary high-throughput screening (HTS) fluorescence-based assay to capture the increased calcium influx mediated by $Ca_V3.3$ in HEK cells. After completion of a HTS campaign of ~77,000 compounds, we identified 5 validated $Ca_V3.3$ potentiators. We then selected two hits to perform medicinal chemistry. From these efforts, we report a novel set of potent and highly selective $Ca_V3.3$ potentiators that enhance $Ca_V3.3$ function in both cell-based molecular pharmacology and high throughput patch clamp electrophysiology as well as modulating a known $Ca_V3.3$ mediated hyperpolarization induced rebound bursting phenomenon in acute mouse brain slices containing TRN. Taken together, these studies identified selective $Ca_V3.3$ potentiators that can modulate $Ca_V3.3$ channel activity relevant for sleep spindles and sleep dependent cognition and represent an exciting step towards the development of a novel class of potential therapeutics for the treatment of sleep disturbances and cognitive deficits in patients with schizophrenia.

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Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.07

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
NIH NIMH/FIC/NCCAM grant R21MH095644
NIH NIMH grant R21MH117776
Contract # HHSN-271-2013-00017-C and HHSN-271-2018-00023-C (NIMH - PDSP)

Title: MRGPRX4, a target of interest in drug development for mental disorders. Towards the identification of active molecules from ethnopharmaceuticals

Authors: *C. GALLO[1], G. POLETTI[1], R. ROJAS[1], J. ALBÁN[2], A. VAISBERG[1];
[1]Univ. Peruana Cayetano Heredia, Lima, Peru; [2]Univ. Nacional Mayor de San Marcos, Lima, Peru

Abstract: Mas-Related G protein-coupled receptor, member X4 (MRGPRX4) was first identified among a family of GPCRs related to the MAS1 oncogene. The MRGPRX4 gene is conserved in chimpanzee, Rhesus monkey, mouse, and rat, and is expressed in primary sensory neurons. Recently, it has been shown that MRGPRX4 is activated by bile acids-and bilirubin and may have a role in cholestatic itch. Altered nociception, including itch, has been reported in schizophrenia/psychosis, affective disorders as well as in other mental disorders. Although an interplay between central and peripheral regulatory processes is suspected, the exact nature of the biological mechanisms implicated is still unknown. Even though there is no clear link between MRGPRX4 and mental disorders yet, a potential contribution of this GPCR to the underlying biological mechanisms is feasible. Consequently, the identification and isolation of specific ligands or interacting molecules will be important for a better understanding of its role in the development of these diseases. Rescuing traditional medicine practices is one of the possible avenues to discover novel pharmacological approaches. We have a repository of 477 extracts from an equal number of plant collections corresponding to 265 species from 87 different plant families used in Peruvian traditional medicine for brain disorders. The collections were done in several localities and geographic regions of Peru. We have identified 20 extracts with high activity (either agonist or inverse agonist) for MRGPRX4 through a functional Gq calcium mobilization assay performed at the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill. These extracts are used in Peruvian traditional medicine for treating diverse behavioral conditions defined either in formal (depression, schizophrenia, anxiety, insomnia) and informal (“sadness”, “madness”, “aching heart”, “fright”) terminology. The extracts are currently being fractionated to isolate and characterize the active molecules.

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Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

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Program #/Poster #: P901.08

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
NIH NIMH/FIC/NCCAM grant R21MH095644
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Contract # HHSN-271-2013-00017-C and HHSN-271-2018-00023-C (NIMH - PDSP)

Title: Cxcr4 and cxcr7(ackr3) as drug targets for mental disorders. discovery of active molecules from ethnopharmaceuticals.

Authors: *A. VAISBERG[1], C. GALLO[1], **G. POLETTI**[1], R. ROJAS[1], J. ALBÁN[2];
[1]Univ. Peruana Cayetano Heredia, Lima, Peru; [2]Univ. Nacional Mayor de San Marcos, Lima, Peru

Abstract: CXCR4 and CXCR7(ACKR3) belong to the chemokine GPCR family and are receptors for CXCL12 (also called SDF-1 alpha). Stimulation of CXCR4 triggers a classical GPCR cascade. CXCR7 instead, functions as a scavenger receptor for CXCL12, and can form heterodimers with CXCR4. Either CXCR7 or the CXCR4/CXCR7 complex induce β-arrestin-mediated internalization and lysosomal degradation of CXCL12-bound receptors. CXCR4 and CXCR7 are expressed in both developing and mature CNS. High co-expression of these receptors has been observed in the globus pallidus, the paraventricular and supraoptic hypothalamic nuclei, in the medial habenula and in the choroid plexus of the lateral ventricles. CXCR4 and CXCR7 have been involved in neurodevelopment, inflammation, neurogenesis, angiogenesis, and in immune cell activation and recruitment, supporting a potential role in the interaction between the nervous and immune systems. CXCR4 has only one synthetic partial agonist and several small molecule antagonists, such as AMD 3100 and T140, among others. CXCR7 is activated by the peptidomimetic TC1402 as well as by the small molecules CCX771 and AMD-3100. No antagonist molecule has been reported yet for CXCR7. AMD 3100 is the only FDA-approved small molecule drug acting on CXCR4/CXCR7; consequently, the identification of novel agonists for CXCR4 and agonist or antagonists for CXCR7 is of high interest. Rescuing traditional medicine practices is one of the possible avenues to discover novel pharmacological approaches. We have a repository of 477 extracts from an equal number of collections corresponding to 265 species from 87 different plant families used in Peruvian traditional medicine for treating brain disorders. We have identified 5 extracts with high activity for CXCR4 and 53 with high activity for CXCR7(ACKR3) through a functional Tango-beta-arrestin assay performed at the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill. The active extracts are used in Peruvian traditional medicine for treating diverse behavioral conditions defined either in formal (depression, insomnia) and informal (“sadness”, “madness”, “aching heart”, “nervousness”) terminology. The top 20 extracts are currently being fractionated to isolate and characterize the active molecules. The isolated molecules will be pivotal not only to explore the potential of CXCR4 and CXCR7 as drug targets for mental disorders, but to advance in the understanding of the pathologic mechanisms involved in their occurrence.

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Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.09

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Multimodal conversational technology for remote assessment of symptom severity in people with schizophrenia

Authors: *H. KOTHARE[1], M. NEUMANN[1], O. ROESLER[1], J. LISCOMBE[1], D. PAUTLER[1], D. SUENDERMANN-OEFT[1], C. YAVORSKY[2], A. KHAN[3], J.-P. LINDENMAYER[3], V. RAMANARAYANAN[1];
[1]Modality.AI, Inc., San Francisco, CA; [2]Valis Biosciences, Inc., Berkeley, CA; [3]Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: The causes of schizophrenia are complex and largely unknown. Current treatments focus on the management of positive or psychotic symptoms. However, negative symptoms like lack of facial and verbal expression, monotone speech, social withdrawal and isolation affect people with schizophrenia on a day-to-day basis and are harder to recognize and interpret. A shortage of mental health services in parts of the world makes it difficult to provide care and support to people with schizophrenia. Additionally, the COVID-19 pandemic exposed the pressing need for clinicians to be able to monitor treatment and symptoms in psychiatric disorders remotely. We present an exploratory study highlighting the feasibility of a novel multimodal conversational platform with real-time automated extraction of speech and facial metrics to assess symptom severity in people with schizophrenia.
Eight participants diagnosed with schizophrenia took part in this study. Their symptom severity was evaluated in clinic using standard clinical psychometric instruments like the Positive and Negative Syndrome Scale (PANSS) and the Brief Negative Symptom Sale (BNSS) along with cognitive assessments like the Wide Range Achievement Test -4 (WRAT-4) Reading. They were then guided by a virtual conversational agent through an interactive session on a cloud-based multimodal dialogue platform that included a battery of tasks to elicit speech and facial behaviours like syllable repetitions, read speech and spontaneous speech. An audio-visual analytics module automatically extracted a variety of measures capturing speech acoustic properties, facial landmark positions and articulatory kinematics during these tasks.
We found that articulation rate (r^2=0.64 p=0.02), loudness(r^2=0.67 p=0.01), internal silence (r^2=0.63 p=0.02) and lip aperture (r^2=0.61 p=0.02) correlated highly with WRAT-4 Reading scores. Vertical position of the eyebrows (r^2=0.89 p<0.01) correlated positively with the PANSS positive subscale whereas measures like cepstral peak prominence (r^2=0.57 p=0.03) and mouth surface area (r^2=0.63 p=0.02) correlated negatively with the PANSS general psychopathology subscale. Metrics like cepstral peak prominence (r^2=0.66 p=0.01) and lower lip velocity (r^2=0.56 p=0.03) also correlated with the BNSS total score.
The small sample size notwithstanding, these observed correlations between standard clinical assessments and speech and visual analytics suggest that audio-visual measures extracted through multimodal conversational interfaces could be an effective tool for remote monitoring of symptoms and the efficacy of treatment strategies in people with schizophrenia.

Disclosures: H. Kothare: A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **M. Neumann:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **O. Roesler:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **J. Liscombe:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **D. Pautler:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **D. Suendermann-Oeft:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc. **C. Yavorsky:** A. Employment/Salary (full or part-time):; Valis Biosciences, Inc. **A. Khan:** A. Employment/Salary (full or part-time):; Nathan S. Kline Institute for Psychiatric Research. **J. Lindenmayer:** A. Employment/Salary (full or part-time):; Nathan S. Kline Institute for Psychiatric Research. **V. Ramanarayanan:** A. Employment/Salary (full or part-time):; Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modality.AI, Inc..

Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.10

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 1K01 MH11313201
Whitehall Foundation

Title: Selectively driving nigrostriatal dopamine transmission impairs cognitive function

Authors: *N. A. MOYA, S. YUN, M. M. MARTIN, J. G. PARKER;
Physiol., Northwestern Universtiy, Chicago, IL

Abstract: Altered dopamine signaling is implicated in psychosis in mental disorders like schizophrenia. In particular, excess nigrostriatal (NS) dopamine signaling is thought to underlie hallucinations, delusions, and thought disorders, symptoms of psychosis that respond to antipsychotic drug treatment. Cognitive impairment, such as a deficit in working memory, is also prevalent in schizophrenia, but is resistant to current treatments. Antipsychotic drugs preferentially block D2 dopamine receptors, which are enriched within the striatum. These observations question whether excess striatal dopamine contributes to cognitive impairment in schizophrenia. However, excess striatal dopamine also impacts D1 receptor signaling in the striatum. Moreover, the striatum is directly and indirectly connected to other brain structures like the prefrontal cortex, with which it may compete for cognitive resources. Therefore, striatal hyperdopaminergia could disrupt cognitive function, but this idea has never been explicitly tested. Here we asked whether excess D1R signaling in the dorsomedial striatum (DMS) might impair cognitive function. To test this idea, we selectively re-expressed the excitatory cation channel TRPV1 in the SNc dopamine neurons of TRPV1 knockout mice. Treating these mice with the TRPV1 agonist capsaicin

increased dopamine release in the striatum but not prefrontal cortex as measured by dLight fluorescence via dual-site, *in-vivo* fiber photometry. This approach improves upon traditional antipsychotic drug screening tools like amphetamine treatment, which increases dopamine transmission throughout the brain and fails to recapitulate the regional dopamine imbalance observed in schizophrenia. Driving NS dopamine transmission induced both increases in locomotion and decreases in cognitive function in an assay of working memory. We are currently using calcium imaging and chemogenetic approaches to dissect the striatal circuit dysfunction underlying these behavioral deficits with the goal of identifying novel therapeutic targets to treat the cognitive symptoms of disorders like schizophrenia.

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Poster

P901. Affective Disorders and Schizophrenia: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P901.11

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 1K01 MH11313201
Whitehall Foundation

Title: Modulating D1 rather than D2 receptor-expressing spiny-projection neurons corresponds to optimal antipsychotic effect

Authors: *S. YUN, B. YANG, M. M. MARTIN, N.-H. YEH, A. CONTRACTOR, J. G. PARKER; Physiol., Northwestern Univ., Chicago, IL

Abstract: Excess dopamine transmission in psychosis is predicted to unbalance striatal output via D1- and D2-dopamine receptor-expressing spiny-projection neurons (SPNs). Antipsychotic drugs are thought to re-balance this output by attenuating striatal D2-receptor signaling. Here we imaged D1- and D2-SPN Ca^{2+} dynamics *in vivo* to determine whether they can predict antipsychotic effect. Initially we compared effective (clozapine and haloperidol) to ineffective (MP-10) antipsychotic treatments. Clozapine and haloperidol normalized hyperdopaminergic D1-SPN ensemble dynamics, while MP-10 only normalized D2-SPN activity. Only clozapine, haloperidol or chemogenetic manipulations of D1-SPNs all also normalized sensorimotor gating. Given this link between D1-SPN modulation and antipsychotic effect, next we evaluated compounds selectively targeted to D1-SPNs. D1R partial agonism, antagonism, or positive modulation of M4 cholinergic receptors all normalized the levels of D1-SPN activity, locomotion, and sensorimotor gating. Our results suggest that D1-SPNs are a more relevant therapeutic target than D2-SPNs in psychotic disorders and adjudicate basic strategies for doing so.

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Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P948.01

Topic: B.09. Network interactions

Support: ERC grant FLEXONEURO 716643

Title: Redundancy in cerebellar circuits facilitates rapid online learning

Authors: *A. PEREZ ROTONDO, D. RAMAN, T. O'LEARY;
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The cerebellum is critically involved in motor control, refining trajectories as movements are being executed. This requires fast, online learning from limited information. What features of cerebellar circuit structure make it particularly suited to online learning? The cerebellum has a distinctive circuit architecture in which each mossy fibre input typically projects onto 250 granule cells, which themselves comprise over half of the neurons in the brain. Each granule cell forms 4 synapses with mossy fibres. The main hypotheses for this sparse input expansion are that it facilitates pattern separation and smooth function approximation. However, we currently lack a theory that explains why this architecture is suited to online motor learning. We show that the large input expansion effectively trades time for space, allowing rapid and accurate learning in an online context. We consider a cerebellar-like network, with sparse connections that map low-dimensional inputs into a high-dimensional internal, 'granule cell' layer. The network is tasked with simultaneously learning an internal model of a motor system, and using this model to better control motor output. Learning happens concurrently with trajectory execution, using a biologically plausible learning rule to adapt synaptic weights. Learning online introduces a narrow time window that severely limits the information available for synaptic plasticity mechanisms to appropriately adjust synaptic weights. We find that the effect of having limited information depends on the spread of the eigenvalues Hessian of the task error. As the number of granule cells increases, the spread decreases. Hence the geometry of the error surface becomes more favourable for online learning, diminishing the effect of information error and allowing for faster learning. This suggests that the large energy cost associated with maintaining the majority of the brain's neurons might be an inevitable cost of precise, fast, motor learning. Our result fills gaps in the understanding of how cerebellar structure is optimised for online learning of motor tasks.

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Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P948.02

Topic: B.09. Network interactions

Title: Modeling of signaling mechanisms underlying cooperative and competitive formation of synaptic plasticity

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Abstract: Several studies have reported clustered formation of synapses, which is thought to be a neurophysiological substrate of synaptic plasticity. Synapse clustering may be achieved by intracellular signaling mechanisms involving synaptic tagging and capture (STC) and plasticity-related proteins (PRPs), synthesized in a synaptic activation-dependent manner. STC may signal to induce cooperative plasticity clustering proximal synapses activated synchronously. In contrast, PRPs are captured through competitiveness among synapses to complete synaptic plasticity. In this study, a model of synaptic plasticity was constructed to examine how the temporal structure of the synaptic input sequence affects the resulting spatial pattern of synaptic formation in the presence of a cooperative and competitive signaling mechanism of plasticity. Firstly, a possible mechanism of cooperative LTP formation was simulated based on STC signaling. Then, the capture mechanism of PRPs was additionally incorporated to simulate synaptic clustering in the presence of cooperative and competitive signaling of plasticity. The present study investigated the cluster formation through these simulations depending on the temporal structure of synaptic input. The simulation results showed that STC facilitated cooperative induction of plasticity over synapses coactivated with close timings, and in contrast, competitive capture of PRPs selectively induced plasticity depending on the temporal relationship between synaptic activations. In addition, the results showed that the competitive mechanism enhances the cooperative induction of plasticity associated with the intensity of synaptic activation. Thus, these results suggest that memory engram represented on the temporal structure of synaptic input sequences is carved as a cluster pattern of synapse formation through the cooperative and competitive induction mechanism of plasticity involving STC and PRPs.

Disclosures: R. Amano: None. **M. Nakao:** None. **K. Matsumiya:** None. **F. Miwakeichi:** None.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

Location: Virtual Only

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Program #/Poster #: P948.03

Topic: B.09. Network interactions

Support: ARO-W911NF-19-1-0402
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NIDCD-R01DC012947-06A1

Title: Using Spiking Neuronal Networks to solve Reinforcement Learning control problems

Authors: D. HASEGAN[1], D. D'ONOFRIO[4], S. GRUNBLATT[4], M. DEIBLE[2], S. CABY[3], H. HAZAN[5], H. ANWAR[4], S. A. NEYMOTIN[4,6];
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Abstract: While Spiking Neuronal Networks (SNNs) have been successfully used to model biological phenomena, their use in solving Reinforcement Learning (RL) problems remains limited. In contrast, Artificial Neural Networks (ANNs) have successfully solved many RL problems while remaining biologically implausible. In this study, we work towards understanding and improving the performance of SNNs solving RL control challenges.

We use the NEURON simulator and NetPyNE to create an SNN interfaced with environments from OpenAI's Gym, such as CartPole. In CartPole, the goal is to balance a vertical pole by moving left/right on a 1-D plane. Our SNN model contains multiple populations of neurons organized in three layers: sensory layer, association/hidden layer, and motor layer, where each neuron is connected by excitatory (AMPA, NMDA) and inhibitory (GABA) synapses. The association and motor layers contain one excitatory population and two inhibitory populations with different synaptic time constants. Each neuron is an event-based integrate-and-fire model with plastic connections between excitatory neurons. We explore the modulation of these plastic connection weights through both evolutionary strategies (ES) and a Reinforcement Learning algorithm that employs Spike Timing-Dependent Plasticity (STDP). An ES update consists of adding together many random perturbations of the connection weights, where each set of random perturbations is weighted by the total episodic reward (e.g., how long the model can keep the pole balanced in Cartpole) it is able to achieve when applied independently. We compare both algorithms' performance against commonly used algorithms (deep reinforcement learning) for solving RL control problems.

In our SNN, the environment activates sensory neurons tuned to specific features of the game state. We split the motor neuronal population into subsets representing each movement choice. The subset with more spiking over an interval determines the action. Note that motor neurons do not receive explicit feedback on how they contributed to action generation. Using RL, we supply intermediary evaluations (reward or punishment) of each action by judging the effectiveness of a move (e.g., moving the CartPole to a balanced position).

Training our model on Cartpole demonstrates effective learning of balancing capabilities by moving the cart left and right, keeping the pole vertical. We are expanding our model's learning in additional control tasks. The model opens up new capabilities for SNNs in RL and could serve as a testbed for neurobiologists aiming to understand learning mechanisms and dynamics in neuronal circuits.

Disclosures: D. Hasegan: None. **D. D'Onofrio:** None. **S. Grunblatt:** None. **M. Deible:** None. **S. Caby:** None. **H. Hazan:** None. **H. Anwar:** None. **S.A. Neymotin:** None.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

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Topic: B.09. Network interactions

Support: e James S. McDonnell Foundation 21st Century Science Initiative Understanding Dynamic and Multi-scale Systems - Postdoctoral Fellowship Award

Title: Heavy-tailed correlations emerge from Hebbian plasticity

Authors: *C. LYNN[1,2], S. E. PALMER[3], C. HOLMES[1];
[1]Joseph Henry Labs. of Physics, Princeton Univ., Princeton, NJ; [2]Initiative for the Theoretical Sci., City Univ. of New York, New York, NY; [3]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: In networks of neurons, correlations and synaptic strengths are heavy-tailed, with a small number of neurons interacting much more strongly than the vast majority of pairs. Yet, it remains unclear whether, and how, such heavy-tailed connectivity can emerge from simple underlying mechanisms. Building upon recent advances in neuroimaging, here we show that the correlations between thousands of neurons in the mouse visual cortex admit heavy-tailed distributions spanning three decades in strength. Moreover, we find that these distributions are robust to variations in the visual stimuli, even persisting during spontaneous activity. To explain these heavy-tailed correlations, we propose a simple model of synaptic change based on Hebbian plasticity: synapses are pruned at random, and the synaptic weight is redistributed throughout the network by either (i) adding weight to existing synapses in a Hebbian fashion or (ii) creating new synapses. Importantly, our model contains only a single parameter $0 \le p \le 1$, which represents the probability of Hebbian growth relative to new synaptic growth. We demonstrate, both analytically and numerically, that the model generates scale-free distributions of connectivity strength, with a power-law exponent $\gamma = 1 + \frac{1}{p}$ that depends only on the probability of Hebbian growth. Our results indicate that heavy-tailed distributions of correlations and synaptic weights may be governed by robust self-organizing principles that do not depend on the biophysical particulars of different neural systems.

Disclosures: C. Lynn: None. **S.E. Palmer:** None. **C. Holmes:** None.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P948.05

Topic: B.09. Network interactions

Title: Ultrafast large-scale simulations of biophysically realistic neurons using deep learning

Authors: *V. J. OLAH, M. J. M. ROWAN;
Dept. of Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Understanding the activity of the mammalian brain requires an integrative knowledge of circuits at distinct scales, ranging from ion channel time constants to synaptic connection probabilities. To understand how multiple parameters contribute synergistically to circuit behavior, neuronal computational models are regularly employed. A major limitation of currently employed models containing anatomically and biophysically realistic neurons is the computational demand when scaled to the size of local circuits. To overcome this limitation, we trained several artificial neural net (ANN) architectures to model the activity of realistic, multicompartmental neurons. We identified a single ANN that accurately predicted both subthreshold and action potential firing, and correctly generalized its responses to previously unobserved synaptic input. Furthermore, ANNs are able to forecast several different facets of neuronal

behavior with high fidelity, such as ionic current dynamics. Importantly, when scaled, processing times were orders of magnitude faster compared with traditional approaches. In order to demonstrate the versatility of our approach, we have constrained our ANN architecture on all major cell classes of the visual cortex from a publicly available database and demonstrated that further training of specific cell types can be significantly accelerated and stabilized by taking advantage of the currently modeled repertoire of cells and transfer learning. Thus, our ANN approach allows for rapid, detailed network experiments using inexpensive, readily available computational resources.

Disclosures: V.J. Olah: None. **M.J.M. Rowan:** None.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

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Program #/Poster #: P948.06

Topic: B.09. Network interactions

Support: NIH NINDS K23NS112339

Title: Effect of multiple timescale adaptation in a Hodgkin-Huxley neural network

Authors: *T. J. RICHNER, B. N. LUNDSTROM;
Neurol., Mayo Clin., Rochester, MN

Abstract: Excitatory neurons are known to exhibit spike rate adaptation in response to stimuli. We've previously shown that spike rate adaptation in single neurons is comprised of multiple time constants and approximates fractional differentiation. We hypothesized that multiple timescale adaptation (MTA) would alter, and possibly stabilize, network dynamics. Further, we were interested to find signatures of MTA that could be measured in human subjects with epilepsy.
We modeled a network of 256 Hodgkin-Huxley neurons in which MTA could be enabled or disabled for comparison. The neurons were partitioned 80% excitatory (AMPA & NMDA) and 20% inhibitory ($GABA_A$ & $GABA_B$). Neurons were arranged into a 2D grid and synapse strengths were probabilistically based on distance, which allowed for positive feedback loops. Network input was low amplitude exponentially-filtered Gaussian noise. As excitatory-to- excitatory synaptic strengths were increased, seizure-like dynamics resulted in the network lacking MTA. In contrast, the network with MTA was resistant to sustained seizures. MTA dampened positive feedback loops among excitatory neurons thereby preventing seizures.
In order to find potential electrophysiological biomarkers of MTA, we analyzed the power spectra and spiking statistics of the network with and without MTA. The average membrane voltage was used to approximate the local field potential. MTA decreased overall spectral power while also increasing power in low frequencies (< 3 Hz). MTA had the most pronounced effect on the interspike intereval (ISI) histogram. MTA flattened the ISI histogram, decreasing counts at short intervals (<50 ms) and increasing counts at longer intervals (>200 ms). We are continuing to explore novel stimulus waveforms that can be used to assay MTA. Further, we are analyzing invasive EEG recordings, microwire recordings, and cortico-cortical evoked potentials from human subjects for biomarkers of MTA.

Disclosures: T.J. Richner: None. **B.N. Lundstrom:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI for the Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study (EPAS), PI for the Neuropace RNS System Responsive Stimulation for Adolescents with Epilepsy (RESPONSE) Study, PI for the Neuroelectrics tDCS for Patients with Epilepsy Study, Investigator for the Mayo Clinic Medtronic NIH Public Private Partnership (UH3-NS95495). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor for intellectual property developed at Mayo Clinic and licensed to Cadence Neuroscience Inc. BNL waived contractual rights to royalties.. F. Consulting Fees (e.g., advisory boards); Mayo Clinic has received consulting fees on behalf of BNL from Epiminder, Medtronic, and Philips Neuro.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

Location: Virtual Only

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Program #/Poster #: P948.07

Topic: B.09. Network interactions

Support: EU H2020 Grant Agreement No. 945539 (Human Brain Project SGA3)
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Title: Theta-gamma phase amplitude coupling in a hippocampus CA1 interneuron network.

Authors: *A. PONZI, M. MIGLIORE;
Inst. of Biophysics, CNR, Palermo, Italy

Abstract: Theta nested gamma oscillations are well known to occur in the hippocampus, but their origin is not clear. Here we construct a CA1 network circuit using detailed multi-compartment cell models optimized to match the electro-physiological properties of OLM, PVBC and PYR cells, with reconstructed 3D dendritic morphologies [1]. Cells are connected in appropriate dendritic domains using facilitating and suppressing synapses with strength and probability matching experimental findings [2,3]. We first validate the circuit properties against experimental findings on fast onset and late persistent synaptic response data [4] on the selective routing of information by OLM and PVBC cells in CA1. By driving the circuit with Schaffer collaterals inputs, we found that theta nested slow and fast gamma oscillations emerge within physiologically plausible parameter regimes. We investigated the mechanism for generation of theta nested gamma oscillations. We find that OLM cells and PYR cells generate gamma oscillations by the network PING mechanism. When OLM cells are close to firing threshold PING occurs in bursts at theta frequency. During PING bursts most of the cells in the network spike synchronously at gamma frequency. Each PING burst lasts three or four gamma cycles. PING bursts are separated by longer periods of irregular spiking activity in the PYR cells and very low activity in the OLM cells. PING bursts are initiated when a few OLM cells cross firing threshold. They spike inhibiting a few PYR cells which recover together after one gamma time scale. This generates synchronized PYR excitation which in turn synchronizes more OLM cells, which in turn further synchronizes more PYR

cells. This PING burst does not continue indefinitely because, besides synchronizing the PYR spiking activity, the increased OLM activity also suppresses the PYR average firing rate. This reduces the excitation onto the OLMs which drop below threshold and the PING burst ends. Slowly OLMs revert to threshold until a few cross threshold initiating the next PING burst. The timescale of OLM reversion to threshold sets the slow theta timescale. It depends on the OLM membrane time constant as well as the PYR to OLM synapses which can show slow facilitation. We show how the theta and gamma timescales depend on network, cellular and synaptic parameters and discuss the relevance to cognitive function of CA1.

[1] Migliore, R., et al. (2018). PLoS CB, 14(9), e1006423.
[2] Ecker, A., et al. (2020). Hippocampus.*30*(11), 1129-1145
[3] Keller, D., Erö, C., & Markram, H. (2018). Frontiers in neuroanatomy, 12,83.
[4] Pouille, F., & Scanziani, M. (2004). Nature, 429(6993), 717-723.

Disclosures: A. Ponzi: None. **M. Migliore:** None.

Poster

P948. Computational Modelling of Synaptic Networks: Learning and Plasticity

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P948.08

Topic: I.06. Computation, Modeling, and Simulation

Title: A nonlinear calcium-based plasticity rule explains long-term stability of synapses

Authors: *B. WANG[1], J. ALJADEFF[2];
[2]Dept. of Neurobio., [1]UCSD, San Diego, CA

Abstract: Activity dependent synaptic plasticity is considered to be a primary mechanism underlying learning and memory. Yet it is unclear whether plasticity rules such as STDP measured in vitro apply in vivo. Network models with STDP predict that activity patterns (e.g., place-cell spatial selectivity) should change much faster than observed experimentally. We address this gap by investigating a nonlinear calcium-based plasticity rule fit to experiments done in physiological conditions. In this model, LTP and LTD result from calcium transients arising almost exclusively from synchronous coactivation of pre- and postsynaptic neurons. We analytically approximate the full distribution of nonlinear calcium transients as a function of pre- and postsynaptic firing rates, and temporal correlations. This analysis directly relates activity statistics that can be measured in vivo to the changes in synaptic efficacy they cause. Our results highlight that both high-firing rates and temporal correlations can lead to significant changes to synaptic efficacy.
The tractability of the single synapse model allows us to systematically explore its network-level implications. Using a mean-field theory, we show that the nonlinear plasticity rule, without any fine-tuning, gives a stable, unimodal synaptic weight distribution characterized by many strong synapses which remain stable over long periods of time, consistent with electrophysiological and behavioral studies. Moreover, our theory explains how memories encoded by strong synapses can be preferentially stabilized by the plasticity rule. We confirmed our analytical results by simulating a spiking recurrent network. While most synapses are weak and undergo rapid turnover, the fraction of strong synapses are

sufficient for supporting realistic spiking dynamics and serve to maintain the network's cluster structure. Our results provide a mechanistic understanding of how stable memories may emerge on the behavioral level from an STDP rule measured in physiological conditions. Furthermore, the plasticity rule we investigate is mathematically equivalent to other learning rules which rely on the statistics of coincidences, so we expect that our formalism will be useful to study other learning processes beyond the calcium-based plasticity rule.

Disclosures: B. Wang: None. **J. Aljadeff:** None.

Poster

P970. Data Analysis and Statistics: Human Data II

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Topic: I.07. Data Analysis and Statistics

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NIH R00-MH111748
Searle Scholar Award

Title: Real time, low latency removal of ballistocardiogram artifacts during simultaneous EEG-fMRI

Authors: *J. LEVITT, Z. YANG, L. D. LEWIS;
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Abstract: Simultaneous EEG-fMRI is an attractive technique for imaging the brain, as it provides the high temporal resolution of EEG and the high spatial resolution of fMRI. Developing real-time analysis of EEG-fMRI signals could expand the applications of this technique to enable closed-loop neurofeedback experiments. However, its application is limited by the presence of ballistocardiogram (BCG) artifact in the EEG signals, caused by subtle movements of the EEG electrodes through the magnetic field of the MR scanner with each heartbeat. Techniques do exist for the post-hoc removal of these artifacts, including the use of an electrically insulated BCG reference layer that records noise signals directly, or by the use of an optimal basis set algorithm (OBS) that models noise locked to each heartbeat. However, these methods are not well suited to closed-loop experimental designs, because they cannot be implemented in real time with low latency and high efficacy. Here, we propose and validate a novel method for removing BCG artifacts in real time using a Kalman filter in combination with a BCG reference layer. To validate our method, we used simulated EEG-BCG data with ground truth signal and noise, created by adding EEG data collected from healthy adults outside the MR scanner to BCG reference layer data (i.e., noise) from the same subjects collected inside the MR scanner. We then tested whether we could recover the original EEG signal using our real-time Kalman filter methodology and compared this to recovery using current gold-standard algorithms. Our results show that the Kalman filter recovers the original EEG waveform and delta wave phase significantly better than OBS, and as well as BCG reference layer regression. Additionally, the Kalman filter also recovered EEG power spectral

density (PSD) better than OBS, and as well as reference layer regression, for frequencies below 15 Hz, though there was no difference for higher frequencies. We then conducted a proof-of-concept experiment demonstrating the efficacy of this method in practice during live recordings with a visual task and found that we could display cleaned EEG data in real time with low latency (typically less than 20ms). An open-source MATLAB-based application is under development to make this method accessible to the neuroscience community. These results show that our method is practical and effective for real-time applications and will enable EEG-fMRI neurofeedback experiments at low latencies, opening the door to investigations of the neural circuit basis of neurofeedback interventions.

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Poster

P970. Data Analysis and Statistics: Human Data II

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Topic: I.07. Data Analysis and Statistics

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Title: Source space reconstruction from simultaneously acquired EEG-fMRI via a multi-level deep transcoder

Authors: *X. LIU[1], P. SAJDA[2];
[2]Biomed. Engin., [1]Columbia Univ., New York, NY

Abstract: Simultaneous EEG-fMRI is a neuroimaging modality which focuses on capturing both high spatial and temporal resolution brain activity, though a current challenge is how to combine the two measures to infer a high resolution spatiotemporal source space. Here we report on a method for symmetrically fusing the two modalities using a multi-level deep transcoder to reconstruct a 2mm x 10ms resolution source space. The approach is completely data-driven and does not require structural images, models of hemodynamics response functions nor lead field models. At the core of the approach is a cyclic convolutional transcoder which maps from EEG to fMRI and vice versa. After training, our model can reconstruct/infer a source space from only EEG and/or fMRI data, namely it solves the EEG source separation/fMRI deconvolution problem and extracts forward/inverse head models and hemodynamic response functions from the data. Source reconstruction results from simulated simultaneous EEG-fMRI data show good correlation with the ground truth, with average correlation coefficients of 0.66±0.0045/0.59±0.0017 for oscillation/sparse sources estimated from fMRI alone and 0.76±0.0017/0.41±0.0011 for oscillation/sparse sources estimated from EEG alone. Compared to classical techniques for EEG sourcing, our transcoding approach has higher correlation with ground-truth even when the ground-truth lead field matrix is used for the classic method. We also evaluated the approach for real simultaneous EEG-fMRI data. Specifically we used data from a simultaneous EEG-fMRI experiment

where subjects performed an auditory odd-ball task. We trained transcoders via a leave-one-subject-out approach and generated a source space for the left out subject. In the group source space we found: 1) prolonged deactivation across regions making up the default mode network (e.g. prefrontal cortex, posterior cingulate cortex, and temporal pole) after both standard and oddball stimuli, 2) activations were observed only after odd-ball stimuli in parieto-occipital lobe/300~350ms post stimulus, 3) activations in the source space where seen in the left and right primary motor cortex/400ms only after oddball trials and these activations were followed by activations in left and right somatosensory cortex/450ms coinciding with right hand index finger button pressing which was the behavioral response required for detection of odd-ball stimuli. In summary, the completely data-driven source space recovered by our approach is consistent with the known spatiotemporal brain dynamics for this task.

Disclosures: X. Liu: None. **P. Sajda:** None.

Poster

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Topic: I.07. Data Analysis and Statistics

Support: European Union, Marie Curie, Horizon 2020, Rhumbo

Title: EEG theta and ERP responses to congruent versus incongruent brands

Authors: *H. DINI[1], A. SIMONETTI[2], L. BRUNI[1], E. BINGE[2];
[1]Dept. of Architecture, Design, and Media technology, Aalborg Univ., Copenhagen, Denmark; [2]Dept. of Marketing and Market Res., Univ. of Valencia, Valencia, Spain

Abstract: Neuroimaging and behavioral studies have shown that brands convey meaning to consumers. How the brain immediately reacts to brand logos followed by either congruent or incongruent pictorial brand cues can deepen the understanding of the semantic processing of brands. Previous studies on linguistics have found different brain responses to congruent vs incongruent stimuli, which was attributed to the process of error monitoring. Our study investigated whether brands lead to the same brain reactions. Thirty-two participants (13 female, mean age 26.84 ± 4.33) performed the task, wearing a 32-channel EEG cap. Forty congruent and forty incongruent 2D brand-related image sequences were shown through a virtual reality headset. Each sequence comprised three images implying a brand, a question, and the brand logo. The congruence manipulation happened in the brand logo. Then, preprocessed signals of the last image were first averaged among each condition to obtain ERP activity, and then the time-frequency activity of each trial was calculated using the Welch method. Time-frequency analysis was implemented on the theta frequency band (4-7 Hz), and time interval of 700 to 1200 ms after stimulus starts. The analyses were implemented on central region electrodes based on literature, and a two-dimensional permutation test was conducted to test the statistical significance. The ERP analysis showed a significant difference between the two conditions (congruent > incongruent) in the N400 component (p= 0.04, effect size= 0.54), in which the incongruent condition had a larger negative peak. The results showed that theta activity of congruent (versus incongruent) condition is significantly lower (p= 0.01, effect size= -0.69).

This study showed that brain response to congruent versus incongruent brand logos differed in both time (ERP) and time-frequency domains. Studies in linguistic field have suggested that difference in the central and mid-frontal region due to stimuli congruence is related to error monitoring process. This study replicated their findings. Thus, we argue there is a higher processing difficulty in mismatched (versus matched) brand logos, leading to a larger error monitoring. Therefore, error monitoring process could be extended to other forms than linguistic, such as images and brands. Moreover, the theta band difference occurred in 700-1200 ms while ERP difference occurred in N400 component. This finding suggests that these two methods capture different aspects of brain activity.

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Poster

P970. Data Analysis and Statistics: Human Data II

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Program #/Poster #: P970.04

Topic: I.07. Data Analysis and Statistics

Support: PN-III-P1-1.1-TE-2019-0502
PN-III-P4-ID-PCE-2020-0935

Title: A machine learning alternative to identifying contrasts during cognitive tasks

Authors: *B. BLIDARESCU[1], C. PISTOL[1], I. OANE[1], A. BARBORICA[1], I. MINDRUTA[2], C. DONOS[1];
[1]Physics Dept., Univ. of Bucharest, Bucharest, Romania; [2]Neurol. Dept., Emergency Univ. Hosp. Bucharest, Bucharest, Romania

Abstract: Motivation: The study of contrasts from event related potentials (ERP) obtained from stereo-EEG (SEEG) is usually performed using permutation cluster analysis (PCLA) in order to find intervals with amplitude differences that reach statistical significance. The sites exhibiting such contrast are considered to have a preferential response for one of the task conditions. However, a major drawback of this approach is that it requires a sufficiently high signal to noise ratio (SNR) to highlight a contrast between the conditions, this in turn requiring an increase in the number of trials per experiment, which is often not feasible in a clinical environment. We propose a novel approach that uses machine learning (ML) to identify the SEEG contacts exhibiting different activation patterns between conditions.**Methods:** 10 patients undergoing presurgical evaluation with intracranial electrodes performed a cognitive task where they were shown angry and happy faces for 1.5s and they were instructed to push a button to classify them. The raw data was notch filtered, common averaged, down-sampled to 256Hz, cropped to [-0.3, 1.0] s, baseline corrected, low-passed with a Savitzky-Golay filter at 15Hz and 45Hz for the ML and PCLA, respectively. We compared the outcome of two analyses: permutation cluster tests between the ERPs of the two conditions, a ML classifier trained on statistical moments (mean, standard deviation, median absolute deviation, skewness and kurtosis) computed on 3 intervals: [0.2,0.4] s, [0.4,0.8] s, [0.8,1] s. The best ML model per contact was chosen by a Hyper-optimization algorithm (Bayes Search) from two types of classifiers (Multi-Layer Perceptron and Random Forest Classifier) that were evaluated using

the Matthews Correlation Coefficient (MCC) metric.**Results:** The PCLA revealed on average 16.3% ± 7.3% contacts per subject with significant contrasts ($p<0.05$). The ML classifier identified on average 26.3% ± 6.6% contacts per subject that allowed better than chance classification (MCC>0.2, equivalent of >60% accuracy). The average Jaccard similarity coefficient per subject was 0.21 ± 0.07 for SEEG contacts exhibiting the angry-happy contrast, and 0.53 ± 0.17 for the brain structures containing contacts exhibiting contrasts.**Conclusion:** Both methods identified contacts located in the brain structures hypothesized by the Pessoa and LeDoux models of facial emotions processing, but also contacts that are not usually associated with facial emotion processing. Further validation on simulated trials with various SNR may disambiguate which method is more resilient to low SNR.

Disclosures: B. Blidarescu: None. **C. Pistol:** None. **I. Oane:** None. **A. Barborica:** None. **I. Mindruta:** None. **C. Donos:** None.

Poster

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PN-III-P4-ID-PCE-2020-0935

Title: Multivariate pattern analysis identifies brain networks in sparse intracranial EEG recordings

Authors: *C. DONOS[1], B. BLIDARESCU[1], C. PISTOL[1], I. OANE[1], I. MINDRUTA[2], A. BARBORICA[1];
[1]Physics Dept., Univ. of Bucharest, Bucharest, Romania; [2]Neurlogy Dept., Emergency Univ. Hosp. of Bucharest, Bucharest, Romania

Abstract: Introduction: The study of cognitive processes using intracranial EEG (iEEG) usually relies on the identification of brain locations where statistically significant differences are observed between two or more task conditions. Multiple brain locations that are activated during the task as considered to be part of the brain network involved in the task realization. In practice, we often do not have enough trials to reach a good signal-to-noise ratio (SNR), and the brain locations where we record iEEG varies from patient to patient. We propose a method for identifying brain networks from sparse iEEG recordings, based on multivariate pattern analysis (MVPA).
Methods: We recorded iEEG using depth electrodes from 10 epilepsy subjects while they were performing a face recognition task. The subjects were shown happy and angry faces and they were asked to push a button to indicate the emotion on the faces. iEEG was epoched, common averaged, filtered with a Savitzky-Golay filter at 15Hz, cropped to [-0.3, 1] s interval and baseline corrected. For each subject and for each contact we first trained a random forest classifier to discriminate the task condition (angry vs happy) and computed the Matthews Correlation Coefficient (MCC). Contacts that had MCC > 0 (better than chance) were preselected for training two MVPA models. The first model aggregates data across contacts and time, while the second model aggregates data across channels and employs time

generalization (trains one model per time sample).
Results: For the first model, the classifier performed above chance level for all subjects, and the mean MCC during cross-validation was 0.45±0.16. For the second model, we optimized the iEEG channels used for classification by adding them to the classifier one by one, starting with the ones that performed best during the random forest screening step. The subset of channels that resulted in the largest area under the curve (AUC) during the training of the second model was considered to outline to brain network observed during the cognitive task. The mean AUC was 0.63±0.07.
Conclusion: As opposed to identifying brain networks by finding individual iEEG channels that exhibit significant contrasts between conditions, we developed a method that identifies the brain networks finding the subset of channels that provide the best classification score.

Disclosures: C. Donos: None. **B. Blidarescu:** None. **C. Pistol:** None. **I. Oane:** None. **I. Mindruta:** None. **A. Barborica:** None.

Poster

P970. Data Analysis and Statistics: Human Data II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P970.06

Topic: I.07. Data Analysis and Statistics

Support: ERC CoG 647954

Title: A standardised framework for re-referencing strategies of human intracranial electrophysiological data

Authors: *G. PARISH[1], F. ROUX[1], L. KOLIBIUS[1], R. CHELVARAJAH[2], D. ROLLINGS[2], V. SAWLANI[2], H. HAMER[3], S. GOLLWITZER[3], G. KREISELMEYER[3], M. TER WAL[1], B. STARESINA[1], M. WIMBER[4], S. HANSLMAYR[4];
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Abstract: In recent years human electrophysiological studies, particularly intracranial and human single neuron studies, have become increasingly popular as the field grows in funding and stature. It is important, therefore, that there is some form of standardisation that enables comparison between studies and findings. Such studies inherently rely on the analysis of electrical signals that are emitted by the combined neural circuitry of the brain. These signals must be recorded in relation to some grounding signal, meaning that the reference signal will play a large role in the resultant waveforms that are ultimately recorded. At the point of recording, there is a general understanding that typical grounding sources will help to minimise surrounding electrical interference whilst not removing much of the original signal. For this reason, grounding references are often situated around the periphery of the head or a specifically purposed impedance wire. However, studies often employ another step of re-referencing, whereby a single or amalgamation of electrodes or micro-wires are selected as an additional grounding reference. In theory, this is pursued to further increase the signal to noise ratio. However, it is often the

case that a re-referencing strategy is chosen to remove signals that are undesirable for the hypothesis in question. Re-referencing might be achieved in any number of ways that are currently preferred by the field, whether it is the subtraction of an average set, an independent-component, or a particular electrode of interest, amongst others. Preferred strategies are often employed on a case-by-case basis, rather than being prescribed from a standardisation of re-referencing methods. We feel that this can murky the underlying theory behind secondary re-referencing, potentially leading to disagreements and an inability to reproduce findings across studies. As such, we here explore a human episodic memory paradigm to assess the effect of a variety of popular re-referencing techniques on resultant oscillatory signals and spike-field coherence, using intracranial EEG data collected from 18 subjects. We comparatively analyse time-frequency space and the degree to which spikes conform to oscillatory signals, with a focus on theta and gamma frequencies. We also examine whether re-referencing strategies maximise cognitive effects in relation to our episodic memory paradigm. Overall, we hope to provide a standardised framework for human intracranial re-referencing methods, such that the field can engage in more transparent and comparable experimentation.

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Poster

P970. Data Analysis and Statistics: Human Data II

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Program #/Poster #: P970.07

Topic: I.07. Data Analysis and Statistics

Support: NIH TL1TR001428

Title: Intracranial artifact classification for cognitive neuroscience research applications

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Abstract: Introduction: Intracranial electroencephalography (iEEG) presents a unique opportunity to extend findings from cognitive studies utilizing non-invasive techniques. However, iEEG data are recorded from patients with drug resistant epilepsy who display EEG containing physiological activity, non-cerebral artifacts, and transient pathological activity including interictal epileptiform discharges (IEDs) or high frequency oscillations (HFOs). IEDs are known to disrupt proper cognitive processes, potentially confounding results in cognitive iEEG studies. In this study, we developed, tested, and validated an automated artifact classifier for continuous task-based iEEG.
Methods: We utilized a large public dataset (DS1) of iEEG data from depth and subdural iEEG electrodes to train and test a random forest classifier (RFC) using a 70/30 cross validation approach. DS1 was collected at St. Anne's University Hospital (Brno, Czech Republic) and Mayo Clinic (Rochester, Minnesota) and contains 3-second data segments (fs =5,000Hz) classified as non-cerebral (n=73,902), pathological (n=67,797), or physiological (n=151,290). Features were extracted to train a RFC to

distinguish events as non-cerebral, pathological, or physiological. Segments were filtered, down sampled to 1200Hz, and processed to extract 66 features related spectral characteristics, morphological shape, anatomical location, and brain state. Performance was validated on continuous iEEG data. Dataset 2 (DS2), collected at Motol University Hospital (Prague, Czech Republic), contains 5-min of continuous recordings (fs =1,000Hz) with expert IED annotations for 2 subjects. Dataset 3 (DS3), collected at the University of Florida Neuromedicine Hospital (Gainesville, FL), contains 8-min of continuous recordings (fs=1200Hz) with expert annotations for 3 subjects.
Results: On DS1, our RFC had class specific performances of 91.9% | 90.6% | 91.36% (physiology), 96.3% | 98.0% | 93.197% (pathology), and 94.6% | 96.6% | 89.9% (non-cerebral artifacts) for accuracy, specificity, and precision. On DS2, our classifier had a sensitivity of 85.1% and specificity of 84.3% for annotated IEDs (pathology). These results suggest that our RFC is capable of successfully classifying iEEG data into three distinct classes with high levels of accuracy, precision, sensitivity, and specificity. Additionally, our classifier was able to achieve similar performance levels on datasets collected at a lower sampling rate not involved in training, suggesting its generalizability.

Disclosures: S. Long: None. **M. Bruzzone:** None. **S. Mitropanopoulos:** None. **A. Gunduz:** None.

Poster

P970. Data Analysis and Statistics: Human Data II

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Program #/Poster #: P970.08

Topic: I.07. Data Analysis and Statistics

Support: MOST, Taiwan Grant 110-2628-B-A49A-509
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National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei,Taiwan

Title: Machine learning approach to assess the severity of neuropsychiatric symptoms of dementia based on electroencephalography signal

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Abstract: Dementia is a neurodegenerative disease in which no cure is available. Current treatments can only help improve some of the symptoms and slow the progression of the disease. Therefore, it is important to diagnose and treat the symptoms associated with dementia early by effectively evaluating symptoms profiles and severity to help maintain the cognitive function and life quality of the patient. The diagnosis of dementia requires extensive observation of clinical history and multiple assessments of clinical questionnaires. However, objective assessment involving other physiological signals or neuroimage remains limited. Therefore, the diagnosis of dementia is subjective, time-consuming and

costly. It is also relatively vague in assessing the severity of the psychological and behavioral symptoms of dementia (BPSD). We aim to use electroencephalogram (EEG) to assist clinical evaluation of dementia severity to reduce the time and resource consumption, and to establish an objective method for automatic detection of BPSD. In this study, we analyzed the EEG data of 108 Alzheimer's disease (AD) (59 women, 49 men) and with a mean age of 78.0 years (SD: 8.6). EEG data from all subjects were further divided into 999 10-second segments. The EEG were first analyzed with 5 sub-frequency bands using a Butterworth filter, and each sub-band was extracted for multiple features, including frequency and nonlinear domain metrics. The extracted EEG features were then used to predict Neuropsychiatric Inventory (NPI) scores associated with EEG segments using machine learning models. Finally, the relationship between the severity of dementia and EEG changes was investigated by searching for significantly correlated features and brain regions in the model. We divided the demented patients into two groups according to the cut-off of NPI score at 14, which is related to the outcome of dementia. Among the models trained using MATLAB, the best performance was achieved by k-nearest neighbors (KNN) with an accuracy rate of 86.4%. The model was further trained using the support vector machine (SVM) and bagging tree algorithm, and the accuracy rate was 83.4% and 85.9% in the validation dataset. Using the KNN method, we established individual model for each EEG channels, and we found the accuracy of Cz, Pz and F8 to be 83.9%, 79.9% and 79.4% respectively. It is evident that the features captured in this study are effective in assessing the severity of neuropsychiatric symptoms of AD. In the future, we hope to assist the clinical assessment of BPSD in patients with dementia with a rapid, non-invasive, low-cost, objective and reliable method.

Disclosures: H. Chien: None. **A. Yang:** None.

Poster

P970. Data Analysis and Statistics: Human Data II

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P970.09

Topic: I.07. Data Analysis and Statistics

Support: Samuel F. Hulbert Chair Endowment

Title: Grammatical, syntactic, and semantic error identification in single-trial brain-computer interface sentence construction using evoked frequency content and machine learning strategies

Authors: *A. W. L. CHIU, C. L. KOUTSOUMPAS, **E. J. WHITESIDE**, E. B. DRONG;
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Abstract: Brain-computer interface (BCI) spellers are currently a means of communication for those with severe neuromuscular deficiencies. These spellers allow users to construct and edit sentences through visually evoked EEG signals. However, the ability of the user to make the necessary corrections when errors occur is a tedious process. For this study, we aim to identify important EEG features and develop machine learning strategies to quickly classify different types of errors in BCI spellers. An OpenBCI 16-channel Ultracortex Mark IV headset with the Cyton and Daisy board setup was used for data acquisition. Subjects were presented with 240 sentences (ranging from 6 to 15 words in length) using an optimal

recognition point (ORP) paradigm where each word was shown in rapid succession (60 words per minute) to simulate the use of a BCI speller in sentence construction. Each sentence had an equal probability of containing either a semantic error (SM), a syntactic error (SY), a spelling error (SP), or no error (Control). Subjects were instructed to press one of two buttons for each trial: a green button for Control or a red button if any error was perceived. EEG features such as ERP (P300, N400, P600 intensities), as well as frequency band power (alpha and theta) were extracted. A linear discriminant analysis (LDA) method was developed to classify these four possible outcomes using 180 randomly selected sentences as the training set. Using only the alpha band as the main feature, we were able to achieve a classification accuracy of 67.8% for Control vs SM; 65.6% for Control vs SP; and 68.9% for Control vs SY. Using only the theta band as the main feature, we were able to achieve a classification accuracy of 57.8% for Control vs SM; 61.2% for Control vs SP; and 62.3% for Control vs SY. This result is promising since this process simulates the real-time error detection procedure in a typical BCI spelling session where decisions are made based on single-trial data without any trial rejection techniques nor aggregated analysis. Further improvement can be achieved by incorporating additional features into the training set, along with other nonlinear boundary conditions.

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Poster

P970. Data Analysis and Statistics: Human Data II

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Time: Thursday, November 11, 2021, 8:30 AM - 9:30 AM

Program #/Poster #: P970.10

Topic: I.07. Data Analysis and Statistics

Support: Sponsored Research Qneuro, Inc.
JSPS KAKENHI 18KK0280

Title: An interpretable EEG latent space captures inter- and intra-individual variability in a team flow task

Authors: *Q. WU[1], S. SHIMOJO[2], M. SHEHATA[2,3];
[1]Div. of Humanities & Social Sci., [2]Div. of Biol. & Biol. Engineering/Computation & Neural Systems, California Insititute of Technol., Pasadena, CA; [3]Electronics-Inspired Interdisciplinary Res. Inst., Toyohashi Univ. of Technol., Toyohashi, Japan

Abstract: Introduction: Brain signals reflect individual traits and states. Traditionally, many studies have been using EEG data to recognize individual identities and predict behaviors or cognitive abilities. However, most of these studies adopted complicated models that focused on prediction performance, sacrificing interpretability (black box). Here, we identified individual differences in a musical team flow task via extracting latent features from EEG data in a highly interpretable, lower-dimensional space to maximize inter-individual and intra-individual variability. To facilitate interpretation of the latent space, we analyzed its relationship to a psychological space, establishing connections between neural data and subjective experiences. **Methods:** We analyzed data collected in a previous study (Shehata et al., 2020).

Briefly, 15 subjects (5 males; age: 18-35 years) forming ten pairs (5 participants were paired twice) played a music rhythm game under three conditions creating three states (team flow, team only, and flow only states). EEG hyperscanning and subjective ratings were collected. We calculated EEG power spectral density (PSD) of four frequency bands (theta, alpha, beta, and low-gamma) at each of the 128 channels. First, we extracted ten principal components (PC) from each frequency band through the principal component analysis (PCA) and then conducted linear discriminant analysis (LDA). The latent dimensions (LD) were determined based on the classification accuracy of each subject and their states (10-fold cross-validation). Finally, we constructed a psychological space based on subjective ratings and conducted a representational similarity analysis (RSA) with the EEG latent space. **Results:** We successfully identified 3 LDs that achieved 100% classification accuracy. Plotting the EEG data in the 3D latent space revealed two levels of segregation. A macrosegregation captured inter-individual differences, and microsegregation captured intra-individual states. Using RSA, we found a significant correlation (Pearson's $r = 0.308$, $p < 0.001$ by permutation) of the trial-by-trial similarity representations between the latent space and the psychophysical space, indicating shared similarity structures between the brain signals and behavioral characteristics. **Conclusion:** Using LDA, we demonstrated both inter- and intra-individual segregations of EEG characteristics in a 3D latent space and mapped the similarity structures in this space onto behavioral traits. Future research would benefit from this approach and look for latent brain features associated with psychophysical traits and states.

Disclosures: Q. Wu: None. **S. Shimojo:** None. **M. Shehata:** None.

Poster

P032. Synapse Maturation and Remodelling IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.01

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Involvement of GluN2B-containing NMDA receptors in the elimination of cortico-motoneuronal synapses during development

Authors: *T. OHNO[1], ***T. OHNO**[1], S. FUKUDA[1], N. MURABE[1], K. SAKIMURA[2], T. HAYASHI[1], M. SAKURAI[1];
[1]Teikyo Univ. Sch. Med., Tokyo 173-8605, Japan; [2]Dept Cell. Neurobiol, Brain Res. Institute, Niigata Univ., Niigata, Japan

Abstract: We previously showed in our *in vitro* slice co-culture model of the corticospinal (CS) projections that CS axons extend over the spinal gray matter during early stages of development but later regress from the ventral side (Ohno et al., 2004). This elimination was further found to be dependent on GluN2B-containing NMDA receptors (Ohno et al. 2010, Isoo et al., 2016). We found *in vivo* that CS axons make direct and transient connections with motoneurons (MNs) at an early postnatal stage in rodents, which had been believed to be present only in higher primates (Maeda et al., 2016; Murabe et al., 2018). We further studied the time course of ratio of cortico-motoneuronal (CM) monosynaptic connections. Positive ratio of CM-EPSCs were shown to reach plateau at postnatal day (P) 8 (65%), then decreased from P14 toward P21 and disappeared thereafter (Ohno et al., 2021). Here, we studied the

involvement of GluN2B-containing NMDA receptors, which we found to be involved in axonal regression from the ventral spinal cord *in vitro*. To conditionally knockout (KO) the GluN2B gene (*Grin2b*) from the forearm MNs, we employed GluN2B-floxed mice and adeno-associated virus encoding Cre recombinase gene (AAV-Cre). Intramuscular injection of AAV-Cre into the forearm muscles of GluN2B-floxed mice at P1 made it possible for AAV-Cre to infect the axon terminals of MNs projected to the forearm muscles and to selectively KO *Grin2b* of those MNs. We clamped GluN2B-KO MNs to +40 mV and recorded NMDA components of EPSCs evoked by electrical stimulation of the posterior funiculus at P9-10. We measured the reduction in the amplitude of the GluN2B component of EPSCs by the application of GluN2B inhibitor, ifenprodil (3 μM) and Ro25-6981 (3 μM). In wild-type MNs, the EPSC amplitudes were inhibited by 78.4 ± 8.5% (mean ± S.E.M.), whereas in conditional GluN2B-KO MNs, EPSC amplitudes decreased by only 16.9 ± 8.5%, indicating that this method successfully KOs GluN2B in the MNs. We then examined the developmental change of the positive ratio of CM-EPSCs on conditional GluN2B-KO MNs. CM direct connections were present in about 30 % of GluN2B-KO MNs even after P21 and preserved at least until P48. These results suggest that CM synapse elimination is dependent at least partly on synaptic activity and post-synaptic GluN2B-containing NMDA receptors.

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Poster

P032. Synapse Maturation and Remodelling IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.02

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant EY030458-02S1
NIH Grant 1R56AG061808-01

Title: Neuronal SIRPα temporally enables microglia activation and synapse refinement during development

Authors: *D. JIANG[1], C. BURGER[1], N. ALBRECHT[2], P. ANDRADE[1], R. D. MACKIN[1], V. AKHANOV[1], J. H. LIANG[1], M. A. SAMUEL[3];
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Abstract: Microglia activation is dynamic, and periods of increased activation precisely align with the window in which developmental neural pruning proceeds. Little is known about the neuron-derived signals that permit microglia activation during these periods and restrict it as synapses mature. Using the murine retina, we show that signal regulatory protein alpha (SIRPα) produced by neurons acts as a permissive cue that temporally enables microglia activation. During developmental synapse pruning, neurons are the dominate developmental source of SIRPα. SIRPα is also temporally regulated: high levels are present during synaptic refinement while lower levels are present in adults. Nanoscopic imaging reveals that SIRPα localizes to the synaptic cleft where it structurally overlaps with its binding partner CD47. Using cell type-specific deletion methods, we show that while microglia-derived SIRPα is

dispensable for microglia activation and synapse engulfment, neuronal SIRPα is required. Deletion of SIRPα from retinal neurons dramatically restricts microglia activation, limits engulfment, and increases synapse number. Conversely, prolonging neuronal SIRPα expression extends the window in which microglia are active. Together, these data identify a neuron-derived cue that enables microglia activation and synapse remodeling and reveal a temporal switch that permits microglia activation at the appropriate developmental time.

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Poster

P032. Synapse Maturation and Remodelling IV

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH RO1 AA027079

Title: The involvement of CD47 and the complement protein C3 in synaptic elimination in sensory-motor circuits during normal development.

Authors: *D. FLOREZ-PAZ, G. Z. MENTIS;
Ctr. for Motor Neuron Biol. and Disease, Depts. of Pathology and Cell Biol. and Neurol., Columbia Univ., New York, NY

Abstract: Proper assembly of sensory-motor circuits requires synapse formation between appropriate neurons for the normal function of the nervous system. Synapse formation requires the activation of different genetic pathways that regulate the number and function of synapses with the appropriate postsynaptic neurons. We previously reported, that C1q is involved in synaptic refinement and elimination of proprioceptive sensory synapses (VGluT1+) on spinal motor neurons. Here, we explored the role of complement protein C3 in synapse engulfment and the interaction of C1q with CD47 as counterpoise signals in synapse development of spinal motor circuits. We systematically quantified the number of VGluT1+ synapses on motor neuron somata and synaptic density in their dendrites, at different ages (P0, P5 and P10) in WT, C1qKO, C3KO, and CD47KO animals. In C3KO animals, we observed an increase in VGluT1+ synapses at P5 compared to WT. Surprisingly, we also found an increase in synapses in CD47KO mice compared to controls at P5 and P10. Using immunohistochemistry, we studied the expression of CD47 in C1qKO and C3KO animals; starting at P5 there was an upregulation of CD47, tagging more synapses in Cq1KO and C3KO animals compared with WT. To investigate a possible protecting role of CD47 in synaptic pruning, we studied the interaction between C1q and C3 with CD47 using quadruple staining against ChAT, C1q or C3, CD47 and VGlut1, showing that at P0 and P5, ~10% of synapses in motor neurons were tagged by both C1q and CD47. Further, we also stained microglia using Iba1, and we confirmed that VGlut1 synapses are engulfed by microglia when tagged by both, CD47 and C1q starting at P0, suggesting that CD47 is not sufficient to protect synapses from engulfment when is also tagged by C1q. To reveal the CD47 source in the spinal cord, we performed RNAscope

experiments and found that CD47 is only expressed in motor neurons, but not in microglia or astrocytes. Together, these results confirm a role of C3 in synapses elimination, but raising the possibility that that CD47 does not provide a synaptic-protecting role for sensory synapses in the spinal cord, as was previously described in other circuits, and likely plays a role in signaling for engulfment of synapses by microglia.

Disclosures: D. Florez-Paz: None. **G.Z. Mentis:** None.

Poster

P032. Synapse Maturation and Remodelling IV

Location: Virtual Only

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Program #/Poster #: P032.04

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant DC04846
Buffett Early Childhood Institute
University of Nebraska at Omaha Office of Research and Creative Activity

Title: Depletion of microglia with PLX5622 in adulthood reverses developmental pruning of the rat glossopharyngeal nerve

Authors: *A. J. RIQUIER, S. I. SOLLARS;
Univ. of Nebraska At Omaha, Omaha, NE

Abstract: The removal of excess synapses, or 'pruning' is a well-established phenomenon of the developing brain. The central projections of the gustatory glossopharyngeal nerve form a terminal field (IX) of synapses with neurons of the nucleus of the solitary tract. The IX reduces in volume by approximately 66% between postnatal day 15 (P15) and P25 (Mangold & Hill, 2008), yet this pruning can be experimentally reverted later in life (Skyberg et al., 2017; Sun et al., 2018), suggesting this reduction may not be a discrete occurrence, but a continuous maintenance throughout the lifespan. The central nervous system macrophages microglia are known to perform synaptic pruning in other sensory systems (e.g. Paolicelli et al., 2011; Schafer et al., 2012; Stevens et al., 2007) including the other gustatory nerves in mice (Sun et al., 2019). To determine if microglia are responsible for pruning and maintenance of the IX, we used daily intraperitoneal injections of the colony-stimulating factor 1 receptor inhibitor PLX5622 to deplete microglia at various points of the rat lifespan, then labeled the IX with a biotinylated dextran amine and quantified its volume. In vehicle-treated control rats, the IX was largest at P14, reduced in volume by approximately 66% by P25 ($p < .01$), then remained at that reduced size through P68 ($p > .1$). In contrast, when microglia were removed from P1-P40 no pruning of the IX occurred; indeed, the IX was statistically identical in size to those of pre-pruning P14 rats ($p > .1$). When PLX5622 treatments were then ceased at P40, microglia returned within three days and pruning resumed; by P68 the volume of the IX had reduced to sizes comparable to adult controls ($p > .1$). These results indicate that microglia are necessary for IX developmental pruning and are capable of such well outside the typical pruning period. To test if normally occurring developmental IX pruning could be reversed, we next took adult control rats whose IX had already pruned and depleted their microglia from P40-P68, which resulted in the IX

expanding to pre-pruning sizes typical of the neonatal rat ($p > .1$). To see if this was a generalizable phenomenon, we repeated the analyses with the somatosensory IX fibers that project to the spinal trigeminal nucleus (SpV). As expected, SpV IX fibers underwent developmental pruning ($p < .01$) and removing microglia during development prevented this pruning ($p > .1$). However, when microglia were allowed to return in adulthood, pruning did not resume; by P68, SpV IX fibers remained at pre-pruning volumes ($p > .1$). Taken together, these data show that microglia continuously maintain the gustatory IX at a reduced size at least several weeks after pruning typically occurs.

Disclosures: A.J. Riquier: None. **S.I. Sollars:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Plexxikon Inc..

Poster

P032. Synapse Maturation and Remodelling IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Brown University New Frontiers Award
Brown University Seed Award

Title: Role of matrix metalloproteinase 9 in neurodevelopmental deficits and experience dependent plasticity in Xenopus laevis.

Authors: *S. V. GORE[1], E. J. JAMES[2], L.-C. HUANG[5], *J. PARK[2], A. BERGHELLA[2], A. THOMPSON[3], H. T. CLINE[5], C. D. AIZENMAN[4];
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Abstract: Valproic acid (VPA) exposure during a critical developmental period in Xenopus tadpoles results in local neural circuit hyperexcitability in the optic tectum, abnormal dendritic development as well as associated behavioral abnormalities, such as lack of schooling, sensory hypersensitivity and increased seizure susceptibility. VPA is a common anti-seizure medication, and prenatal exposure to VPA results in a higher incidence of Autism spectrum disorders (ASD) in humans, and causes brain abnormalities associated with ASD in other organisms. Previous microarray studies from the lab have shown that VPA exposure results in remarkable alterations in gene expression, including a greater than two-fold increase in matrix metalloproteinase 9 (MMP9). MMP9 is a secreted endopeptidase targeting extracellular matrix proteins, creating permissive environments for neuronal development and plasticity. Developmental dysregulation of MMP9 is implicated in development of neurodevelopmental disorders (ND). Here we test the hypothesis that chronically elevated MMP9 activity during early neurodevelopment is responsible for neural circuit hyperconnectivity observed in *Xenopus* tadpoles after early exposure to VPA, a known teratogen associated with ND in humans. We found that overexpressing MMP9 in the Xenopus tectum mimics effects of VPA on synaptic connectivity, and blocking MMP9 activity pharmacologically or genetically reverses effects of VPA on physiology and behavior. We further show that during normal neurodevelopment MMP9 levels are tightly regulated by neuronal activity and

required for structural plasticity. These studies show that MMP9 plays a critical role in both normal and abnormal development.

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Poster

P032. Synapse Maturation and Remodelling IV

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH F30 Grant MH118804

Title: Cell-type specific deletions of Neuroligin 2 reveal a vital role of synaptic excitation-inhibition balance in mice

Authors: *C. M. LONGLEY, J. E. MESSIER, Z.-L. CAI, J. PARK, W. CHEN, M. XUE;
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Abstract: The spatiotemporal relationship between synaptic excitation (E) and inhibition (I) orchestrates the patterns of neuronal activity in the brain. Excitation and inhibition stay relatively proportional to each other over different temporal and spatial scales. This proportionality, often referred to as E-I balance, is thought to be critical for neuronal functions, and disruption of E-I balance has been hypothesized as a key etiology of many neurodevelopmental and psychiatric disorders. However, causal evidence demonstrating the importance of E-I balance has been scarce. Here we show that Neuroligin 2 (Nlgn2), a postsynaptic cell adhesion molecule exclusively expressed at inhibitory synapses, selectively regulates GABAergic inhibition without affecting glutamatergic excitation in mouse cortical excitatory and inhibitory neurons. Deletion of Nlgn2 early in development from pyramidal neurons, somatostatin (Sst)-expressing, parvalbumin (Pv)-expressing, or vasoactive-intestinal peptide (Vip)-expressing interneurons leads to a cell-autonomous reduction in synaptic inhibition onto each of these neuron types, thereby disrupting the E-I balance. Even though constitutive Nlgn2 knockout mice are viable, conditional deletion of Nlgn2 in either glutamatergic or GABAergic neurons unexpectedly causes postnatal lethality, indicating an essential role of E-I balance in survival. Simultaneous loss of Nlgn2 in both glutamatergic and GABAergic neurons results in viable mice with developmental delay, suggesting that re-establishing E-I balance partially restores neuronal functions. Together, our results indicate that Nlgn2 plays a critical role in the development of inhibitory synapses onto both excitatory and inhibitory neurons and provide evidence for a vital role of maintaining a proper E-I balance in brain functions and organism survival.

Disclosures: C.M. Longley: None. **J.E. Messier:** None. **Z. Cai:** None. **J. Park:** None. **W. Chen:** None. **M. Xue:** None.

Poster

P032. Synapse Maturation and Remodelling IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P032.07

Topic: B.06. Synaptic Transmission

Support: European Research Council grant

Title: Input and output connectivity mapping reveals integrating properties of corticoclaustral and intraclaustral circuits

Authors: *A. M. SHELTON, D. K. OLIVER, S. J. BUTT, A. M. PACKER;
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Abstract: The claustrum is highly interconnected with many other structures in the brain. However, our knowledge of the organizing principles governing extra- and intra-claustral connectivity remain incomplete. The present study investigates the architecture of circuits between the claustrum and neocortex and within the claustrum itself. Immunohistochemistry, retrograde tracing, *in vitro* whole-cell patch-clamp electrophysiology, dual-color optogenetic circuit mapping, and *in vivo* calcium imaging of neural activity were used to assess the extent to which claustrum neurons receive common input from multiple cortical areas. We determined that individual claustrum neurons frequently integrate inputs from more than one cortical site, most commonly between regions of the frontal cortex. Additionally, we found that neurons in the claustrum receive inputs from an array of sensory and associative cortical areas, albeit to a lesser extent. Retrograde labelling further demonstrated that the degree of input integration from frontal cortical regions depends on the output target of claustrum neurons. Finally, optogenetic mapping revealed that intraclaustral connectivity was found to be far more frequent than previously reported in coronal slices, particularly among neurons that did not share the same output target. Our findings shed light on the organizing principles of claustrum input and output connectivity, demonstrating the relationship between cortical projections, local claustral connectivity, and claustral outputs. Claustrum projection neurons pool inputs from multiple sites around the brain and display a high degree of connectivity with each other that is influenced by output target. This work provides mechanistic evidence of the claustrum as an intrinsically integrative structure with the capacity to perform local transformations of cortical input via distinct intraclaustral pathways.

Disclosures: A.M. Shelton: None. **D.K. Oliver:** None. **S.J. Butt:** None. **A.M. Packer:** None.

Poster

P032. Synapse Maturation and Remodelling IV

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Topic: B.06. Synaptic Transmission

Support: N.K. and V.S. are supported from a technical award from the McKnight foundation, a Brain Initiative of the National Institutes of Health (U01 MH109100), and National Science Foundation Neuro Nex grant.
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Title: Cortex layer 5 innervates the thalamic reticular nucleus

Authors: *B. CARROLL[1], V. SAMPATHKUMAR[2], N. B. KASTHURI[2], S. SHERMAN[3];
[2]Neurobio., [1]Univ. of Chicago, Chicago, IL; [3]Dept Neurobiol, Univ. Chicago, Chicago, IL

Abstract: A major cortical efferent and the primary source of inhibition to dorsal thalamus, the thalamic reticular nucleus (TRN) is well-positioned to regulate corticothalamic communication. Whereas cortical inputs had been previously thought to originate solely in layer 6 of cortex (L6), we recently demonstrated with light microscopy that axons of cortical layer 5 (L5) cells also produce varicosities in TRN. Our experiments employed viral tracing in the genetic mouse line Rbp4-Cre, which selectively expresses Cre-recombinase in L5. Using injections of Cre-dependent adeno-associated viruses (AAVs) in cortex, we labelled L5 neurons and examined the nature of their labelled varicosities in the somatosensory domain of TRN. First, we used light microscopy and a Cre-dependent AAV encoding the fluorescent label enhanced yellow fluorescent protein (EYFP) to localize the resulting label in TRN and demonstrate that varicosities arising in L5 are restricted to edge regions of TRN, where resides a subpopulation of inhibitory cells projecting to higher-order thalamus. In contrast, L5 varicosities are absent in TRN's core, containing cells that project to first-order thalamus; we also showed through labelling of corticofugal axons from both L5 and L6 with EYFP expression independent of Cre that these core cells receive L6 inputs. Second, we used electron microscopy and Cre-dependent AAVs encoding enhanced ascorbate peroxidase (APEX2) to test that these varicosities include bona fide terminals onto TRN cells. We delivered two APEX2 viruses, one to label mitochondria in L5 cells of primary somatosensory cortex and the other to label cytoplasm in L5 cells of primary motor cortex. By doing so, we established that L5 from these areas provides synaptic innervation of TRN cells. Together, these experiments established evidence that cortical afferents to TRN include L5, and that these L5 inputs impact inhibition of higher-order, but not first-order, nuclei in dorsal thalamus.

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Poster

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Topic: B.06. Synaptic Transmission

Support: This material is based upon work supported by the Naval Information Warfare Center (NIWC) Atlantic and the Defense Advanced Research Projects Agency (DARPA) under

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Title: Spatiotemporal mapping of extracellular field potentials in different layers of mouse somatosensory cortex

Authors: *V. JAIN, M. FORSSELL, P. GROVER, M. CHAMANZAR;
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Abstract: ***Background:*** Somatosensory cortex mediates and transforms sensory information across different layers. While the laminar organization of the neural circuit structure in the somatosensory cortex is well characterized, the complex dynamics of functional integration within these layers still remains elusive. Electrophysiological response has been to elucidate the neuronal circuit connections under different pathological states or stimulation conditions. Here we report the results of a systematic study based on a series stimulation-recording experiments to detect extracellular field potentials in different layers of the somatosensory cortex in response to electrical stimulation in each layer. ***Method:*** Coronal brain slices were prepared from 3-6 weeks old C57BL6 mice of either sex. Each layer of the somatosensory cortex was stimulated using a Pt-Ir bipolar electrode. A single biphasic pulse (cathodic phase first) with 200µs pulse width was applied as the extracellular stimulation signal to each layer of the somatosensory cortex and the local field potentials (LFPs) were recorded in different layers at different locations within the somatosensory cortex within a 1 mm lateral range. The amplitude of the stimulation signal was chosen such that the effect of volume conduction is minimized, ensuring local stimulation of the cortical layer of interest. ***Results:*** The results from the present study revealed a widespread activation of neural circuits in different layers on stimulating layer 5 which is in accord with the laminar organization whereas stimulation of Layer 1, Layer 2/3 and Layer 6 evoked a confined response in nearby layers. Interestingly, Layer 4 stimulation leads to comprehensive activation of Layer 2/3 and Layer5. ***Conclusion:*** In conclusion, current work divulges network connections across the cortical laminae mediated through synaptic transmission, which can be used to better understand information processing in neuronal networks and as a baseline to study the impaired neural signal transmission under different pathological conditions.

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Poster

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Title: Rapid homeostatic modulation of transsynaptic nanocolumn rings

Authors: *P. MUTTATHUKUNNEL[1], P. FREI[2], S. PERRY[3], D. DICKMAN[3], M. MÜLLER[2]; [1]Dept. of Mol. Life Sci., [2]Univ. of Zurich, Zurich, Switzerland; [3]Univ. of California, Department of Neurobiology, CA

Abstract: Robust neural information transfer relies on a delicate molecular architecture of chemical synapses and even subtle changes in the molecular organization of synapses may profoundly affect synaptic transmission and animal behavior. Neurotransmitter release is controlled by a specific arrangement of proteins within presynaptic active zones. How the specific presynaptic molecular architecture relates to postsynaptic organization, and how synaptic nano-architecture is transsynaptically regulated to achieve stable synaptic transmission remains enigmatic. Using STED microscopy, we here discovered that presynaptic nano-rings formed by the active-zone cytomatrix protein scaffold Bruchpilot (Brp) precisely align with glutamate receptors (GluRs) nano-rings composed of ~6 GluR clusters at the *Drosophila* NMJ. Individual rings harbor ~5 transsynaptically-aligned Brp-GluR 'nanocolumns'. Transsynaptic nanocolumn rings are partially masked by unaligned GluR clusters. Genetic manipulations of GluR subunits and the auxiliary GluR subunit Neto revealed a GluR subtype-specific nano-organization: While GluRs containing the GluRIIA subunit predominantly localize to nanorings, GluRIIB 'nanoclusters' can be found both, inside and outside of nanorings. Intriguingly, acute GluR impairment rapidly triggers the formation of new transsynaptic nanocolumns on the minute time scale during homeostatic plasticity. We reveal distinct phases of structural transsynaptic homeostatic plasticity, with postsynaptic reorganization preceding presynaptic modulation. Finally, the auxiliary GluR subunit Neto promotes structural and functional homeostatic plasticity. Thus, transsynaptic nanocolumns arrange in stereotypic rings that are rapidly modulated during homeostatic plasticity to stabilize synaptic efficacy.

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Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P068.01

Topic: A.03. Stem Cells and Reprogramming

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NRF-2017R1A3A1078210
NRF- 2019R1F1A1063932

Title: Dysfunction of NMDA receptors in neuronal models of an autism spectrum disorder patient with a DSCAM mutation and in Dscam-knockout mice

Authors: C.-S. LIM[1], M. KIM[2], ***J. CHOI**[2], M. ISLAM[2], Y.-K. LEE[4], Y. XIONG[1], K.-W. SHIM[3], J.-E. YANG[2], R. LEE[2], J. LEE[2], P. PARK[2], J.-H. KWAK[5], H. SEO[5], C. KIM[6], J.-H. LEE[7], Y.-S. LEE[8], S.-K. HWANG[5], K. LEE[5], J.-A. LEE[4], B.-K. KAANG[2];
[1]Dept of Pharmacol, Wonkwang Univ. Sch. of Med., Jeonbuk, Korea, Republic of; [2]Sch. of Biol. Sci., [3]Interdisciplinary Program in Bioinformatics, Seoul Natl. Univ., Seoul, Korea, Republic of; [4]Dept. of Biotech. and Biol. Sci., Hannam Univ., Daejeon, Korea, Republic of; [5]Sch. of Medicine, Kyungpook Natl. Univ., Daegu, Korea, Republic of; [6]Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [7]Kyung Hee Univ. Sch. of Dent., Seoul, Korea, Republic of; [8]Dept. of Physiol., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Heterogeneity in the etiopathology of autism spectrum disorders (ASD) limits the development of generic remedies, requires individualistic and patient-specific research. Recent progress in human-induced pluripotent stem cell (iPSC) technology provides a novel platform for modeling ASDs for studying complex neuronal phenotypes. In this study, we generated telencephalic induced neuronal (iN) cells from iPSCs derived from an ASD patient with a heterozygous point mutation in the *DSCAM* gene. The mRNA of DSCAM and the density of DSCAM in dendrites were significantly decreased in ASD compared to control iN cells. RNA sequencing analysis revealed that several synaptic function-related genes including NMDA receptor subunits were downregulated in ASD iN cells. Moreover, NMDA receptor (R)-mediated currents were significantly reduced in ASD compared to control iN cells. Normal NMDA-R-mediated current levels were rescued by expressing wild-type DSCAM in ASD iN cells, and reduced currents were observed by truncated DSCAM expression in control iN cells. shRNA-mediated DSCAM knockdown in control iN cells resulted in the downregulation of an NMDA-R subunit, which was rescued by the overexpression of shRNA-resistant DSCAM. Furthermore, DSCAM was co-localized with NMDA-R components in the dendritic spines of iN cells whereas their co-localizations were significantly reduced in ASD iN cells. Levels of phospho-ERK1/2 were significantly lower in ASD iN cells, suggesting a potential mechanism. A neural stem cell-specific *Dscam* heterozygous knockout mouse model, showing deficits in social interaction and social memory with reduced NMDA-R currents. These data suggest that *DSCAM* mutation causes pathological symptoms of ASD by dysregulating NMDA-R function.

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Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P068.02

Topic: A.03. Stem Cells and Reprogramming

Support: A Cure for Ellie

Title: Dars2-related leukoencephalopathy: possibility of dysregulated noncanonical functions of mitochondrial aspartyl-trna synthetase?

Authors: *S. GUANG[1,2], C. L. NEMETH[1,2], M. YING[1,2], A. FATEMI[1,2];
[1]Kennedy Krieger Inst., Baltimore, MD; [2]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: DARS2-related leukoencephalopathy, also called Leukoencephalopathy with Brainstem and Spinal cord involvement and Lactate elevation (LBSL), is a rare disorder with a wide phenotypic spectrum. Classic LBSL is characterized by childhood-onset slowly progressive spasticity, cerebellar ataxia and dysfunction of the dorsal column. Early onset cases with cerebral hypoplasia and early demise, as well as mild adulthood-onset cases, were also reported. LBSL is caused by mutations in the *DARS2* gene, which encodes mitochondrial aspartyl-tRNA synthetase (mt-AspRS). mt-AspRS is synthesized in cytosol and transported to mitochondria, responsible for attaching aspartate to its corresponding tRNA. Nearly all patients are compound heterozygous for *DARS2* mutations, of which, one is most frequently a splice mutation in intron 2, which causes exon 3 skipping, a frameshift, and a premature termination codon. A subset of point mutations have been studied regarding aminoacylation activity, architecture, localization and solubility. None of them cause gross structural or functional perturbations, except for the R263Q mutant, which impairs enzyme activity. Altogether, the housekeeping aminoacylation activity seems not be the major target, pointing to the possibility that mt-AspRS moonlights in the cells by performing noncanonical functions such as regulating splicing or translation, as has been reported for several cytosolic aminoacyl-tRNA synthetases. We generated cerebral organoids for seven LBSL patients and three controls using an unguided protocol and performed SMARTseq2. After quality control, 809 cells were used for downstream analysis. At least six cell identities were found in our dataset. We uncovered two patient subgroups which presented unique profiles of differentially expressed genes. Patients carrying at least one missense mutation showed downregulated expression of genes related to mRNA processing and splicing, which was exacerbated in neuronal cells. Patients carrying two splice site mutations showed upregulated genes related to RNA splicing and translation. Inspired by these findings, we identified some genes, such as *LGMN*, *SLIRP*, *CAST* and *PDCD4*, which were spliced differently across LBSL patient groups. Furthermore, transcript analyses of *DARS2* showed decreased levels of normal transcripts in LBSL patients and transcripts skipping exon 3 coexist with normal transcripts within individual control cells, but LBSL cells might express solely abnormal transcripts within an individual cell. A full understanding of these findings may help to reveal noncanonical functions of *DARS2* and the identification of therapeutic targets.

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Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Program #/Poster #: P068.03

Topic: A.03. Stem Cells and Reprogramming

Support: Glut1 Deficiency Foundation
TTUHSC Institutional Funds

Title: Modeling Glut1 Deficiency Syndrome at the Human Blood-Brain Barrier In Vitro Using CRISPR-Cas9 Edited Induced Pluripotent Stem Cells

Authors: *I. PERVAIZ[1], F. ZAHRA[2], C. M. MIKELIS[2], A. J. AL-AHMAD[2];
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Abstract: Background: Glucose represents one of the major energy sources for the central nervous system (CNS). Glucose uptake is mostly occurring across the blood-brain barrier (BBB), via the involvement of glucose transporters (GLUTs). At the BBB, such transport is mostly mediated via GLUT1 also known as solute carrier family 2, facilitated glucose transport member 1. In addition to the importance of glucose for neuron metabolism, there is growing evidence that brain microvascular endothelial cells (BMECs) lining the BBB are highly glycolytic. Yet our current understanding of glucose metabolism at the BBB remains limited. GLUT1 deficiency syndrome (G1D) is an autosomal dominant childhood form of epilepsy affecting GLUT1 activity. It is often characterized by early onset of seizures, gait disorders, and intellectual disability. A major issue is the lack of a robust *in vitro* model of G1D to understand the pathophysiology of the BBB. The aim of this study is to develop and characterize G1D-BMECs by gene editing using induced pluripotent stem cells (iPSCs). **Methods:** Heterozygous *SLC2A1*+/- iPSC (IMR90)-c4 were produced by the CRISPR-Cas9 method. Such iPSCs were differentiated into BMECs using established protocols. Cell phenotyping, barrier function, glucose uptake, and metabolism were assessed in the system. **Results:** *SLC2A1*+/- iPSCs were viable and showed no significant differences in terms of phenotype or growth, compared to unedited iPSCs. Differentiated *SLC2A1*+/- BMECs showed similar *SLC2A1* expression, at mRNA level to the control, but showed reduced GLUT1 expression at the protein level, as well as reduced glucose uptake. A decreased barrier function was observed in these cells, without any major changes in tight junction complex and glucose metabolism, as well as impaired angiogenesis. **Discussion:** Our data suggest that *G1D-BMECs* display reduced GLUT1 expression and glucose uptake, reduced barrier tightness, and angiogenesis thus, recapitulating findings documented *in vivo*. Taken together, our data suggest that G1D-BMECs can be a potential tool to model G1D at the BBB *in vitro*.

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Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Program #/Poster #: P068.04

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant NS111965

Title: Contribution of GABA-A receptor subunit deletions to human Angelman syndrome neuronal phenotypes

Authors: T. M. ROBINSON[1], C. L. SIROIS[2], S. J. CHAMBERLAIN[2], ***E. S. LEVINE**[1];
[1]Neurosci., [2]Genet. and Genome Sci., Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: Maternal deletion of chromosome 15q11-q13 causes Angelman syndrome (AS), a genetic disorder in which individuals present developmental delays, language impairment, intellectual deficits, motor ataxia, and seizures. The gene located in this region that is primarily responsible for AS is UBE3A, which encodes a ubiquitin protein ligase. This gene is normally imprinted in the brain, and expression in neurons is only from the maternal allele. Thus, a maternal deletion of this region, which is the most common cause of AS, results in a complete loss of UBE3A expression in neurons. Several non-imprinted genes in the region are also affected, including a cluster of GABA-A receptor subunit genes (GABRB3, GABRA5, and GABRG3), which encode the β3, α5, and γ3 subunits, respectively. AS can also be caused by loss of function mutations of UBE3A. When AS results from mutations of UBE3A, the symptoms of affected individuals pertaining to cognition, motor function, and seizures are less severe compared to the symptoms caused by a maternal deletion. This suggests that in 15q11-q13 deletion patients the loss of other genes in the region contribute to AS pathophysiology. We have previously shown that human AS neurons containing a maternal 15q11-q13 deletion have impaired maturation of resting membrane potential (RMP) and action potentials (APs), increased excitability, and decreased GABA-mediated synaptic transmission compared to neurons derived from unaffected controls. In the present studies, we used novel isogenic iPSC lines derived from a patient with a UBE3A mutation and a CRISPR-corrected counterpart to examine the contributions of UBE3A and the GABA-A receptor subunits to AS neuronal phenotypes. Maturation of RMP and AP firing were affected in UBE3A mutation neurons to a similar extent as AS deletion neurons. UBE3A mutation neurons also displayed increased excitability, but of a lesser magnitude than seen in AS deletion neurons. Spontaneous inhibitory synaptic activity was not altered in UBE3A mutation neurons, in contrast to the decreased frequency and amplitude of spontaneous inhibitory synaptic currents seen in AS deletion neurons. We hypothesize that the hemizygous loss of the GABA-A receptor subunit cluster contributes to the more severe cellular phenotypes in AS deletion neurons. Ongoing experiments are exploring whether decreasing the expression of these genes in UBE3A mutation neurons using antisense oligonucleotides (ASOs) will mimic the cellular phenotypes seen in AS deletion neurons, including decreased inhibitory synaptic signaling and neuronal hyperexcitability. These studies may identify novel targets for therapeutic development in AS.

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Poster

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Topic: A.03. Stem Cells and Reprogramming

Support: SC EPSCOR stimulus award 18-SR04
NIH/NIGMS 5P20GM103641-07

Title: Novel discoveries for warburg micro syndrome protein rab3gap1 in modulation of neurite outgrowth and interactions with axon elongation and an ER Golgi trafficking factor

Authors: *J. VACHARASIN[1], P. S. GHATE[2], D. NOWLING[1], S.-H. CHEON[1], M. H. COWEN[3], V. KAY[1], M.-K. LAWLOR[1], M. MCCORD[1], E. CHUKWURAH[4], M. WALLA[1], S. B. LIZARRAGA[1];

[1]Univ. of South Carolina, Columbia, SC; [2]St. Jude Children's Res. Hosp., Memphis, TN; [3]Univ. of South Carolin, Columbia, SC; [4]Case Western Reserve Univ., Cleveland, OH

Abstract: Mutations in Rab3Gap1 are known to cause Warburg Micro syndrome, a neurodevelopmental disorder that results in delayed motor development, hypoplasia, and other abnormalities. However, the neuronal function of Rab3Gap1 is not well defined. We find that knockdown of RAB3GAP1 leads to a reduction in neurite outgrowth in human stem cell derived neurons. Using a combination of mass spectrometry, co-immunoprecipitation, and colocalization analysis we identified two novel interactors of RAB3GAP1: the axon elongation factor Dedicator of cytokinesis 7 (DOCK7) and the TATA modulatory factor 1 (TMF1) a modulator of Endoplasmic Reticulum (ER) to Golgi trafficking. DOCK7, TMF1, and Rab3GAP1 are expressed during fetal stages of brain development. To further understand the function of Rab3GAP1 its interactors, we used genome editing to target exon 7 of Rab3GAP1. This is an exon that is commonly mutated in patients with Warburg Micro syndrome. We find that the subcellular localization of TMF1 and DOCK7 to the ER-Golgi compartment is altered in RAB3GAP1 mutant cells. The ER-Golgi compartment is important in autophagy and Rab3Gap1 has been previously shown to be important in the formation of the autophagosome. We find that the induced exon 7 mutation in Rab3GAP1 also leads to alterations in autophagy. Taken together our work identifies a novel role for Rab3GAP1 in neurite outgrowth and two novel interactors of Rab3GAP1 which could provide additional mechanisms that underlie the pathogenesis of Warburg Micro Syndrome.

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Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant U54 HD090256

Title: Function of the Trinucleotide (CGG) Repeats Within the FMR1 Gene in Human Neurons

Authors: *C. L. SIROIS, M. LI, Y. GUO, T. KORABELNIKOV, Y. XING, B. LEVESQUE, A. BHATTACHARYYA, X. ZHAO;
Waisman Ctr., Univ. of Wisconsin-Madison, Madison, WI

Abstract: The 5’ UTR of the *FMR1* gene contains trinucleotide CGG repeats, that, when expanded beyond a certain threshold, can lead to one of several disorders depending on the length of the repeats. Repeats that range from 55 to 200 CGGs lead to either Fragile X Tremor and Ataxia Syndrome (FXTAS) or Fragile X Primary Ovarian Insufficiency (FXPOI), while repeats beyond 200 CGGs lead to silencing of the FMR1 gene and cause Fragile X Syndrome (FXS), a neurodevelopmental disorder that causes 2-5% of all autism cases. Recent research has shown that repeats below 55 CGGs are also correlated with certain health conditions, leading to CGG repeat lengths to be further subdivided into low zone (less than 24

CGG), normal (24-42 CGG), and gray zone (42-54) categories. To investigate the function of these CGG repeats *FMR1* in human neurons, we generated two human embryonic stem cell (hESC) lines lacking the CGG repeats in FMR1 (H1ΔCGG, H13ΔCGG) using genome editing and differentiated these cells into neurons. We found that removal of the CGG repeats does not affect *FMR1* expression at the mRNA or protein level in either hESCs, neural progenitors, or early post-mitotic neurons. Interestingly, *FMR1* mRNA in neurons lacking CGG repeats exhibit altered localization. Our results demonstrate that CGG repeats in *FMR1* may have a function in early neural development, which may have important implications for CRISPR-based gene therapy approaches that aim to remove the expanded CGG repeats from the *FMR1* gene.

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Poster

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Topic: A.03. Stem Cells and Reprogramming

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Schlumberger Foundation Faculty for the Future Award
Eagles Autism Foundation

Title: Identifying Cellular Phenotypes of Dup15q syndrome Using CRISPR-edited Human iPSC-derived neurons

Authors: *M. ELAMIN[1], A. DUMARCHEY[2], C. STODDARD[2], S. J. CHAMBERLAIN[2], E. S. LEVINE[1];
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Abstract: Dup15q syndrome is a neurodevelopmental disorder caused by maternal, but not paternal, duplications in the 11.2-13.1 region of the long arm of chromosome 15. Affected children typically exhibit intellectual disability, developmental delay, autism, and epilepsy. It is thought that *UBE3A*, the gene encoding the ubiquitin protein ligase E3A, underlies many Dup15q behavioral phenotypes because it is the only imprinted gene that is expressed solely from the maternal allele. Nevertheless, the exact role of *UBE3A* is yet to be determined. To identify cellular phenotypes in human Dup15q neurons, we used an induced pluripotent stem cell (iPSC) line derived from an individual with an isodicentric 15q duplication. This iPSC line was also edited using CRISPR technology to generate an isogenic line with the extra genetic material completely removed. Whole-cell patch-clamp recordings revealed a hyperexcitability phenotype in Dup15q neurons characterized by an increased voltage-gated sodium current, larger action potential amplitude, greater firing frequency, and increased excitatory synaptic transmission compared to isogenic control neurons. Normalizing *UBE3A* gene expression throughout in vitro development with the use of antisense oligonucleotides (ASO) prevented these cellular phenotypes, indicating that increased *UBE3A* expression is necessary for the establishment of these cellular phenotypes. A later treatment with

the *UBE3A* ASO was only partially effective at reversing these cellular deficits. Overexpression of *UBE3A* in an iPSC line from an unaffected individual with a paternal 15q duplication was achieved by using an ASO targeting the antisense transcript that is responsible for silencing paternal *UBE3A*. We found that *UBE3A* overexpression affected sodium currents, action potential amplitude, and firing rate, similar to the cellular phenotypes observed in Dup15q neurons. Increased expression of *UBE3A* was not sufficient, however, to affect excitatory synaptic transmission, suggesting a contributing role for other genes in the duplicated region. Elucidating the functional relevance of *UBE3A* and other genes to Dup15 cellular phenotypes will enrich our knowledge of the pathophysiological mechanisms underlying this disorder and aid in the development of novel therapeutics.

Disclosures: M. Elamin: None. **A. Dumarchey:** None. **C. Stoddard:** None. **S.J. Chamberlain:** None. **E.S. Levine:** None.

Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P068.08

Topic: A.03. Stem Cells and Reprogramming

Support: A Cure for Ellie

Title: Investigation into the disease mechanism of Leukoencephalopathy with Spinal Cord and Brain Stem Involvement and Lactate Elevation (LBSL) using patient iPSC-derived motor neurons

Authors: *S. BAEK[1], C. L. NEMETH[1,3], B. O'BRIEN[1], S. GUANG[1], M. YING[2], A. FATEMI[1,3]; [1]Moser Ctr. for Leukodystrophies, [2]Hugo W. Moser Res. Inst., Kennedy Krieger Inst., Baltimore, MD; [3]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Leukoencephalopathy with Brainstem and Spinal Cord involvement and Lactate Elevation (LBSL) is an autosomal recessive disorder characterized by dorsal column dysfunction which results in slowly progressive gait difficulty, spasticity, ataxia, and proprioceptive deficits. Hallmark MRI shows progressive loss of white matter volume unique to dorsal columns and lateral corticospinal tracts of the spinal cord, and select regions of the brainstem and cerebral cortex. Most of the individuals diagnosed with LBSL are compound heterozygote for mutations in the *DARS2* gene, which encodes mitochondrial Aspartyl-tRNA Synthetase that conjugates the amino acid aspartate to its cognate tRNA during protein translation within mitochondria. Established knockout mouse models have been studied but fail to recapitulate the human condition. We utilized induced Pluripotent Stem Cells (iPSCs) reprogrammed from peripheral blood mononuclear cells (PBMCs) of patients to further investigate the pathological manifestation of the disease. Using a rapid differentiation protocol, we derived patient iPSCs into motor neurons and show reduced neurite outgrowth and reduced spontaneous firing in LBSL cells compared to control using IncuCyte live cell imaging and electrophysiological analysis, respectively. Our western blot analysis indicates reduced DARS2 in motor neurons compared to iPSCs in both control and LBSL patients; however, LBSL cells show a greater reduction of DARS2 in both conditions compared with controls. Despite reduced DARS2 protein, translation of mitochondrial proteins appears intact within

LBSL neurons. Finally, analysis of mitochondria using the Seahorse XFe96 Cell Mito Stress Test reveals reduced baseline oxygen consumption as well as spare capacity of LBSL patient cells suggesting an overall reduction of mitochondrial flexibility and fitness. Interestingly, these findings suggest that mitochondrial impairment and neuronal growth deficits are independent of mitochondrial translation. This model may serve as a useful testbed for future therapeutics aimed at understanding LBSL disease mechanism.

Disclosures: S. Baek: None. **C.L. Nemeth:** None. **B. O'Brien:** None. **S. Guang:** None. **M. Ying:** None. **A. Fatemi:** None.

Poster

P068. Stem Cell Approaches in Autism and Neurodevelopmental Disorders

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P068.09

Topic: A.03. Stem Cells and Reprogramming

Support: ERA-NET NEURON under Grant No. 01EW1902 (DECODE!)
Horizon 2020 Research and Innovation Programme under Grant No. 728018 (Eat2beNICE)

Title: Investigation of CDH13's role in neurodevelopmental disorders using a set of generated isogenic induced pluripotent stem cell lines (iPSC) and iPSCs carrying different CDH13 variants in a functional intronic SNP rs2199430

Authors: *M. VITALE, J. ZÖLLER, K. LESCH;
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Abstract: CDH13 has been identified as a risk gene for various neurodevelopmental disorders and is involved in cell migration, neurite outgrowth, and axon guidance. CDH13 is predominantly in parvalbumin and somatostatin interneurons. This indicates that CDH13 functions at the inhibitory synapse thus implying an involvement in neuronal network activity. A well-functioning neuronal network activity is controlled by interaction between a certain excitation (E) and inhibition (I) ration via balanced synaptic communication between the glutamatergic and GABAergic neurons. Since it is known that the disruption of the E/I balance is present in many neurodevelopmental disorders, impact on the E/I balance by CDH13 particularly in the modulation of inhibitory synaptic activity is possible. The aim is to investigate CDH13's role in the E/I balance by using induced pluripotent stem cell (iPSC) lines.
We are using iPSCs from healthy individuals carrying a GG, AA and AG genotype in the SNP rs2199430 and we generated a $CDH13^{+/-}$and a $CDH13^{-/-}$cell line using CRISPR/Cas9. The CRISPRed lines and the unmodified iPSCs are then differentiated into three neuronal subtypes: serotonergic, glutamatergic, and GABAergic neurons. These subtypes are generated by using a small-molecule a or a transcription-based reprogramming differentiation approach.CDH13 levels will be compared I) between neuronal subtypes derived from the same iPSC line and II) between neuronal subtypes derived from different iPSC cell lines and finally III) in the co-cultures experiments. Since previous studies have shown that CDH13 is an inhibitor of neurite outgrowth, we would like to investigate this in our cell line as we expect that the

$CDH13^{-/-}$ and $CDH13^{+/-}$ will enhance neurite outgrowth. This will be assessed using microfluidics devices and a neurite outgrowth assay (Thermofisher).To explore the neuronal network activity, experiments using the microelectrode array (MEA) will be done. For this reason, the glutamatergic and GABAergic neurons will be co-cultured to mimic the E /I imbalance: the aim is to co-culture different combinations of GABAergic and glutamatergic neurons derived from the different CDH13 genotype iPSCs.This would allow us to comprehend if the different genotypes affect the neuronal activity in distinctive ways. In conclusion, CDH13's role in the E/I balance and its cellular mechanism is far from being understood. Using different CDH13 SNP variants and the isogenic iPSC lines with a gene dose-dependent deficiency of CDH13 will facilitate investigation of CDH13's mechanism and elucidate the role of CDH13 in the etiopathogenesis of a wide spectrum of neurodevelopmental and psychiatric disorders.

Disclosures: M. Vitale: None. **J. Zöller:** None. **K. Lesch:** None.

Poster

P070. Development of Sensory Systems I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P070.01

Topic: A.07. Developmental Disorders

Support: Student Blugold Commitment Differential Tuition funds through the University of Wisconsin-Eau Claire Office of Research Sponsored Programs

Title: Methylene chloride alters morphological development in zebrafish larvae

Authors: *C. OWENS, S. GAREY, A. EASKER, N. TITERA, B. CARTER;
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Abstract: Methylene chloride is a volatile organic compound commonly used as a solvent in paints, in the production of pharmaceuticals, and as an extraction solvent in the food industry. In epidemiological studies, environmental exposure to methylene chloride has been associated with increased Autism Spectrum Disorder (ASD) prevalence. How this chemical impacts brain formation and general embryonic development is not known. Our objectives were to (1) determine how methylene chloride can affect development in zebrafish using dose-dependent titrations and (2) identify phenotype-concentration thresholds in zebrafish larvae for morphological and behavioral analyses. In these experiments, methylene chloride was emulsified with ethanol into embryo solution. Unsexed zebrafish larvae were treated with methylene chloride at 10 hours post-fertilization (hpf) with concentrations from 0 to 500 parts per million (ppm). Larvae were imaged using brightfield microscopy between 24hpf and 120hpf for several morphological features: mortality, length, spinal curvature, eye size, cardiac edema, yolk edema, head edema. DanioScope software (Noldus) was used to quantify these features. R studio was used for performing ANOVA and post hoc testing for significant differences between means. Methylene chloride treatment resulted in dose-dependent morphological changes in zebrafish embryos across the time course of observation; the lowest observable adverse effect level (LOAEL) was measured to be 200ppm. Long-term, characterizing the impact of methylene chloride on brain development may contribute to improvement of understanding ASD and inform data-driven environmental regulations.

Disclosures: C. Owens: None. **S. Garey:** None. **A. Easker:** None. **N. Titera:** None. **B. Carter:** None.

Poster

P070. Development of Sensory Systems I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P070.02

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 DC016413
NIH Grant EYE030623
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Sloan Research Fellowship
Leon Levy Foundation
an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness
Research to Prevent Blindness Career Development Award

Title: The organization of the gravity-sensing system in zebrafish

Authors: *Z. LIU[1], D. G. C. HILDEBRAND[3], J. L. MORGAN[2], N. SLIMMON[1], M. W. BAGNALL[1]; [1]Neurosci., [2]Ophthalmology, Washington Univ. in St. Louis, Saint Louis, MO; [3]Lab. of Neural Systems, The Rockefeller Univ., New York, NY

Abstract: Motor circuits develop in sequence from those governing fast movements to those governing slow. Here we examine whether upstream sensory circuits are organized by similar principles. Using serial-section electron microscopy in larval zebrafish, we generated a complete map of the gravity-sensing (utricular) system from the inner ear to the brainstem. We find that both sensory tuning and developmental sequence are organizing principles of vestibular topography. Patterned rostrocaudal innervation from hair cells to afferents creates a directional tuning map in the utricular ganglion, forming segregated pathways for rostral and caudal tilt. Furthermore, the mediolateral axis of the ganglion is linked to both developmental sequence and temporal kinetics. Early-born pathways carrying phasic information preferentially excite fast escape circuits, whereas later-born pathways carrying tonic signals excite slower postural and oculomotor circuits. These results demonstrate that vestibular circuits are organized by tuning direction and kinetics, aligning them with downstream motor circuits and behaviors.

Disclosures: Z. Liu: None. **D.G.C. Hildebrand:** None. **J.L. Morgan:** None. **N. Slimmon:** None. **M.W. Bagnall:** None.

Poster

P070. Development of Sensory Systems I

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Program #/Poster #: P070.03

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH grant R01GM098026

Title: Elucidating the role of PAX-6 transcription factor in C. elegans neuronal asymmetry

Authors: *A. KELLY, R. XIONG, Y.-W. HSIEH, C.-F. CHUANG;
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Abstract: Brain asymmetry has been observed in many organisms including humans at multiple levels such as molecular and functional. Reduced or reversed brain asymmetry is associated with specific neurological disorders and diseases like dyslexia and autism. Understanding the molecular mechanisms underlying brain asymmetry will provide insight in the development of strategy for treating associated neurological disorders. However, investigating brain asymmetry directly in humans is difficult. Thus model organisms like the nematode *C. elegans* provide the opportunity to study a system that has functionally similar mechanisms to our own. This study focuses on investigating the role of an ortholog of human PAX6 transcription factor in asymmetric development of one olfactory neuron pair in *C. elegans*. This neuron pair further undergoes differentiation into two subtypes that each enables the *C. elegans* nematode to sense different chemicals in their environment. To dissect the structure and function relationship of the PAX-6 protein in neuronal asymmetry, we crossed fluorescent markers of this neuron pair into various *C. elegans* mutants of the human PAX6 ortholog and analyzed neuronal asymmetry phenotypes using fluorescence microscopy techniques. Our results suggest that the PAX6 ortholog is required for the asymmetrical development of the olfactory neuron pair. Additionally, the neuronal asymmetry phenotype in *pax-6* mutants correlates with defects in axon connection that is essential for the specification of normal neuronal asymmetry. Since PAX6 plays a major role in the development of the human eye, central nervous system, and pancreas, an important prospect of this project is that it could provide insight to diseases and disorders that occur in some of these structures.

Disclosures: A. Kelly: None. **R. Xiong:** None. **Y. Hsieh:** None. **C. Chuang:** None.

Poster

P070. Development of Sensory Systems I

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Program #/Poster #: P070.04

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: P. Sloan Research Fellowship
Whitehall Foundation Research Award
NIH R01

Title: Cellular and molecular mechanisms of mok-1 function in left-right neuronal asymmetry

Authors: *R. XIONG[1], X. WANG[2], C.-F. CHUANG[1];
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Abstract: The developing nervous system generates a large diversity of cell types with distinct patterns of gene expression and functions. One way to establish neuronal diversity is to specify neuronal subtypes across the left-right axis. The *C. elegans* left and right AWC olfactory neurons communicate to specify asymmetric subtypes, AWC^{OFF} and AWC^{ON}. The default AWC^{OFF} is specified by a Ca^{2+}-regulated kinase cascade that is activated by influx of Ca^{2+} through the voltage-gated Ca^{2+} channel UNC-2/UNC-36. Intercellular communication between the two AWC neurons and other neurons through the NSY-5/innexin gap junction network antagonizes *unc-2/unc-36* Ca^{2+} signaling in the induced AWC^{ON} cell. Our recent data suggest that voltage- and calcium-activated SLO BK potassium channels *slo-1* and *slo-2* acts redundantly downstream of *nsy-5* to inhibit *unc-2/unc-36* Ca^{2+} signaling in the specification of AWC^{ON}. To identify the genes required for *slo-1* function in inhibiting *unc-2/unc-36* Ca^{2+} signaling for promoting AWC^{ON}, we performed a non-biased forward genetic screen to isolate *mok* (modifier of K^+ channel) mutants that suppress the *slo-1(gf)* $2AWC^{ON}$ phenotype. *mok-1*(*vy11)* is one of the mutants identified from this screen. The $2AWC^{OFF}$ phenotype of *mok-1*(*vy11)* mutants is suppressed by loss-of-function mutations in the Ca^{2+} channel gene *unc-36*, suggesting that *mok-1* acts upstream of the *unc-2/unc-36* Ca^{2+} signaling pathway. Together, our results suggest a model in which *nsy-5* inhibits *unc-2/unc-36* Ca^{2+} signaling through *slo-1* and *mok-1*. We identified the mutation responsible for the *vy11* phenotype using whole genome sequencing with the help of Alex Boyanov in the Oliver Hobert lab. Further genetic analysis and behavior analysis of the *vy11* mutant, as well as molecular characterization of *mok-1* will be presented in the meeting.

Disclosures: R. Xiong: None. **X. Wang:** None. **C. Chuang:** None.

Poster

P070. Development of Sensory Systems I

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Program #/Poster #: P070.05

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NSF CBET-1747506
NSF IOS-1921065
NIH R01NS118562

Title: Competition and refinement in a developing sensorimotor circuit

Authors: *B. MCFARLAND[1], H. JANG[1], Y. KURMANGALIYEV[2], T. A. GODENSCHWEGE[3], A. NERN[4], C. R. VON REYN[1,5];
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Abstract: Sensorimotor neurons may receive inputs from multiple sensory neuron cell types that have to be integrated across space and time and transformed into an appropriate behavioral response. Many factors influence the output of sensorimotor neurons including the number of pre-synaptic partners, the location and density of synapses, and underlying intrinsic properties. Few sensorimotor circuits, however, have been fully characterized across development. Understanding how wiring and intrinsic properties develop is important in understanding sensorimotor circuit function and is also clinically relevant as miswired sensorimotor circuits are thought to underlie multiple neurodevelopmental disorders. Here, we investigate developmental wiring and intrinsic properties in a well-established sensorimotor escape circuit (the Giant Fiber circuit) in *Drosophila melanogaster*. We first investigate the timecourse of circuit formation focusing on visual projection neurons (VPNs) as they compete for space on the dendrites of a shared post-synaptic partner, the Giant Fiber (GF). We find one VPN, LC4, first makes contact at a proximal location on GF approximately 24 hours puparium formation (hAPF). A second VPN, LPLC2, contacts distal GF dendrites approximately 24 hours later. This segregation is maintained across development. We also find that during this partner matching period, a third VPN, LPLC1, contacts GF during development but does not maintain connections into adulthood. Next, using RNA-sequencing data generated for all three VPNs across development, we investigate the timecourse of synaptic and ion channel genes that determine intrinsic properties. We find that many synaptic genes and ion channels are upregulated by 60hAPF, a time when contacts between GF and all VPNs peak. Finally, we investigate how the early loss of LC4 leads to anatomical and functional compensation in the GF circuit. We find that early expression of Kir2.1, an inward-rectifying potassium channel, results in ablation of the majority of LC4 input. We perform whole-cell current-clamp electrophysiology on head-fixed adult flies while presenting visual stimuli known to elicit escape behaviors through the GF circuit, a looming stimulus mimicking an object approaching on a direct collision course. Surprisingly, following LC4 ablation, we find that GF output is different from previous data showing GF output when LC4 is still present but silenced, suggesting LC4 ablation causes circuit level changes that effect output function. Overall, our data suggests inputs to the GF circuit are segregated, and that the circuit adapts to developmental perturbation to preserve function.

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Poster

P070. Development of Sensory Systems I

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Program #/Poster #: P070.06

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: 1R15DC016407-01A1

Title: EphrinAs and EphAs are expressed in lingual epithelium and repel gustatory and somatosensory neurites

Authors: M. AKSU[1], A. J. GEORGE[1], K. H. DOSHI[2], D. CHO[3], M. RUSSO[4], J. HWANG[5], R. W. TREFFY[6], J. WONG[1], A. JENNINGS[1], M. K. L. PILON[7], *M. ROCHLIN[1];

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Abstract: Ephs and ephrins are cell surface proteins that act as ligands and receptors for one another, initiating signaling cascades that can cause repulsion, arborization, or growth promotion of axons. EphrinAs are lipid-linked and interact primarily with EphAs, whereas ephrinBs are transmembrane and interact primarily with EphBs. In embryonic day 14.5 (E14.5) mouse tongue, when gustatory afferents have just entered fungiform papillae (FP) epithelium, *in situ* hybridization and immunostaining revealed that ephrinA1, A3, A4, and A5 are broadly distributed in the dorsal epithelium and present at a higher level than observed in the mesenchyme. The FP epithelium and the papilla core tissue traversed by afferents exhibited lower levels of ephrinAs than surrounding epithelium. At E16.5, ephrinA mRNA levels are higher throughout the dorsal lingual epithelium compared to E14.5, and more clearly excluded from the nerve path within papillae. A variety of EphAs are also expressed in the epithelium at these stages. In E14.5 geniculate ganglia, EphA/ephrinA expression varies in intensity and localization, with some restricted to Phox2B-positive (oral sensory, mostly gustatory) neurons and others restricted to Prrxl1-positive neurons (aural somatosensory) neurons. Rat geniculate and trigeminal neurites are repelled dose-dependently by stripes of ephrinA-Fc as well as EphA-Fc fusion proteins in vitro, demonstrating that both forward signaling (via axonal EphAs) and reverse signaling (via axonal ephrinAs) can occur. We are examining Phox2b-Cre::tdTomato mice to determine if triple knockout mice lacking ephrinA1, A3, and A4 exhibit aberrant innervation within lingual FP. Our data also raise the possibilities that reverse signaling guides geniculate axons, and that Eph/ephrin signaling among dorsal lingual epithelial cells contributes to their organization.

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Poster

P070. Development of Sensory Systems I

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Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant R37-HD081168 (to M.S.B.)
Sloan Scholarship (to L.J.G.)

Title: Thalamic contributions to sensory processing in developing somatosensory and motor cortex

Authors: *L. J. GÓMEZ[1], J. C. DOOLEY[2], G. SOKOLOFF[4], M. S. BLUMBERG[3];
[2]Dept. of Psychological and Brain Sci., [3]Dept Psychol, [1]Univ. of Iowa, Iowa City, IA; [4]Psychological and Brain Sci., The Univ. of Iowa, Iowa City, IA

Abstract: Primary somatosensory (S1) and motor (M1) cortex interdependently process sensory input throughout life. Previous studies of sensory processing in adult animals have indicated that M1 relies on

S1 for sensory input; however, in developing animals this is not always the case. Specifically, we recently demonstrated in postnatal day (P)12 rats that S1 and M1 process sensory inputs differently depending on submodality: Whereas tactile inputs are conveyed to M1 via S1 (congruent with the classical model), S1 and M1 receive proprioceptive input in parallel from an unknown common source. Parallel proprioceptive input to S1 and M1 is likely important for shaping somatotopy and connectivity within and between them; thus, establishing the source of this input will better inform our understanding of their development. To determine the structures that convey proprioceptive input to cortex, we first performed retrograde tracing from the forelimb representation of S1 and M1 at P12 using wheat germ agglutinin. We found that both the ventral posterolateral (VPL) and posterior medial (POm) thalamic nuclei project to S1 and M1 at this age; we did not detect projections to both S1 and M1 from any other thalamic or extra-thalamic structure, suggesting that VPL and/or POm are the best candidate sources of proprioceptive input. To assess their contributions to proprioceptive processing in S1 and M1, we are recording extracellular activity in S1 and M1 at P12 in response to proprioceptive stimuli. Following a baseline period of recording, we pharmacologically inactivate VPL or POm and measure changes in proprioceptive responses in S1 and M1. We also test the possibility that both VPL and POm convey proprioceptive inputs to cortex by inactivating the two structures simultaneously. By delineating the pathways through which S1 and M1 receive parallel sensory input in early development, these experiments will help clarify how sensory input contributes to their functional development.

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Poster

P070. Development of Sensory Systems I

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Program #/Poster #: P070.08

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH DC 013791
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NIH DC 012441

Title: Neurogenesis and fate of olfactory bulb granule cells

Authors: *T. LIBERIA, K. HAN, C. A. GREER;
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Abstract: In most regions of the mammalian CNS neurogenesis occurs embryonically and decreases quickly after birth. However, neurogenesis of granule cells (GCs) targeted to the olfactory bulb (OB), the largest population of interneurons in the OB, begins embryonically but continues robustly throughout life. GCs constitute a heterogeneous population based on timing of neurogenesis, location of their somata in the granule cell layer (GCL), regionalization of their progenitors, morphological variability and differential gene expression, among other characteristics. The apical dendrites of GCs establish reciprocal dendrodendritic synapses with lateral dendrites of mitral/tufted cells (MC/TC) in the external plexiform layer (EPL). Interestingly, the distribution of GC somas in the GCL may play a role in establishing these

local circuits in the EPL. It has been suggested that superficial GCs preferentially contact TC dendrites in the superficial EPL, while GCs localized to deeper laminae within the GCL establish synapses predominately with MC dendrites. As shown previously, the timing of neurogenesis is a key determinant of the location of GC somata in the GCL. GCs generated postnatally are preferentially incorporated into the deeper regions of the GCL, while those born embryonically are integrated into superficial portions of the GCL. Despite the importance of timing, the precise organization of GCs generated at specific time points is not fully understood. Similarly, their integration into EPL synaptic circuits depending on the timing of neurogenesis is uncertain. We have used CD1 mice (males & females) to address these questions. First, we inject BrdU i.p. to specifically label GCs born at embryonic day (E)17, postnatal day (P)0, P7, P21, P55, P175 and analyze their distribution within the GCL. Second, we study the integration of new GCs into the circuitry by electroporating GC progenitor cells at P0 with pUbC-tdTomato to specifically label future GCs, and immunohistochemistry to analyze the temporal expression of synaptic markers in those labeled GCs. Our results demonstrate that GC somata have different distribution patterns depending on their birthdate, but they do not differ between sexes. Interestingly, this applies not only when we compare embryonic with postnatal stages, but when we compare among postnatal timepoints. Our results thus far show that the heterogeneous organization of GCs persists throughout their neurogenesis in both embryonic and postnatal periods. Currently we are digging deeper into how sublaminar location in the GCL and timing of neurogenesis may be reflected in the expression of synaptic markers at the dendrodendritic synapses.

Disclosures: T. Liberia: None. **K. Han:** None. **C.A. Greer:** None.

Poster

P070. Development of Sensory Systems I

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Topic: A.08. Development of Motor, Sensory, and Limbic Systems

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Title: Experience-dependent actin organization specifies dendritic properties in cortical interneurons

Authors: *X. HOU[1], M. MORISHIMA[2], J. SUGI[1], K. SAKIMURA[3], Y. KAWAGUCHI[2,4], S. SUGIYAMA[1];
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Abstract: The cell-type specific properties and connectivity of inhibitory neurons underlie their ability to spatiotemporally shape information processing. Despite much progress in parsing information on interneuron diversity, the mechanisms of differentiation have not been elucidated. We demonstrated the first determinants that specified dendritic properties via experience-dependent actin organization. Cell-type specific expression and membrane-associated distribution of actin-binding proteins allowed interneurons to select their unique dendritic morphologies from a variety of multipolar and bipolar shapes. Morphological transdifferentiation in the juvenile visual cortex affected physiological properties, and hence cortical function and plasticity, to enable visual acuity.Therefore, actin organization activated by individual experience modified dendritic morphology and increased the heterogeneity of intracortical circuits to enable functional individuality.

Disclosures: X. Hou: None. **M. Morishima:** None. **J. Sugi:** None. **K. Sakimura:** None. **Y. Kawaguchi:** None. **S. Sugiyama:** None.

Poster

P091. Metabotropic Receptors: Cellular Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P091.01

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01MH104641

Title: Oxytocin excites pyramidal neurons of the rat ventral subiculum

Authors: *J. R. HOWARD, S. W. HARDEN, C. J. FRAZIER;
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Abstract: Central oxytocin receptors (OTRs) are involved in the regulation of fear, anxiety, and advanced social behaviors, but much remains unknown about the neurons that express OTRs, the effects of OTR activation at a cellular level, or the extent to which these vary at different stages of development. The ventral subiculum (vSB), a primary output center of the hippocampus, plays an important role in fear association, and is known to express OTRs with high density in both rodents and humans. This study uses whole-cell patch clamp recordings from acute brain slices of Sprague Dawley rats (p16-p40) to characterize the electrophysiological effects of OTR activation in vSB pyramidal neurons. Glutamate and GABA receptor antagonists were continuously applied to reduce influence of synaptic inputs. Voltage-clamp experiments performed at -60 mV demonstrated that acute exposure to a low concentration of selective OTR agonist [Thr4,Gly7]-oxytocin (TGOT, 10 nM) produces an excitatory shift in holding current which is prevented by exposure to selective OTR antagonist (L-368, 1 μM). We found the excitatory effect of OTR activation was significantly greater in juveniles (p16-p27) than adults (p28-p40). When pyramidal neurons were categorized as burst firing (BF) or regular spiking (RS), the excitatory effects of TGOT were found to be the same between both types of neurons in juvenile rats but greater in BF neurons of adult rats. Current-clamp experiments in juvenile rats demonstrate that OTR activation by 10 nM TGOT raises resting membrane potential and increases spontaneous firing rate. Using current-clamp ramps to investigate action potential dynamics we found that OTR activation significantly

decreased action potential rheobase (without affecting threshold) and reduced peak amplitude. Together these findings demonstrate that low concentrations of OTR agonists can robustly excite vSB neurons in an age and cell-type dependent manner.

Disclosures: J.R. Howard: None. **S.W. Harden:** None. **C.J. Frazier:** None.

Poster

P091. Metabotropic Receptors: Cellular Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P091.02

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01MH118258

Title: Cellular and molecular mechanisms of NK3 receptor-mediated excitation of basolateral amygdala neurons

Authors: *S. LEI, B. HU;
Univ. of North Dakota, Grand Forks, ND

Abstract: The tachykinins refer to two peptides encoded in rodents by the Tachykinin 1 (Tac1) and Tac2 (TAC3 in humans) genes, which are involved in neurotransmission and neuromodulation in the central nervous system. Tac1 encodes a precursor protein that produces two peptides, substance P (SP) and neurokinin A (NKA), whereas Tac2/TAC3 encodes neurokinin B (NKB). SP, NKA and NKB bind to three G-protein-coupled receptor subtypes, NK1, NK2, and NK3, respectively. NKB is an endogenous high-affinity agonist for NK3 receptors, which couple to $G\alpha_{q/11}$ to activate PLCβ, resulting in the production of IP_3 to facilitate intracellular Ca^{2+} release and diacylglycerol to activate PKC. While high density of NK3 receptors was distributed in the basolateral nucleus of amygdala (BLA), the effects and involved mechanisms of NK3 receptor activation have not been determined. Here, we used the in vitro slice recording techniques and found that activation of NK3 receptors by application of the selective NK3 agonist, senktide, increased the excitability of BLA principal neurons in rat amygdala slices. NK3 receptors excited BLA neurons by activating a cation channel and depressing an inwardly rectifying K^+ (Kir) channels. Further pharmacological experiments indicated that G protein-gated inwardly rectifying K^+ (GIRK) channels were involved in NK3 receptor-induced excitation of BLA neurons. NK3 receptor-mediated excitation of BLA neurons required the function of PLCβ, but was independent of intracellular Ca^{2+} release and PKC activity. PLCβ-elicited depletion of PIP_2 was required for NK3-induced excitation of BLA neurons. Our results may provide one of the cellular and molecular mechanisms to explain the physiological functions of tachykinins in the amygdala.

Disclosures: S. Lei: None. **B. Hu:** None.

Poster

P091. Metabotropic Receptors: Cellular Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P091.03

Topic: B.03. G-Protein Coupled Receptors

Support: RO1 MH118258

Title: Neuromedin B excites neurons of the lateral nucleus of the central amygdala by a PLCß and PKC-dependent inhibition of inwardly rectifying K^+ channels

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Abstract: Neuromedin B (NMB) is a mammalian orthologue of the bombesin family of neuropeptides first isolated from the porcine spinal cord. NMB is a neuroendocrine modulator that activates the hypothalamic-pituitary axis and modulates stress, fear, and anxiety-like behaviors. In the mammalian brain, the amygdala is composed of a collection of nuclei that are critically involved in these behaviors with its central division considered the behaviorally relevant output nuclei. NMB activates G-protein coupled receptors in the central division of the amygdala and leads to the activation of phospholipase Cβ (PLCβ) that generates the secondary messengers inositol trisphosphate (IP3) and diacylglycerol (DAG). The release of IP3 and DAG leads to an increase in intracellular calcium and the activation of protein kinase C (PKC), respectively. However, it remains unknown how activation of NMB-induced intracellular signaling regulates neuronal activity in the central amygdala. Here we show using *in vitro* whole-cell patch-clamp techniques that NMB increased neuronal activity in the lateral subdivision of the central amygdala. NMB induces significant potentiation of action potential firing that was dependent upon functional G-proteins, PLCβ, and PKC. NMB depolarized resting membrane potentials that were specific to the NMB receptor as well as elevated membrane time constants. Current-voltage traces before and after the treatment with NMB support the involvement of inwardly rectifying potassium channels, likely GIRK2/3. The activity of G-proteins, PLCβ, and PKC were required for the inhibition of the GIRK2/3 channels. These results suggest that NMB can modulate neuronal activity in the central amygdala, which may explain NMB involvement in fear and anxiety related disorders.

Disclosures: C. Boyle: None. **S. Lei:** None.

Poster

P091. Metabotropic Receptors: Cellular Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P091.04

Topic: B.03. G-Protein Coupled Receptors

Title: Group II and III metabotropic glutamate receptors regulate long-term potentiation via the Gβγ-SNARE pathway

Authors: *Z. ZURAWSKI[1], S. HUYNH[1], M. POTCOAVA[1], C. DELBOVE[3], H. HAMM[4], S. T. ALFORD[2];
[2]Dept. of Anat. and Cell Biol., [1]Univ. of Illinois at Chicago, Chicago, IL; [3]Neurobio., Univ. of Chicago, Chicago, IL; [4]Pharmacol., Vanderbilt Univ., Nashville, TN

Abstract: Long term potentiation (LTP) is a form of synaptic plasticity that represents a critical step in learning and memory. Following LTP induction, the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors (AMPARs) located postsynaptically in synapses and which mediate synaptic transmission is increased. The higher the density of AMPARs, the greater the excitatory postsynaptic current (EPSC) underlying the synaptic response. Thus, the insertion of AMPARs into the postsynaptic membrane is necessary for maintaining LTP. AMPA receptor insertion is mediated through the fusion of trafficking vesicles with the postsynaptic plasma membrane, a type of exocytosis. The exocytosis of AMPARs is facilitated by SNARE protein complexes consisting of proteins such as SNAP-25. Gβγ, as liberated by Gi/o-coupled G-protein coupled receptors (GPCRs), such as Group II metabotropic glutamate receptors (mGluRs) can inhibit exocytosis through binding to SNAREs such as SNAP25, competing with fusogenic calcium sensors. These interactions have mainly been studied presynaptically. The effect of Gβγ on the exocytosis and insertion of AMPARs into the postsynaptic membrane is unknown. To test whether Gβγ can regulate and more specifically inhibit the exocytosis of AMPAR bearing vesicles, a combination of extracellular field recording and whole cell recording of mice hippocampus slices was used. By comparing the effects of LTP on wild type mice vs SNAP-25Δ3 mice, whose mutant SNAP-25 protein is unable to bind Gβγ, we can test whether Gβγ can regulate the exocytosis of AMPAR bearing vesicles through binding to the SNAP-25 t-SNARE complex. From extracellular field recordings, we show that the use of a group II mGluR agonist can inhibit LTP in wild type but not SNAP-25Δ3 mice. From whole cell recording, we show that LTP is able to increase the amplitude of post LTP mini EPSCs while having no effect in wild type mice. Previously, SNAP-25, syntaxin1A, syntaxin3, syntaxin4, and VAMP2 have been shown to be implicated in the process of exocytosis of AMPAR bearing vesicles. In vitro functional studies show that Gβγ can inhibit synaptotagmin and SNARE-dependent lipid mixing in reconstituted systems containing SNAP25, syntaxin1A, and syntaxin3, but not syntaxin4. Thus, we show that Gβγ from Group II mGluRs can inhibit the insertion of AMPA receptor-bearing vesicles with the postsynaptic plasma membrane by binding to a SNARE complex containing SNAP-25.

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Poster

P091. Metabotropic Receptors: Cellular Modulation

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P091.05

Topic: B.03. G-Protein Coupled Receptors

Title: Noradrenaline-dependent regulation of serotonin and non-serotonin neurons in the dorsal raphe

Authors: *J. KHAMMA[1], D. COPELAND[1], H. HAKE[2], S. GANTZ[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Univ. of Washington, Seattle, WA

Abstract: Serotonin neurons are implicated in a variety behavioral processes, such as alertness and mood regulation. The dorsal raphe is the primary location of serotonin neurons in the brain, and it receives noradrenergic input that is excitatory via activation of Gαq protein-coupled alpha 1-adrenergic receptors ($\alpha1\text{-}A_R$). However, it is unclear if the excitatory effects of noradrenaline are present in both serotonin and non-serotonin dorsal raphe neurons. In the present study, we assayed the presence of $\alpha1\text{-}A_R$ in serotonin and non-serotonin dorsal raphe neurons using fluorescent *in situ* hybridization (RNAscope), tryptophan hydroxylase (TpH) immunostaining, and whole-cell patch-clamp recordings in dorsal raphe brain slices from adult male and female C57bl/6j mice. In neuronal populations containing serotonin reuptake transporter (SERT) and vesicular GABA transporter (vGAT) mRNA, to identify serotonin and GABA neurons respectively, we assayed mRNA levels for two $\alpha1\text{-}A_R$ isoforms: $\alpha1a\text{-}A_R$ and $\alpha1b\text{-}A_R$. The majority of serotonin (97%) and GABA (85%) neurons contained at least one of the two $\alpha1\text{-}A_R$ isoforms, and many had both. Of the neurons that had a single isoform, serotonin neurons predominately expressed $\alpha1b\text{-}A_R$ while GABA neurons expressed $\alpha1a\text{-}A_R$, suggesting serotonin and GABA neurons are biased towards a specific $\alpha1\text{-}A_R$ isoform. Additionally, we assayed mRNA levels for the ion channel responsible the $\alpha1\text{-}A_R$-dependent synaptic current, glutamate delta 1 receptor ($GluD1_R$). $GluD1_R$ mRNA levels were comparable between serotonin and GABA neurons, suggesting both neuron populations have the ion channel to produce the $\alpha1\text{-}A_R$-dependent synaptic current. To confirm if both neuronal populations had an $\alpha1\text{-}A_R$-dependent synaptic current, whole-cell patch-clamp recordings were made using an internal solution containing biotin. Brain slices were fixed in 4% paraformaldehyde for 1 hour at room temperature prior to immunostaining. Most neurons immunostained for TpH (TpH+, 72%) while 28% neurons were TpH-. Electrical stimulation of the brain slice evoked an $\alpha1\text{-}A_R$-dependent synaptic current in nearly all recorded TpH+ neurons (96%). In contrast, the $\alpha1\text{-}A_R$-dependent synaptic current was not observed in TpH- neurons (0%). Thus, activation of $\alpha1\text{-}A_R$ by synaptically released noradrenaline may be a distinct characteristic of serotonin neurons. Taken together, the data provide evidence that serotonin and GABA dorsal raphe neurons are differentially regulated by noradrenaline, which may consequently affect how these population of neurons respond to anxiogenic or threatening stimuli.

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Poster

P091. Metabotropic Receptors: Cellular Modulation

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Program #/Poster #: P091.06

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01NS102306

Title: Subcellular localization of alpha1-adrenergic receptors in the locus coeruleus

Authors: Z. LUYO[1], *D. A. MITRANO[2];
[1]Program in Neurosci., [2]Mol. Biol. and Chemistry; Program in Neurosci., Christopher Newport Univ., Newport News, VA

Abstract: The locus coeruleus (LC) is the major source for norepinephrine (NE) in the brain. The LC projects to areas involved in learning and memory, reward, arousal, attention, and autonomic functions related to stress. There are three types of adrenergic receptors that respond to NE, alpha1-, alpha2-, and beta-adrenergic receptors. Previous works has shown that the alpha1-adrenergic receptor (AR) to be present in the LC, however, with some confounding functional studies. For example, it was shown that alpha1-ARs in the LC are involved in some of the motivational effects of stimulation of the medial forebrain bundle, which was reduced by injection of the alpha1-AR antagonist terazosin (Lin et al., 2007). Another study showed that during novelty-induced behavioral activation, the alpha1-AR antagonist prazosin reduced c-fos expression in brain regions known to contain motoric alpha1-ARs, except for the LC, where c-fos expression was enhanced (Stone et al., 2006). Despite new research delineating more specific connectivity of the neurons in the LC, and some roles of the adrenergic receptors, the alpha1-ARs have not been localized at the subcellular level in the LC. Therefore, in order to try and gain a greater understanding of the behavioral pharmacological studies, we used immunohistochemistry at the electron microscopic (EM) level to determine more specifically what types of cells contain the alpha1-AR in the LC and when in neurons, what neuronal elements contain the receptor. We hypothesized, based on previous work in the nearby ventral periaqueductal gray area (Porter-Stransky et al., 2019), that the alpha1-AR would be found mainly presynaptically in axon terminals, and possibly glial elements. Single labeling immunohistochemistry at the EM revealed that about 38% of labeled elements that contained the alpha1-AR were glial elements, while approximately 50% of the labeled elements were axon terminals or small unmyelinated axons in the LC. Currently, we are using double labeling immunohistochemistry at the EM level to determine whether the alpha1-ARs are found in astrocytes or other types of glial elements, and further, the neurochemical identity of the axon terminals the receptors are found on. This neuroanatomical study will hopefully shed light on how the alpha1-ARs are modulating activity of the LC.

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Poster

P091. Metabotropic Receptors: Cellular Modulation

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Topic: B.03. G-Protein Coupled Receptors

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Title: Cb_1-receptor contributes to anandamide inhibition of voltage gated sodium channels in neocortical neurons

Authors: *L. J. STEIGER[1], G. B. MATTHEISEN[3], S. M. SMITH[2];
[2]Pulmonary and Critical Care Med., [1]VA Portland Healthcare Syst. and Oregon Hlth. &, Portland, OR;
[3]PCCM, OHSU, Portland, OR

Abstract: Voltage-gated sodium channels (VGSCs) generate action potentials and are therefore essential for inter- and intracellular communication in excitable cells. VGSC function is regulated by endogenous molecules indicating their modulation is of physiological importance. Additionally, VGSC current inhibition is a mechanism for a wide range of effective therapeutics. It has been proposed that endocannabinoids inhibit multiple VGSC isoforms through a direct mechanism independent of the major central cannabinoid receptor, CB_1. Here, in patch-clamped murine neocortical neurons expressing VGSC α-subunits Nav1.1, 1.2, 1.3 and 1.6, we present evidence that the endogenous cannabinoid, anandamide (AEA), inhibits VGSC currents indirectly via CB_1-receptor signaling. Inhibition by AEA was strong and ubiquitous, occurring in >99% of neurons tested (n > 200). AEA (10 μM) almost completely blocked VGSC currents in voltage-clamped recordings. In current clamp recordings, AEA decreased repetitive action potential firing in response to stepwise current injections. These effects were concentration dependent with a half maximal reduction in action potential firing occurring at 3.3 ± 0.5 μM (n = 7) AEA. Prior reports indicate that AEA-mediated inhibition of VGSC currents occurs independent of the canonical cannabinoid signaling pathways. However, AEA inhibition of sodium channels was strongly attenuated in neurons from CB_1-null mutant mice. CB_1 null-mutant neurons had significantly lower block after 1000 seconds of AEA application versus their wild-type sister cultures (32 ± 7%, n = 7 versus 91 ± 4%, n = 6, $P < 0.0001$). Like other indirect VGSC blockers, the time course of inhibition by AEA was well described by f(t) = a+(b*exp(-(x/tau)^2)) where t, T, and A & B, represent time, the time constant, and constants respectively. In the absence of a functional CB_1 receptor copy, T increased from 555 ± 94 s to 2245 ± 618 s ($P = .0008$). To further explore the role of G-protein coupled receptor signaling in this inhibitory pathway, we utilized GDPβS, which inhibits G-protein cycling. Whereas AEA (10 μM) inhibited VGSC current by 71 ± 7% (n = 8), measured 250 s after onset of application, inclusion of GDPβS (2 mM) in the recording pipette led to only 3 ± 3% inhibition (n = 6, $P < 0.0001$). Taken together, these results indicate that CB_1 is a major player in the mechanism by which AEA inhibits VGSC currents and that other GDPβS sensitive components also contribute. The role of CB_1 described here indicates that modulation of VGSCs should be considered as a potential mechanism underlying the AEA-mediated retrograde signaling that regulates synaptic plasticity.

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Poster

P091. Metabotropic Receptors: Cellular Modulation

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01NS105615
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Title: Chronic activation of Gp1 mGluRs leads to distinct refinement of neural network activity through non-canonical p53 and Akt signaling

Authors: *Y. YOOK[1], D.-C. LIU[2], S. SORIANO[2], S. LIZARAZO[1], D. E. EAGLEMAN[1], N.-P. TSAI[1,2];
[1]Mol. and Integrative Physiol., [2]Neurosci. program, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Group 1 metabotropic glutamate receptors (Gp1 mGluRs), including mGluR1 and mGluR5, are critical regulators for neuronal and synaptic plasticity. Dysregulated Gp1 mGluR signaling is observed with various neurological disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, and autism spectrum disorders. It is well established that acute activation of Gp1 mGluRs leads to elevation of neuronal intrinsic excitability and long-term synaptic depression. However, it remains unknown how chronic activation of Gp1 mGluRs can affect neural activity and what molecular mechanisms might be involved. In the current study, we employed a multielectrode array (MEA) recording system to evaluate neural network activity of primary mouse cortical neuron cultures. We demonstrated that chronic activation of Gp1 mGluRs leads to elevation of spontaneous spike frequency while burst activity and cross-electrode synchronization are maintained at the baseline. We further showed that these neural network properties are achieved through proteasomal degradation of Akt that is dependent on the tumor suppressor p53. Genetically knocking down p53 disrupts the elevation of spontaneous spike frequency and alters the burst activity and cross-electrode synchronization following chronic activation of Gp1 mGluRs. Importantly, these deficits can be restored by pharmacologically inhibiting Akt to mimic inactivation of Akt mediated by p53. Together, our findings reveal the effects of chronic activation of Gp1 mGluRs on neural network activity and identify a unique signaling pathway involving p53 and Akt for these effects. Our data can provide insights into constitutively active Gp1 mGluR signaling observed in many neurological and psychiatric disorders.

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Poster

P091. Metabotropic Receptors: Cellular Modulation

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Program #/Poster #: P091.09

Topic: B.03. G-Protein Coupled Receptors

Support: Grant-in-Aid for Young Scientists (B) 17K17239

Title: Lidocaine suppresses cell proliferation and induces apoptosis of myofibroblasts

Authors: *T. MATSUMURA, S. MAEDA;
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Abstract: Lidocaine inhibits nerve conduction as a sodium channel blocker, as well as suppressing proliferation and inducing apoptosis in fibroblasts. The induction of apoptosis by lidocaine is mediated by G-protein-linked receptors and involves the activity of cAMP and PKC. Myofibroblasts, a differentiated form of fibroblasts, produce extra-cellular matrix molecules (ECM) that regulate tissue strength and

resilience. However, imbalanced ECM secretion leads to tissue fibrosis. Although myofibroblasts serve an important role in wound healing and nerve regeneration after surgical procedures, the effects of lidocaine on myofibroblasts are not known. In the present study, we investigated the effect of lidocaine on cell proliferation and induction of apoptosis in myofibroblasts. Normal human dermal fibroblasts (NHDF, Promo Cell GmbH, Germany) were grown in culture, and stimulated with 5 ng/ml of TGF-β, which induced differentiation of dermal fibroblasts into myofibroblasts. The cell counting kit-8 (CCK-8) (#96992, Sigma) was used to investigate cell viability of fibroblasts and myofibroblasts after adding lidocaine (0.1 and 1 mg/ml). For detection of apoptosis, 24 h after seeding, cells were treated with lidocaine (at 0.001, 0.01 and 0.1 mg/ml) and, at three days post treatment, tested with the Apoptotic/ Necrotic/ Healthy Cells Detection Kit (#ab176749, abcam). Significant reduction in proliferation of fibroblasts and myofibroblasts was seen with 1 mg/ml lidocaine compared with untreated controls on day 3 ($p < 0.001$: Dunnett test). Apoptosis was detected in myofibroblasts as well as fibroblasts 3 days after administering 0.1 mg/ml lidocaine. We showed that lidocaine also suppresses cell proliferation and induces apoptosis of myofibroblasts. Further studies are needed to confirm which biochemical pathways in myofibroblast apoptosis were modulated by lidocaine. Conclusively, lidocaine might be a therapeutic agent for wound repair and reinnervation after surgery through the utilization of physiochemically tuned myofibroblasts.

Disclosures: T. Matsumura: None. **S. Maeda:** None.

Poster

P091. Metabotropic Receptors: Cellular Modulation

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Program #/Poster #: P091.10

Topic: E.04. Voluntary Movements

Support: University of Texas at Dallas

Title: Local antagonism of α2 adrenergic receptors in the primary motor cortex blocks vagus nerve stimulation induced motor map plasticity.

Authors: *C.-T. TSENG[1], C. A. THORN[2];
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Abstract: Vagus nerve stimulation (VNS) paired with rehabilitation training has been shown to promote the recovery of motor function following stroke. Recent studies have shown that VNS enhanced recovery of motor function following stroke relies on VNS facilitated reorganization of the somatotopic cortical motor map. In addition, noradrenergic innervation in the primary motor cortex (M1) has been shown to be critical for this form of VNS-driven neural plasticity to occur. However, the mechanisms underlying noradrenergic regulation of VNS-dependent cortical plasticity remain unclear. In M1, noradrenergic α2 receptors (α2-ARs) are widely expressed and are known to play a role in synaptic communication and plasticity. In this study, we examined whether local activation of α2-ARs in rat M1 is required for VNS-induced motor map plasticity. Twenty-nine female Sprague-Dawley rats, 10-12 weeks old at the start of

behavioral training, were trained to perform a lever pressing task with their right forelimb. Once criterial performance was reached, rats were implanted with VNS electrodes around the left cervical vagus nerve along with intracortical cannula targeted to the M1 forelimb area contralateral to the trained limb. After surgical and behavioral recovery, subjects were randomly assigned to a treatment group and received a final ten training sessions in which intracortical infusions of either α2-AR antagonists (yohimbine or RS79948) or control vehicle were administered, and VNS or sham stimulation was paired with correct lever press performance (veh|sham: n = 7; veh|VNS: n = 6; drug|sham: n = 6; drug|VNS: n = 10). Twenty-four hours after the final treatment session, intracortical microstimulation was used to examine the reorganization of the cortical motor map. Consistent with previous studies, we found that VNS paired with forelimb training resulted in the enlargement of the map representation of task-relevant musculature in M1. Intracortical α2-AR antagonism blocked this VNS-driven reorganization of the motor map. Our results suggest that local activation of α2-ARs is necessary for VNS-induced plasticity in the motor cortex, providing insight into the noradrenergic neuromodulatory mechanisms that may underlie VNS-dependent cortical plasticity.

Disclosures: C. Tseng: None. **C.A. Thorn:** None.

Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

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Program #/Poster #: P094.01

Topic: B.04. Ion Channels

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Robert J and Nancy D Carney Institute for Brain Science (AF)

Title: Voltage-gated calcium channels at peripheral Trpv1-lineage nerve endings contribute to local calcium dynamics linked to heat hypersensitivity

Authors: *R. Y. MEIR[1], E. J. LOPEZ SOTO[1], D. M. DUBREUIL[2], S. DASTE[1], A. FLEISCHMANN[1], D. LIPSCOMBE[1];
[1]Dept. of Neurosci., Brown Univ., Providence, RI; [2]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Voltage-gated calcium (Ca_V) channels play a critical role in transmitting information about noxious stimuli, and they regulate excitation-dependent calcium entry and transmitter release at presynaptic afferents in spinal cord dorsal horn. Intrathecal $Ca_V2.2$ channel block reduces sensory transmission and alleviates neuropathic pain in humans. The bifurcating axon of nociceptors support signal detection in peripheral organs and central transmission of nocifensive information in the spinal cord. Axon endings at peripheral sites innervate target organs including skin where they detect sensory stimuli. A feature of sensory nerve endings is their ability to rapidly alter sensitivity to sensory stimuli,

for example, following injury. Transient sensory hypersensitivity is an important adaptive response, whereas prolonged hypersensitivity can lead to chronic pain. Our lab recently showed that peripheral $Ca_V2.2$ channels are essential for transient heat hypersensitivity in skin; intradermal ω-conotoxin MVIIA (ω-CgTx MVIIA), a highly selective $Ca_V2.2$ channel inhibitor, occluded capsaicin-induced transient, heat hypersensitivity *in vivo*, whereas intradermal ω-agatoxin IVA, a selective $Ca_V2.1$ channel inhibitor, had no effect (DuBreuil et al., 2021). Here we present evidence that $Ca_V2.2$ channels in *Trpv1* nerve endings in skin are activated by intradermal capsaicin. Sensory axon endings in skin are generally inaccessible to electrophysiological analyses, and highly specific antibodies for immunostaining for $Ca_V2.2$ protein are not available. We therefore applied 2-photon imaging of *Trpv1*$^{GCaMP6f+/-}$ mice, along with vascular labeling by intravenous Texas Red dextran, to measure intracellular calcium signals evoked by capsaicin in *Trpv1* nociceptor nerve endings. We co-imaged blood vessels to use as a reference both during image acquisition and post-acquisition motion correction. Data acquisition and analyses were performed masked to the experimental conditions. Capsaicin injection caused motion distortion that we could not correct at early time points, but GCaMP6f signals at 5, 15, and 30 mins post injection were recorded. At 15 mins, nerve endings treated with ω-CgTx MVIIA showed significantly reduced capsaicin-induced Ca^{2+} signals as compared to capsaicin alone indicating the presence of functional $Ca_V2.2$ channels (n = 122 nerves, 3 mice capsaicin alone; n = 146 nerves, 3 mice capsaicin with ω-CgTx MVIIA). These data suggest a critical, yet underappreciated role for peripheral $Ca_V2.2$ channels in mediating local calcium dynamics at *Trpv1*-nociceptor nerve endings in skin under conditions that trigger heat hypersensitivity.

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Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P094.02

Topic: B.04. Ion Channels

Support: NS055251
HL126887
GM083270
Warren Alpert Fellowship Award
NS116123

Title: Voltage-gated calcium ion channels in Trpv1 nerve endings in skin support the release of proinflammatory mediators

Authors: *A.-M. N. SALIB[1], D. M. DUBREUIL[3], M. J. CRANE[2], E. J. LOPEZ SOTO[1], A. M. JAMIESON[2], D. LIPSCOMBE[1];
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Abstract: Voltage-gated $Ca_V2.2$ channels are important for the transmission of noxious stimuli centrally, in the dorsal horn of the spinal cord and, recently shown by our lab, for robust, transient capsaicin-induced heat hypersensitivity in peripheral Trpv1 nociceptor nerve endings in skin (DuBreuil et al., 2021). The lab also showed that the P2X7 receptor blocker, A438079, reduces capsaicin-induced heat hypersensitivity implicating ATP in this signaling cascade and its likely release from Trpv1 nociceptors. Further, we find that intradermal injections of a P2X7 receptor agonist (BzATP) alone can elicit heat hypersensitivity, within 30 mins, in both wild type (WT; n=6) and in $Ca_V2.2$ global knockout (KO) mice (n=7). P2X7 receptors are expressed by non-neuronal cells suggesting that the activation of P2X7 receptors in capsaicin-induced hypersensitivity depends on neuroimmune signals. Here, we show that interleukin-1α (IL-1α) is detected in the interstitial space in mouse hindpaw within 15 minutes of intradermal capsaicin injection. At this time point, mice exhibit maximum levels of hypersensitivity to heat and mechanical stimuli. In $Ca_V2.2$ KO mice, IL-1α levels induced by intradermal capsaicin are reduced by 70% compared to wild type (6-8 animals per group; p =0.0400). These data suggest that IL-1α is released in skin in response to capsaicin activation of Trpv1 nerve endings, and that block of neuronal $Ca_V2.2$ channel activity blunts this transient neuroimmune response. To assess the role of $Ca_V2.2$ channels in prolonged, maladaptive forms of neurogenic inflammation, we compared paw withdrawal behavioral responses in WT and $Ca_V2.2$ KO mice following intraplantar injection of Complete Freund's Adjuvant (CFA). We observed reduced heat hypersensitivity in $Ca_V2.2$ KO mice 1 day and up to 5 days following CFA treatment when compared to WT mice (p= 0.005) .These findings support other data from our lab showing marked reductions (60%) in levels of IL-1 spontaneously released from hindpaw skin explants from $Ca_V2.2$ KO animals (n=3) when compared to WT controls (n= 3; p = 0.006) (DuBreuil et al., 2021). Our data suggest that $Ca_V2.2$ channels are necessary for neuroimmune signaling in skin under conditions that trigger both transient and long-lasting heat hypersensitivity.

Disclosures: A.N. Salib: None. **D.M. Dubreuil:** None. **M.J. Crane:** None. **E.J. Lopez Soto:** None. **A.M. Jamieson:** None. **D. Lipscombe:** None.

Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P094.03

Topic: B.04. Ion Channels

Support: NIH Grant R35GM141802

Title: $Ca_v2.3$ R-type calcium channels in the thalamus modulate visceral nociception

Authors: S. M. GHODSI[1], S. M. JOKSIMOVIC[2], T. TIMIC STAMENIC[1], S. MAKSIMOVIC[1], V. JEVTOVIC-TODOROVIC[3], J. HEINSBROEK[1], *S. TODOROVIC[1];
[1]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [2]Childrens Hosp. of Philadelphia, Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Aims: All sensory tracts from the spinal cord innervate in the ventrobasal thalamus (VB) and relay to the cortex. Reticular thalamic nucleus (RTN) is the main source of GABAergic input to the

thalamus and is thought to regulate nociception by influencing activity of thalamocortical VB neurons. Previous studies have shown the role of $Ca_v2.3$ channels in tuning the firing mode of RTN. Herein, we used *in vivo* calcium imaging paired with mouse genetics, patch-clamp electrophysiology *ex vivo* and behavior assays to interrogate the role of thalamic $Ca_V2.3$ channels in visceral pain transmission in real time. **Methods**: Male C57Bl/6J mice were stereotaxically injected with AAV1-CaMKII-GCaMP6f plasmid followed by implanting a 0.6-mm diameter GRIN lens tangent to the border of RTN and VB. Visceral pain is induced by intraperitoneal injection of 0.6% acetic acid and scoring writhing reflex for 30 minutes. *In vivo* calcium imaging sessions were performed by placing the mouse in a novel open-field arena and recording baseline (30 min) followed by 30 min of pain behavior. Spontaneous inhibitory postsynaptic potentials (sIPSPs) were interrogated using patch-clamp recordings in acute brain slices from CACNA1E null and control mice. **Results:** Initial behavior assays show that $Ca_V2.3$ deficient mice have significantly higher writhing scores compared to WT littermates. Although the bulk analysis of calcium transients shows no significant difference between the baseline and pain assay, event-dependent analysis of calcium signals shows a significant increase in the activity of VB neurons paired with pain reflexes in the subjects of about 2-fold. Recordings of sIPSCs in VB thalamus from WT and mutant mice showed no differences in average decay and amplitude. However, the average frequency of sIPSCs was decreased in $Ca_V2.3$ KO animals more than 2-fold (WT: 7.35 ± 1.12 Hz; $Ca_V2.3$ KO animals: 2.78 ± 0.50 Hz). **Conclusions:** Our *in vivo* calcium imaging data determined the direct involvement of VB in visceral nociception. Moreover, our pain behavior assays and patch-clamp data show that the thalamic $Ca_V2.3$ R-type calcium channels play a critical role in regulating visceral pain relay to the cortex. We have also demonstrated that $Ca_V2.3$ null subjects have less inhibitory GABAergic input to VB, likely causing thalamic neurons to fire in the tonic mode rather than rebound bursting which results in lower pain threshold in the $Ca_V2.3$ KO subjects.

Disclosures: S.M. Ghodsi: None. **S.M. Joksimovic:** None. **T. Timic Stamenic:** None. **S. Maksimovic:** None. **V. Jevtovic-Todorovic:** None. **J. Heinsbroek:** None. **S. Todorovic:** None.

Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P094.04

Topic: B.04. Ion Channels

Support: NIH grant R35GM141802

Title: $Ca_V3.1$ T-type calcium channels regulate activity of the dorsal subiculum by supporting burst firing

Authors: *S. JOKSIMOVIC[1], S. GHODSI[2], J. A. HEINSBROEK[2], S. M. TODOROVIC[3];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Anesthesiol., Anschutz Med. Campus Univ. of Colorado, Denver, CO; [3]Anesthesiol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Aims: The subiculum is the main output structure of the hippocampal formation. Using *ex vivo* patch-clamp electrophysiology, we previously showed that the $Ca_V3.1$ isoform of T-type calcium

channels (T-channels) has a crucial role in regulating burst firing of subicular neurons. Here, we aimed to confirm and further explore these findings using more selective *in vivo* imaging and genetic approaches focused on the dorsal subiculum (dSub), which is critically involved in spatial memory processing. **Methods**: Adult male C57BL/6J mice were stereotaxically injected with AAV1-CaMKII-GCaMP6f followed by implanting a 1-mm diameter GRIN lens tangent to the dSub. *In vivo* calcium imaging sessions were performed at baseline and 20 min after intraperitoneal injection of vehicle, 5 and 7.5 mg/kg TTA-P2 (pan-selective T-channel antagonist) by placing the mouse in an open-field arena. The target gene silencing was conducted by injecting AAV vectors expressing shCa_V3.1 (AAV2-GFP-U6-mCACNA1G-shRNA) or control (scrambled shRNA) into the dSub. Spontaneous action potential (AP) firing and intrinsic excitability were assessed using patch-clamp recordings in acute brain slices from shCa_V3.1 and control mice. **Results:** Successful GCaMP transfection and lens implantation were confirmed by immunohistochemistry in each subject 10-12 weeks post-surgery. The dose-dependent decrease in calcium transients' amplitude after i.p. injection of relatively low doses of TTA-P2 demonstrates the critical role of T-type calcium currents in the dSub activity. Specifically, we noted a 35% decrease in the average calcium amplitude after the injection of 7.5 mg/kg TTA-P2, as compared to the vehicle ($P<0.001$, one-way ANOVA followed by Tukey's test). Importantly, the calcium activity after the vehicle injection was not different from the baseline measurement. The firing frequency did not follow the same pattern: even the dose of 7.5 mg/kg did not significantly affect the calcium event frequency. Regarding patch-clamp experiments, we detected a drastically lower AP firing frequency in shCa_V3.1 GFP+ neurons ($P=0.002$ vs. control GFP+ neurons). As expected, the bursting properties were also compromised in these neurons, as assessed with a lower number of APs per current injection ($P=0.023$, two-way RM ANOVA) and per burst ($P=0.011$) in the shCa_V3.1 group. **Conclusions:** Based on our *in vivo* calcium imaging and patch-clamp data in the dSub-specific Ca_V3.1 knock-down mice, as well as our previous *in vitro* results, we propose that Ca_V3.1 T-channels are the main driving force behind the bursting activity of dSub neurons, and are thus able to modulate cognitive functions mediated by the subicular circuitry.

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Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P094.05

Topic: B.04. Ion Channels

Support: Schram Foundation
DFG

Title: Dynamic calcium channel nanoclusters in hippocampal synapses

Authors: A. EL KHALLOUQI[1], A. PALMEIRA DO AMARAL[2], A. BIKBAEV[2], J. HECK[3], M. D. MARK[4], S. HERLITZE[5], *M. HEINE[1];
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Abstract: Presynaptic calcium channels are key components for the transmission of information between neurons. Their kinetic properties as activation state and conductivity but also their spatial arrangement are critical parameters shaping the release probability of synapses. P/Q-channels ($Ca_V2.1$) are essential for many synapses in the mammalian brain, where they represent the main population of voltage-gated calcium channels. Within the presynaptic membrane $Ca_V2.1$-channels are found in a clustered organization. Multiple binding sites to scaffold proteins as well as their C-terminal involvement in phase separated scaffold clusters are discussed to cluster calcium channels in the synapse. Here, we asked the question, whether these clusters are formed in a synapse-specific manner and whether they adopt to the activity history of the synapse? We used single-particle tracking photoactivation localisation microscopy (sptPALM) to directly monitor the endogenous population of $Ca_V2.1$-channels under different conditions of network activity. The strong confinement of $Ca_V2.1$-channels within the active zone (AZ) as well as their intrinsic local mobility suggest an ongoing reorganisation. Investigating the $Ca_V2.1$ channel population in glutamatergic and GABAergic synapses uncovered differences in their organisation. In glutamatergic synapses, most $Ca_V2.1$-channels are concentrated within one central nanocluster, defined by a steep increase in channel density. Whereas in GABAergic synapses, $Ca_V2.1$-channels are organized at least in two smaller nanoclusters. Artificial clustering of $Ca_V2.1$-channels by photoactivatable cross-linkers did not induce a growth of these clusters, as expected, but a shrinkage. This indicates a defined freedom of local mobile channels within the cytomatrix of the AZ. Inducing acute changes in the activity of synapses by electrical or chemical manipulations affected this previously described local organisation of $Ca_V2.1$-channels and thus promotes the idea that local rearrangements in the molecular environment are essential for fast changes in synaptic activity. Concluding, the organization of the endogenous $Ca_V2.1$-channel population within the presynaptic membrane probed by single-molecule imaging let argue that channel nanoclusters are probably formed by two mechanisms, molecular crowding within the presynaptic membrane and liquid phase separation of presynaptic scaffold proteins where $Ca_V2.1$-channels are linked to.

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Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

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Program #/Poster #: P094.06

Topic: B.04. Ion Channels

Support: R01 DC014093
R21DC018242
R01 NS110742-01
University or Iowa Distinguished Scholar Award

Title: Role of presynaptic Ca_V2 channels in regulating synaptic vesicle release

Authors: *P. VEERARAGHAVAN[1], R. GORAL[1], D. GUERRO-GIVEN[2], C. THOMAS[2], P. VALINO RAMOS[1], N. KAMASAWA[2], S. M. YOUNG, Jr[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: The efficiency of synaptic transmission relies on the levels and localization of voltage-gated Ca^{2+} channels (VGCCs) at the presynaptic active zone (AZ). Ca_V2 channels, a subset of VGCCs, includes $Ca_V2.1$, $Ca_V2.2$ and $Ca_V2.3$ that are primarily expressed in mammalian central nervous system synapses. Among them, $Ca_V2.1$ is most efficient in triggering action potential (AP)-mediated synaptic vesicle (SV) release. During development, many fast firing presynaptic terminals modify from having mixed Ca_V2 subtypes to either $Ca_V2.1$ dominant or exclusive. Further, to achieve AP temporal precision and fast firing rate, Ca_V-SV coupling (relative positioning of Ca_V channels to SVs) switches from microdomain (loosely coupled) at immature stage to nanodomain (tightly coupled) SV release at mature stage. However, it is still unknown if these SV release states depend on the Ca_V2 subtype. Calyx of held (calyx), a fast firing presynapse like many central synapses transforms from having mixed Ca_V2 subtypes to $Ca_V2.1$ and switches its release state form micro- to nanodomain during development. Therefore, to understand the relation between Ca_V2 subtype and SV release states we conditionally knocked out (CKO) $Ca_V2.1$ or both $Ca_V2.1/2.2$ at calyx using either $Ca_V2.1^{fl/fl}$ mouse or using our novel mouse model, $Ca_V2.1^{fl/fl}/2.2^{fl/fl}$. We examined the changes in calcium current (I_{Ca}), readily releasable pool (RRP), SV release kinetics and AZ ultrastructure during development. We observed a partial compensation of I_{Ca} in both $Ca_V2.1$ and $Ca_V2.1/2.2$ CKO calyces. However, we found distinct changes in RRP size and SV release kinetics in either $Ca_V2.1$ or both $Ca_V2.1/2.2$ ablated calyces without altering AZ ultrastructure during both micro- and nanodomain release state. Hence, we propose that Ca_V2 channels play differential role in SV release states during development. This study will highly impact our current understanding on how different Ca_V2 channels regulate release in a native neuronal circuit.

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Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

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Program #/Poster #: P094.07

Topic: B.04. Ion Channels

Support: R01 DC014093
R21DC018242
R01 NS110742-01
Iowa Distinguished Scholar Award

Title: The C-terminus of $Ca_V2.1$ alpha$_1$ subunit is a key regulator of Ca_V2 subtype abundance at the presynaptic terminal

Authors: *J. LI[1], S. M. YOUNG, JR[2];
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Abstract: The C-terminus of $Ca_V2.1$ α1 subunit is a key regulator of Cav2 subtype abundance at the presynaptic terminal Jianing Li[1], Samuel M. Young, Jr[1,2]1.Department of Anatomy and Cell Biology, Cell& Developmental Biology Program, University of Iowa, Iowa City, IA 52242, USA2.Department of Otolaryngology, Iowa Neuroscience Institute, Aging Mind Brain Initiative, University of Iowa, Iowa City, IA 52242, USAIn the central nervous system (CNS), there are multiple subtypes of voltage-gated calcium channels (VGCCs). Synaptic transmission in CNS is mainly mediated by Ca_V2 family, and $Ca_V2.1$ is more efficient in triggering neurotransmitter release compared to $Ca_V2.2$ and $Ca_V2.3$ due to its higher abundance and closer proximity to synaptic vesicles (SV). Moreover, the presynaptic terminals become increasingly $Ca_V2.1$ dominant during development. However, molecular mechanisms regulating presynaptic Ca_V2 subtype abundance remains unknown. Cytoplasmic domains in Ca_V2 α_1 subunit are implicated in controlling presynaptic Ca_V2 subtype abundance. To determine which cytoplasmic regions controlling Ca_V2 subtype abundance at the presynaptic terminal, we expressed Ca_V2 hybrid construct: $Ca_V2.1/2.3$ II-III loop+ C-terminus hybrid, $Ca_V2.1/2.3$ II-III loop hybrid, $Ca_V2.1/2.3$ C-terminus hybrid, in a $Ca_V2.1$, $Ca_V2.2$ null background at the calyx of Held presynaptic terminal. We identified that cytoplasmic C-terminus plays a key role in regulating Ca_V2 subtype abundance at the presynaptic terminal. Our research shed light on molecular mechanisms regulating presynaptic Ca_V2 subtype abundance and neuronal circuit output.

Disclosures: J. Li: None. **S.M. Young:** None.

Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

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Program #/Poster #: P094.08

Topic: B.04. Ion Channels

Support: Vanderbilt University McGavock Chair

Title: Activity-dependent clustering of L-type calcium channel complexes with Shank3 and CaMKII

Authors: *Q. YANG[1], L. HU[1], J. C. QUAY[1], K. R. ERICKSON[1], R. J. COLBRAN[2];
[1]Vanderbilt Univ., Nashville, TN; [2]Dept Molec Physiol & Biophysics, Vanderbilt Univ. Sch. Med., Nashville, TN

Abstract: Neuronal excitation-transcription (E-T) coupling induces new mRNA transcription and is essential for normal learning and memory. One major pathway that initiates E-T coupling is initiated by the activation of voltage-gated L-type Ca^{2+} channels (LTCCs) in the plasma membrane. LTCC-dependent E-T coupling increases phosphorylation of the nuclear CREB transcription factor, which can be induced by local Ca^{2+} increases within a nanodomain close to the channel, without requiring Ca^{2+} increases in the bulk cytosol or nucleus. Formation of this LTCC nanodomain may involve clustering of the major neuronal LTCC α1 subunits ($Ca_V1.2$, $Ca_V1.3$), but the molecular basis for LTCC clustering is poorly understood. Previous studies in our lab found that LTCC-dependent E-T coupling requires direct binding of the $Ca_V1.3$ α1 subunit N- and C-terminal domains (NTD and CTD, respectively) to Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), a major neuronal signaling protein, and to Shank3, a scaffolding

protein, respectively; as well as a novel CaMKII-Shank3 interaction[1,2]. We hypothesized that these three protein-protein interactions contribute to LTCC clustering. Preliminary data indicate that neuronal depolarization increases the size of $Ca_V1.3$ LTCC clusters in rat primary cultured hippocampal neurons. A series of co-immunoprecipitation (co-IP) experiments from transfected HEK293T cell lysates indicate that Shank3 can assemble multimeric $Ca_V1.3$ LTCC complexes under basal conditions. Moreover, activated, but not inactive, CaMKII can assemble homo-multimeric $Ca_V1.3$ LTCC complexes, as well as heteromeric $Ca_V1.3$-$Ca_V1.2$ complexes in this co-IP assay. We also used fluorescence microscopy to examine $Ca_V1.3$ clustering in the plasma membrane of transfected HEK293T cells. The co-expression of Shank3, but not CaMKII, enhances $Ca_V1.3$ cluster size under basal conditions. However, the addition of an LTCC agonist (BayK8644) to cells co-expressing CaMKII increased the size of $Ca_V1.3$ clusters. Ongoing studies are examining the dynamics of LTCC cluster formation. Taken together, our findings reveal novel molecular mechanisms contributing to neuronal LTCC clustering that may be required to initiate long-range signaling to the nucleus during learning and memory. 1. Wang et al., 2017. J Biol Chem. 292(42) 17324, PMC56555102. 2. Perfitt et al., 2020. J Neurosci. 40(10) 2000. PMC7055140

Disclosures: Q. Yang: None. **L. Hu:** None. **J.C. Quay:** None. **K.R. Erickson:** None. **R.J. Colbran:** None.

Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P094.09

Topic: B.04. Ion Channels

Title: Characterization of Synapsin1 Cre conditional $Ca_v1.2$ knockout mouse model

Authors: *A. KLOMP[1], A. PLUMB[2], J. MEHR[1,3], H. WEN[1], D. MADENCIOGLU KUL[1], A. J. WILLIAMS[1];
[1]Psychiatry, [2]Univ. of Iowa, Iowa City, IA; [3]Rutgers Univ., New Brunswick, NJ

Abstract: L-type voltage gated Ca^{2+} channels (LVGCC) are transmembrane proteins that allow influx of Ca^{2+} into excitable cells. Of the four LVGCCs, $Ca_v1.2$ is most highly expressed in the brain. $Ca_v1.2$ has roles in dendritic development, synaptic plasticity, neuronal survival, and cognitive and affective behaviors. The $Ca_v1.2$ alpha subunit is encoded by *CACNA1C*. Genetic studies have linked single nucleotide polymorphisms (SNPs) and rare variants within *CACNA1C* with neuropsychiatric disorders including autism, bipolar disorder, and schizophrenia. While there is evidence that $Ca_v1.2$ is involved in cognitive and affective function, it is unclear whether $Ca_v1.2$'s primary role is in neurons or glia. $Ca_v1.2$ haploinsufficient mice exhibit antidepressant-like phenotypes, hypoactivity, anxiety-like behaviors, increased fear responses, and social deficits; and mice lacking $Ca_v1.2$ in neural progenitors (Nestin-Cre) exhibit cognitive deficits in learning tasks. Furthermore, loss of $Ca_v1.2$ has been shown to reduce maturation of oligodendrocytes and growth of myelin, and overexpression of $Ca_v1.2$ increases myelin expression, so it is clear that $Ca_v1.2$ plays an important role in myelination. However, it is unclear if the deficits in these mice are due to loss of $Ca_v1.2$ from neurons or other derivatives of neuronal progenitor cells: astrocytes or oligodendrocytes. We have investigated the effects of loss of $Ca_v1.2$ from Synapsin1

expressing cells, which should target most CNS neurons but not glia. Previous work with Synapsin1 Cre (Syn-Cre) $Ca_v1.2$ knockout mice ($Ca_v1.2$ cKO) identified a significant deficit in extinction of fear learning and a shift in inhibitory/excitatory balance in the lateral amygdala. No abnormalities in motor function or anxiety were found in the open field test and light dark box. Our behavioral data indicates that $Ca_v1.2$ cKO mice have normal baseline motor function though female KOs display impaired motor learning on the rotarod task. Latency to float on the forced swim test was significantly higher in the cKO mice and this effect appears to be driven largely by the female cKOs. On the social preference/recognition task, the male cKO mice were impaired, but no effect was seen in females. Similar to previous work, no effects of genotype were identified on the elevated zero maze, thigmotaxis, or sucrose preference. We conclude that the antidepressant, motor, social, and learned fear-related phenotypes in $Ca_v1.2$ mutant mice may be driven at least in part by changes in neuronal function as a result of loss of neuronal $Ca_v1.2$, whereas basal anxiety-like phenotypes in $Ca_v1.2$ deficient mice may be occurring through changes in astrocytes or oligodendrocytes.

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Poster

P094. Voltage Gated Calcium Channels: Physiology and Disease

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Program #/Poster #: P094.10

Topic: B.04. Ion Channels

Support: UMB SOM ATIP Grant
1R01HL149926-01
5T32GM008181-34

Title: Using induced pluripotent stem cell-derived neurons to evaluate the role of $Ca_V1.2$ in the pathogenesis of autism spectrum disorder.

Authors: *K. G. HEROLD, M. A. BAMGBOYE, D. C. O. VIEIRA, D. DISILVESTRE, J. O. OWOYEMI, A. L. MEREDITH, I. E. DICK;
Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Autism spectrum disorder (ASD) is a neurological disorder characterized by repetitive, restricted behaviors, interests, and activities along with a range of challenges in communication skills and social interaction. Pathway and genetic analyses have indicated a strong connection between ASD and the dysregulation of Ca^{2+} signaling. In particular, the L-type Ca^{2+} channel (LTCC) has been repeatedly identified as associating with ASD in multiple GWAS and functional studies, and genetic mutations within this channel family have been shown to be causative of ASD. In fact, mutations within the $Ca_V1.2$ LTCC have been identified as one of the few monogenic causes of ASD, resulting in a multisystem disorder known as Timothy syndrome (TS). TS patients harbor a single *de novo* point mutation within $Ca_V1.2$, which causes severe cardiac arrhythmias, long-QT syndrome and ASD. TS is one of the most penetrant genetic forms of ASD, making it an ideal model system with which to gain traction on

understanding the role of Ca^{2+} dysfunction in ASD. Interestingly, preliminary results from our lab have demonstrated marked differences in channel gating due to distinct TS mutations. Such differences may underlie the differential phenotypes of select $Ca_V1.2$ mutations. To probe the effects of these mutations on neuronal function, we utilized human induced pluripotent stem cell (iPSC)-derived neurons harboring select $Ca_V1.2$ mutations. Patch clamp recordings of these cells yield distinct LTCC currents enabling evaluation of the biophysical properties of wildtype and mutant channels in the context of a human neuron. In addition, these cells enable robust recordings of neuronal action potentials with distinct AP morphologies. Pharmacological dissection enables the evaluation of the relative contribution of the mutated channel and select Ca^{2+} dependent proteins on the electrical properties of the membrane. Overall, as Ca^{2+} disruption may be a recurrent feature of ASD, studying rare mutations such as TS, may provide insight into the pathogenesis of ASD beyond TS.

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Poster

P106. Modulation: Pharmacology

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Program #/Poster #: P106.01

Topic: B.06. Synaptic Transmission

Support: NIH Grant 1R01DA048946-01

Title: Characterization and opioid sensitivity of nucleus accumbens interneurons expressing neuropeptide y

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Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Mu opioid receptor (MOR) agonists such as morphine and fentanyl are known to regulate the activity of GABAergic interneurons in the ventral tegmental area and hippocampus, both areas known to be important for reward processing. Though the nucleus accumbens (NAc) is a critical structure in the reward circuit, the effects of MOR agonism on interneurons in this brain region are not well understood. We sought to characterize MOR expression and function within the NAc specifically in the low threshold spiking interneurons (LTSIs). While it is understood these cells participate within local circuitry of the striatum and can synapse with medium spiny neurons (MSN) to modulate their output, the understanding of how opioid receptors modulate these cells has never been explored. Using fluorescent *in situ* hybridization, we identified LTSIs based on co-expression of neuropeptide Y (NPY) and somatostatin (SST) and found that a large majority (87%) also expressed the MOR in both male and female mice between 6 and 16 weeks of age. There was a small number of NPY cells that did not express SST, known as neurogliaform interneurons. These interneurons were in lower abundance in NAc than dorsal striatum and it was difficult to find and record these cells using electrophysiology, so this subpopulation was not studied further. We were able to examine the functional consequences of MOR expression in LTSIs using electrophysiology. Cell attached and whole cell current clamp recordings were used to assess intrinsic

excitability and revealed decreases in evoked or spontaneous action potential spiking after bath application of DAMGO, a MOR specific agonist. Through optogenetic experiments to examine synaptic output from LTSIs to MSNs, we found DAMGO application reduces GABAerigic output by more than 40% to both populations of MSNs, those expressing D1 or D2 dopamine receptors. All electrophysiological experiments were done in both male and female mice of 6-12 weeks in age. These data indicate that while LTSIs only comprise about 1% of neurons in the NAc they have opioid sensitive synaptic transmission that can alter the overall function of NAc circuitry.

Disclosures: C.L. Retzlaff: None. **P.E. Rothwell:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.02

Topic: B.06. Synaptic Transmission

Support: RO1 AG057767
RO1 AG061937
Dale and Deborah Smith Center for Alzheimer's Research and trEatment
Kenneth Stark Endowment

Title: Riluzole Improves Glucose Metabolism and Confers Long-term Procognitive Effects in Alzheimer's Disease Mice

Authors: *C. A. FINDLEY, S. A. MCFADDEN, K. N. HASCUP, E. R. HASCUP;
Neurology, Neurosci. Institute, Ctr. for Alzheimer's Dis., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Background: It is well established that glutamatergic neurotransmission plays an essential role in learning and memory. In Alzheimer's disease (AD), glutamate dynamics shift with disease progression, inciting cognitive impairment and further perpetuating disease pathology. Several studies have demonstrated procognitive effects in male AD mice with prodromal administration of a glutamatergic modulator (riluzole). The current study aimed to investigate the short- and long-term effects of prodromal riluzole treatment in two AD mouse models. Methods: Male and female C57BL/6 (littermate control), AβPP/PS1 (transgenic), and $APP^{NL-F/NL-F}$ (knock-in) mice received either vehicle- (1% sucrose) or riluzole- (356 μM) treated drinking water (voluntary oral administration) between 2-6 months of age. Separate cohorts of mice were assayed either immediately following treatment cessation (6 months of age) or 6 months post-treatment (12 months of age). Insulin and glucose tolerance testing (ITT, GTT) were performed to examine metabolic function, followed by Morris water maze (MWM) to determine cognitive ability. Results: Riluzole-treated male $APP^{NL-F/NL-F}$ (n=18) and littermate control (n=12) mice showed significantly improved peripheral glucose tolerance compared to genotype-matched vehicle-treated controls ($p<0.05$, 0.01, respectively). No significant differences were observed for insulin sensitivity with treatment. Riluzole did not have a long-term impact on peripheral glucose or insulin tolerance. MWM results indicated that spatial learning was not significantly different at either time point.

However, riluzole significantly improved long-term spatial memory in 12-month-old $APP^{NL-F/NL-F}$ and AβPP/PS1 male mice compared to genotype-matched vehicle-treated controls on measures of platform entries, latency to first entry, and duration in platform proximity ($p<0.05$). No effects were observed in female mice with riluzole treatment. Conclusions: Besides known glutamatergic modulatory effects, riluzole also improves peripheral glucose metabolism, a potentially beneficial effect as metabolic syndrome is a risk factor for AD. Procognitive effects were also observed 6 months post-treatment in both $APP^{NL-F/NL-F}$ and AβPP/PS1 male mice. These findings highlight the importance of peripheral glucose homeostasis on cognitive function in AD mouse models. Further, sex differences in responsiveness to riluzole treatment potentially indicate differing glutamatergic pathologies with disease progression.

Disclosures: C.A. Findley: None. **S.A. McFadden:** None. **K.N. Hascup:** None. **E.R. Hascup:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.03

Topic: B.06. Synaptic Transmission

Support: NIH Grant AA026531

Title: Acute ethanol in basolateral amygdala modulates GABA circuits and anxiety-like behavior in male, but not female, rats

Authors: S. MUNSHI[1], L. ALBRECHET-SOUZA[2], N. W. GILPIN[2,3], J. G. TASKER[1,3];
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Abstract: Accumulating evidence suggests sex-dependent behavioral changes following alcohol administration. The basolateral amygdala (BLA) plays a critical role in the development of alcohol use disorder (AUD). Although earlier studies have shown that corticotropin releasing hormone (CRH) and ethanol increases the central amygdala GABAergic transmission, the role of the BLA CRH system in ethanol effect is unknown. We previously observed that ethanol increased GABA release onto BLA principal neurons via activation of parvalbumin-positive interneuron axons. In the present study, we tested the hypotheses that the acute ethanol modulation of GABA inhibitory inputs to BLA principal neurons (i) has a higher threshold in females, (ii) is dependent on CRHR1 activation, and (iii) causes differential dose-dependent anxiety-related behaviors in males and females. Using *ex vivo* whole-cell patch-clamp recordings from BLA pyramidal neurons in amygdala slices from adult Wistar rats, we found that ethanol caused a dose-dependent increase in spontaneous IPSC (sIPSC) frequency, with a threshold of 22 mM, in principal neurons from male rats; ethanol had no effect on sIPSCs at non-toxic concentrations in female rats, and increased the sIPSC frequency only at the toxic non-physiological concentration of 88 mM, revealing a striking sex difference in acute alcohol sensitivity. In slices from male rats, the CRHR1 antagonist (R121919, 2 μM) reduced, but did not abolish completely, the effect of ethanol on sIPSC frequency. *In vivo* bilateral intra-BLA injections of 22 mM ethanol, but not 44 mM,

produced anxiolytic effect in males tested in the elevated plus maze; intra-BLA ethanol had no effect at either concentration in females. Due to the inverted U-shaped dose-dependent anxiolytic effect observed in males, we further determined whether ethanol changes the inhibition-to-excitation balance in the BLA by testing for an acute ethanol effect on excitatory transmission; however, ethanol (44 mM) had no effect on excitatory postsynaptic currents, suggesting that the observed behavioral change in males is not due to a change in the excitation-inhibition balance in the BLA. Taken together, these data suggest a sex-difference in the ethanol regulation of anxiety-like behavior that is mediated by modulation of inhibitory synaptic circuits in the BLA. This finding may provide a neurobiological substrate that contributes to the differential susceptibility and behavioral manifestations of AUD in males and females.

Disclosures: S. Munshi: None. **L. Albrechet-Souza:** None. **N.W. Gilpin:** None. **J.G. Tasker:** None.

Poster

P106. Modulation: Pharmacology

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Program #/Poster #: P106.04

Topic: B.06. Synaptic Transmission

Support: Migraine Research Foundation (New York, USA)
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MICINN and FEDER grant CEX2018-000792-M

Title: Novel $Ca_V2.1$-modulators to treat Hemiplegic Migraine

Authors: *M. IZQUIERDO-SERRA[1], S. A. SERRA[1], S. E. WARD[2,3], P. J. BESWICK[2], J. M. FERNÁNDEZ-FERNÁNDEZ[1];
[1]Univ. Pompeu Fabra, Barcelona, Spain; [2]Univ. of Sussex, Brighton, United Kingdom; [3]Cardiff Univ., Wales, United Kingdom

Abstract: Human mutations in the *CACNA1A* gene, encoding the pore-forming α_{1A} subunit of the voltage-gated $Ca_V2.1$ calcium channel, cause most of the familial and sporadic hemiplegic migraine (FHM/SHM) cases. Hemiplegic Migraine (HM) mutations induce a gain of $Ca_V2.1$ channel activation that specifically enhances cortical excitatory transmission to favor initiation and propagation of cortical spreading depression, a key process in migraine pathophysiology. Accordingly, there are pharmacological evidences suggesting that reduction of $Ca_V2.1$ activity can provide a new therapeutic approach for the treatment of HM and the relief of common migraine. Currently the only truly $Ca_V2.1$-selective inhibitors are peptide toxins of the agatoxin family, which are not suitable therapeutic tools: their mode of inhibition can give rise to undesirable side effects and peptides have limited utility for *in vivo* studies. Therefore, low-molecular-weight compounds that selectively modulate $Ca_V2.1$ activity could emerge as new drugs to treat migraine.

Here we have employed a high-throughput study using automated patch clamp to identify novel selective $Ca_V2.1$-inhibitors. From an initial set of 80 compounds recognized as potential $Ca_V2.1$ blockers *in silico*, our results highlighted six novel small organic molecules with higher selectivity for $Ca_V2.1$ inhibition (over $Ca_V2.2$ and $Ca_V1.2$ blockade) as prospective elements to develop HM therapeutic tools. Next, in a low-throughput evaluation of the compounds, we studied their effect on the wild-type "healthy" and gain-of-function FHM mutant $Ca_V2.1$ channels. We identified novel potent and selective inhibitors of $Ca_V2.1$ capable of preventing the excessive activity of $Ca_V2.1$ channels produced by human mutations leading to HM, with minor effects on the wild-type channel (in order to reduce/prevent potential side effects). In addition, to validate the potential therapeutic use of the best candidates, we tested if the reduction of excessive $Ca_V2.1$ activity was sufficient to prevent hyper-excitability on cortical networks observed in HM mouse model, a gain-of-function $Ca_V2.1$ knock-in animal. Interestingly, our study featured a selective $Ca_V2.1$ inhibitor that diminished excitability of the aberrant neuronal network with minor effects on the healthy cortical neuronal network from wild-type mice. This novel molecule that modulates the $Ca_V2.1$ channel activity and reverts its pathological gain-of-function effect may contribute to the development of a new, effective and safe treatment for both hemiplegic and common migraine.

Disclosures: M. Izquierdo-Serra: None. **S.A. Serra:** None. **S.E. Ward:** None. **P.J. Beswick:** None. **J.M. Fernández-Fernández:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.05

Topic: B.06. Synaptic Transmission

Title: Dopamine Autoreceptor Functioning is Attenuated Following Chronic Blockade of Dopamine Transporters

Authors: *R. L. PACE, P. A. NALAN, D. B. LESTER;
Psychology, Univ. of Memphis, Memphis, TN

Abstract: Extracellular dopamine levels are mediated in part by dopamine transporters (DATs) and dopamine autoreceptors (DARs). DATs are responsible for the reuptake of dopamine into the presynaptic terminal, and DAR activation inhibits dopamine release. Using in vivo fixed potential amperometry in anesthetized mice, the current study sought to better understand whether these two neural mechanisms work collectively or independently. Stimulation parameters specifically designed to assess DAR functioning were applied during nucleus accumbens (NAc) dopamine recordings following chronic administration of the DAT inhibitor cocaine (20 mg/kg i.p. daily for 7 days). Dopamine recordings took place 24 hours after the last cocaine administration, and DAR functioning was assessed before and after an in-test injection of cocaine (8th injection for the cocaine group and 1st injection for the control group). DAR functioning was significantly attenuated in mice that received chronic cocaine (-37% compared to control mice). The in-test cocaine injection had opposing effects on DAR functioning in the chronic cocaine mice and controls, with DAR functioning increasing 20 min post-injection in the chronic cocaine mice and decreasing in control mice. These results highlight compensatory mechanisms employed at the

level of the presynaptic membrane to counteract chronic blockade of dopamine reuptake and increased levels of extracellular dopamine. A better understanding of the interactions between DATs and DARs may lead to improved treatments for dopamine-related disorders such as ADHD, depression, and substance use disorder.

Disclosures: R.L. Pace: None. **P.A. Nalan:** None. **D.B. Lester:** None.

Poster

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Program #/Poster #: P106.06

Topic: B.06. Synaptic Transmission

Support: Office of the Principal Scientific Advisor (PSA) to the Government of India Grant: Prn.SA/Epilep/2017(G)

Title: Altered $GABA_A$ receptor subunit configuration in drug-resistant epilepsy (DRE): A possible cause of benzodiazepine resistance

Authors: *J. BANERJEE[1], D. SHARMA[2], A. B. DIXIT[6], S. DEY[2], M. TRIPATHI[3], R. DODDAMANI[2], M. C. SHARMA[4], S. LALWANI[5], P. CHANDRA[2];
[1]Biophysics, [2]Neurosurg., [3]Neurol., [4]Neuropathology, [5]Forensic Med. & Toxicology, All India Inst. of Med. Sci. (AIIMS), N, New Delhi Delhi, India; [6]Univ. of Delhi, Delhi, India

Abstract: Benzodiazepines (BZDs), positive allosteric modulators at $GABA_A$ receptors, are widely used an anti-convulsant for the treatment of patients with severe forms of epilepsies. A large number of patients with drug-resistant epilepsy (DRE) do not respond to BZDs. BZDs bind at the classical benzodiazepine binding site located at the interface of α-and γ- subunit of the $GABA_A$ receptors. The selectivity of benzodiazepine responsiveness is primarily determined by the type of the α subunits, with α1-, α2-, α3-, and α5-containing $GABA_A$ receptors being sensitive to BZDs. While α3-, and α5-containing $GABA_A$ receptors are insensitive to BZDs. This study was designed to investigate if altered configuration of $GABA_A$ receptor subunits could contribute to BZD-resistance in patients with DRE. Brain specimens were obtained from patients with various DRE pathologies like mesial temporal lobe epilepsy, focal cortical dysplasia, Rasmussen's encephalitis, dysembryoplastic neuroepithelial tumor and ganglioglioma undergoing resective surgery. Region matched cortical tissues from patients with mature healthy brain, who underwent autopsies for causes other than brain pathology, were used as controls. Resected cortical samples obtained from surrounding areas of brain tumors during surgical resection in patients with low-grade gliomas without any history of seizures were used as non-seizure controls for electrophysiological studies. Differential gene and cellular expression of $GABA_A$ receptor subunits were evaluated and validated using qPCR and immunohistochemistry. Whole cell patch-clamp recordings were performed on pyramidal neurons of resected cortical samples obtained from patients with DRE to measure the spontaneous $GABA_A$ receptor activity. We observed upregulation of α4-subunit containing $GABA_A$ receptors both at mRNA and protein level in DRE samples as compared to controls, while α1-subunits containing $GABA_A$ receptors did not show any significant changes. Treatment with flumazenil, a BZD

binding site antagonist, did not affect the kinetics of GABAergic events in samples obtained from patients with DRE pathologies. However, flumazenil significantly reduced the frequency and amplitude of spontaneous GABAergic activity recorded from pyramidal neurons of non-seizure control samples. Our results demonstrated that enhanced expression of α4-containing $GABA_A$ receptors may contribute to benzodiazepine resistance in patients with DRE.

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Poster

P106. Modulation: Pharmacology

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Program #/Poster #: P106.07

Topic: B.06. Synaptic Transmission

Support: Grant-in-Aid for Scientific Research (C), 17K01975 and 21K07293
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the Takeda Science Foundation
the Uehara Memorial Foundation

Title: Risperidone Mitigates Enhanced Excitatory Neuronal Function and Repetitive Behavior Caused by an ASD-Associated Mutation of SIK1

Authors: *M. BADAWI[1], T. MORI[1,2], T. KURIHARA[1], T. YOSHIZAWA[3], K. NOHARA[1], E. KOUYAMA-SUZUKI[1], T. YANAGAWA[4], Y. SHIRAI[1], K. TABUCHI[1,2];
[1]Dept. of Mol. and Cell. Physiology, Shinshu Univ. Sch. of Med., Matsumoto, Japan; [2]Dept. of NeuroHealth Innovation, Inst. for Biomed. Sciences, Interdisciplinary Cluster for Cutting Edge Research, Shinshu Univ., Matsumoto, Japan; [3]Res. Ctr. for Supports to Advanced Science, Shinshu Univ., Matsumoto, Japan; [4]Dept. of Oral and Maxillofacial Surgery, Fac. of Medicine, Univ. of Tsukuba, Tsukuba, Japan

Abstract: Six mutations in the salt-inducible kinase 1 (SIK1)-coding gene have been identified in patients with early infantile epileptic encephalopathy (EIEE-30) accompanied by autistic symptoms. Two of the mutations are non-sense mutationsthat truncate the C-terminal region of SIK1. It has been shown that the C-terminal truncated form of SIK1 protein affects the sub-cellular distribution of SIK1 protein, tempting to speculate the relevance to the pathophysiology of the disorders. We generated SIK1-mutant (SIK1-MT) mice recapitulating the C-terminal truncated mutations using CRISPR/Cas9-mediated genome editing. SIK1-MT protein was distributed in the nucleus and cytoplasm, whereas the distribution of wild-type SIK1 was restricted to the nucleus. We found the disruption of excitatory and inhibitory (E/I) synaptic balance due to an increase in excitatory synaptic transmission and enhancement of neural excitability in

the pyramidal neurons in layer 5 of the medial prefrontal cortex in SIK1-MT mice. We also found the increased repetitive behavior and social behavioral deficits in SIK1-MT mice. The risperidone administration attenuated the neural excitability and excitatory synaptic transmission, but the disrupted E/I synaptic balance was unchanged, because it also reduced the inhibitory synaptic transmission. Risperidone also eliminated the repetitive behavior but not social behavioral deficits. These results indicate that risperidone has a role in decreasing neuronal excitability and excitatory synapses, ameliorating repetitive behavior in the SIK1-truncated mice.

Disclosures: M. Badawi: None. **T. Mori:** None. **T. Kurihara:** None. **T. Yoshizawa:** None. **K. Nohara:** None. **E. Kouyama-Suzuki:** None. **T. Yanagawa:** None. **Y. Shirai:** None. **K. Tabuchi:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.08

Topic: B.06. Synaptic Transmission

Support: NIH GM118801

Title: Characterization of oxygen-level dependent isoflurane effects on proximal vs distal dendritic excitatory inputs using a high-flow brain slice chamber

Authors: *S. KLEIN, R. A. PEARCE;
Anesthesiol., Univ. of Wisconsin, Madison, WI

Abstract: Background: Isoflurane is a commonly used anesthetic with multiple targets in the brain. It has been shown to differentially modulate ascending vs. descending excitatory synapses in neocortex.[1] Here, we sought to characterize its effect on the analogous distal temporoammonic (TA) relative to the proximal Schaffer Collaterals (SC) pathways. Recent findings also indicate that isoflurane affects excitatory synaptic transmission by targeting mitochondrial complex I. Therefore, we also tested effects at differing oxygen levels to stress ATP production. **Methods:** Coronal hippocampal brain slices (400 μm) prepared from 2-4 month old C57BL/6J mice were perfused in a high flow chamber (Scientific Systems Design) at 16 mL/min with aCSF (32°C) aerated with high O_2 (95%O_2-5%CO_2) or low O_2 (70%O_2-25%N_2-5%CO_2) levels. Field EPSPs (fEPSPs) were measured in stratum radiatum in response to SC stimulation at the CA1/CA2 border and stratum lacunosum-moleculare in response to TA stimulation at CA1/subiculum border. Slices were stimulated either once per 20 s (alternating pathways) or 20 stimuli at 50 Hz every 60 s (SC only). **Results:** Isoflurane (100-850 μM) suppressed the SC fEPSP to a greater degree than the TA fEPSP, in a concentration-dependent manner, with no significant O_2 level-dependent differences. Following a 30-min application, isoflurane was removed, and responses recovered quickly (20 min), but to a steady state fEPSP slope that was smaller than the original baseline. We term this unexpected, persistent decrease in fEPSP slope, “isoflurane-induced long-term depression” (iso-LTD). The amplitude of iso-LTD was greater at high O_2 levels, for both TA and SC pathways. To further stress the energy-intensive synaptic machinery, we applied trains of 20 stimuli (50 Hz) every 60 s. fEPSP depression during repeated stimulation was increased during isoflurane application (425 μM), to equal

degrees at low and high O_2 levels, and at low O_2 levels the depression persisted following isoflurane washout. **Conclusions:** Isoflurane acutely suppressed SC more than TA responses, independent of O_2 level. By contrast, iso-LTD was O_2 level-dependent and affected both pathways equally. Finally, O_2 level-dependent recovery was the reverse for trains vs single stimuli applied to the SC pathway. **References:** 1. Raz, *Front Syst Neurosci* **8**:191 (2014); 2. Zimin, *Br J Anesth* **120**:1019 (2018).

Disclosures: S. Klein: None. **R.A. Pearce:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.09

Topic: B.06. Synaptic Transmission

Support: Biology Department at IUPUI
R33DA041876

Title: Generation of transgenic tools to delineate striatal neurabin function

Authors: *W. COREY[1], A. J. BAUCUM, II[1,2,3];
[1]Biol., Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [2]Pharmacology/toxicology, [3]Stark Neurosci. Res. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Amphetamine abuse in the US has been steadily increasing, and in some areas poses a greater threat than the opioid crisis. A key brain region involved in drug seeking and drug taking is the striatum. The dorsal and ventral subdivisions of the striatum work in concert to mediate the reinforcing and motor behavioral effects of amphetamine. Therefore, understanding how amphetamine alters striatal function is a key component in devolving novel therapeutics for drug abuse and addiction. The main output neurons of the striatum are GABAergic, medium-spiny neurons (MSNs), and striatal functionality is mediated by neuroplastic changes in MSN activity. Within MSNs, dopaminergic receptor activation triggers a cascade of reversable phosphorylation, which is facilitated by the activation of specific protein kinases and inhibition of specific protein phosphatases. In comparison to abundant protein kinase expression, only four serine/threonine protein phosphatases are expressed in the striatum. However, serine/threonine protein phosphatases, such as PP1, gain their target specificity by interacting with phosphatase-targeting proteins. Within the striatum, the neurabins, termed neurabin and spinophilin, are the most abundant PP1 targeting proteins in dendritic spines. Spinophilin's expression in the striatum has been strongly characterized, and spinophilin has been shown to regulate striatal-dependent motor-skill learning and amphetamine-induced locomotor sensitization. In contrast to spinophilin, neurabin's expression within the striatum and its involvement in these striatal-dependent behaviors has not been fully probed. We found that neurabin expression in the striatum is not sex-dependent but is age-dependent. In addition to this data, we also present validation of a new global neurabin knock-out mouse model and preliminary data on the generation of a conditional knock-out mouse model. These mice will be utilized to probe neurabin's involvement in striatal-dependent motor-skill learning and amphetamine-dependent locomotor sensitization. Understanding neurabin's expression in the striatum, and its role in these key striatal

behaviors could, along with spinophilin, provide a druggable target for therapeutics designed to address drug abuse and addiction.

Disclosures: W. Corey: None. **A.J. Baucum:** None.

Poster

P106. Modulation: Pharmacology

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P106.10

Topic: B.06. Synaptic Transmission

Support: Departmental grant from Anesthesiology Department at Columbia University

Title: $Gaba_A$ receptors containing the α4 subunit modulate emergence/recovery following anesthesia with different general anesthetics in mice

Authors: *M. T. MANSOURI, P. S. GARCIA;
Dept of Anesthesiol., Columbia Univ. Irving Med. Ctr., New York, NY

Abstract: Introduction: Transitions into conscious states are partially mediated by inactivation of sleep networks and activation of arousal networks. Our previous work demonstrated that the GABA Type A receptor ($GABA_AR$) antagonist, flumazenil, can promote wakefulness in patients with idiopathic hypersomnia. Also, we reported that intravenous flumazenil could hasten EEG and behavioral correlates of emergence from isoflurane anesthesia in rats. **Objective:** As the $GABA_AR$ mediates the clinical effects of many common general anesthetics, we aimed to evaluate the role of $GABA_ARs$ containing the alpha-4 subunit (GABRA-4) in emergence and recovery from three different anesthesia regimens: inhaled isoflurane, injected ketamine/xylazine and injected ketamine in mice. **Methods:** Age-matched, adult male (n=32; 26-30 g) mice genetically manipulated to knock-out (KO) the gabra4 gene and wild-type (WT) littermates were used. Following the administration of isoflurane (1.5%, 90 min), ketamine/xylazine (K/X, 90/5 mg/kg, intraperitoneal) and ketamine (90 mg/kg, intraperitoneal), loss of righting reflex (LORR), minimal alveolar concentration (MAC), emergence (return of righting reflex; RORR) and recovery (sticky dot notice) were recorded. Cognitive performance was also evaluated using spontaneous Y-maze alternation test. **Results:** We demonstrated that genetic ablation of GABRA-4, hastens emergence from anesthesia from each tested anesthetic regimen without significant changes in recovery characteristics. The cognitive performance of mice in a working memory assessment (Y-maze) was not different among these groups. Although loss of righting reflex appears to be delayed in α4 knockout animals, the minimal alveolar concentration of isoflurane to suppress movement was not different between the two groups, indicating α4 $GABA_ARs$ in the spinal cord are not key mediators of anesthetic-induced immobility. Pharmacologic studies with a gaboxadol (a preferred GABRA-4 agonist) confirm these specific effects occur during emergence from anesthesia via α4-containing $GABA_A$ receptors without an associated change in recovery and/or cognitive performance. **Conclusion:** We conclude that there are important differences in the neural substrates mediating emergence and recovery. These findings confirm that α4-containing $GABA_A$ receptors are involved in hastening wakefulness.

Disclosures: M.T. Mansouri: None. **P.S. Garcia:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.01

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1R01NS104008 - 01A1

Title: Neuron glia interactions in adult hormone modulated plasticity in male and female canaries (Serinus canaria)

Authors: P. A. MASSA[1], A. P. BOGARD[1], E. E. SANDMAN[1], G. F. BALL[2], *F. N. MADISON[1]; [1]Dept. of Biol., Hope Col., Holland, MI; [2]Univ. of Maryland, College Park, MD

Abstract: In temperate zone species such as canaries (Se*rinus canaria*) the neural circuitry regulating song behavior undergoes well-defined changes across the seasons. In males, increased daylengths in the spring initiates an increase in gonadal volumes and circulating testosterone driving marked changes in brain morphology and song frequency. Females given exogenous testosterone in adulthood, also demonstrate male-like changes in brain morphology and song behavior. More specifically, the telencephalic nucleus HVC (acronym is proper name), a key nucleus for song production, undergoes well-defined seasonal changes in neuroplasticity with a high rate of neurogenesis mediating marked changes in HVC volume. Much is known about the neural circuitry driving song behavior, however, the mechanisms underlying the morphological changes in adult hormone-modulated brain plasticity remain to be elucidated. In mammals, astrocytes, specialized glial cells that promote neuron migration and survival, have been shown to mediate maturation and plasticity of neuronal networks. In male songbirds, astrocytes parallel seasonal plasticity, suggesting that astrocytes may play a role in hormone-modulated neurogenesis. We therefore sought to investigate the role of astrocytes in adult hormone modulated neuroplasticity in male and female canaries. Males were castrated and females were photoregressed and housed in our aviary on short days (8L:16D) for at least 6 weeks. Birds were surgically implanted with either a 10 mm testosterone-packed Silastic implant or an empty implant as a control for 7 days. Brains were extracted, sectioned, and HVC volumes were quantified in Nissl stained sections. Brain sections were also double-labeled via immunohistochemistry for glial fibrillary acidic protein (GFAP) and neuronal nuclear protein (NeuN). Both males and females treated with testosterone had larger HVC volumes compared to controls. Preliminary evidence demonstrates increased GFAP-immunoreactivity in the ventricular and neurogenic subventricular zone suggesting that astrocytes may play a role in the guidance and survival of new neurons migrating to HVC in both male and female canaries.

Disclosures: P.A. Massa: None. **A.P. Bogard:** None. **E.E. Sandman:** None. **G.F. Ball:** None. **F.N. Madison:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.02

Topic: B.07. Synaptic Plasticity

Support: Grant-in-Aid for Scientific Research on Innovative Areas, 19H05430

Title: Astrocyte dependency of synchronous activities in the neonatal hippocampal networks

Authors: *R. IDE, Y. SHINDO, K. HOTTA, K. OKA;
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Abstract: The dynamics of the mammalian central nervous system change dramatically around the first week after birth. During this period, immature neurons extend their neurites and establish large number of synapses to form a functional neuronal network. The formation of this network in the mammalian brain depends on not only genetic programs but its neural activities. Neural activities in the neonatal hippocampal neurons are regulated by their principal neurotransmitters: GABA and glutamate.Synchronized activities in the neural network is a typical characteristic on the neonatal period. They were observed only in the immature networks when GABA behaves as an excitatory neurotransmitter (Yamanaka et al. 2018). Although excitatory GABA and glutamate are thought to trigger the synchronous network events, the details of their mechanism remain unclear. In particular, the contribution of astrocytes to these events is largely unknown. Previous paper has stated astrocytes synchronized local neuronal activity via extra-synaptic NMDA receptors (Carmignoto et al. 2006). However, it is not clarified how astrocytes orchestrate the synchronization of large population of neuronal activities.Astrocytes generate spontaneous and evoked Ca^{2+} transients. The density of astrocytes and the number of gap junctional coupling between astrocytes increases during the first postnatal week. Moreover, astrocytes change their protein expression profiles in the same period. Astrocytes also regulate synapse formation and extracellular ion concentrations through these changes in properties.In this work, we studied the mechanism of synchronous network events and the role of astrocytes in these events. We observed the cellular events of each neuron by Ca^{2+} imaging to examine its contribution to the synchronous network events. These events were transient; they disappeared until the second postnatal weeks *in vitro*. They were mediated by activation of $GABA_A$ receptors because the inactivation of $GABA_A$ receptor abolished them. Synchronization was observed in networks with/without astrocytes, and there was a trend of negative correlation between the frequency of synchronized network events and the number of astrocytes. The networks with high percentage of astrocytes show more neurons with sporadic activities. However, the ratio of astrocytes did not change the fraction of neurons participating in synchronized network events. These results suggest that the activities of GABAergic neurons cause synchronized network events, and astrocytes contribute to network events indirectly via synapse formation, rather than through direct involvement including the release of glutamate.

Disclosures: R. Ide: None. **Y. Shindo:** None. **K. Hotta:** None. **K. Oka:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.03

Topic: B.07. Synaptic Plasticity

Support: Wings for Life
Moseley

Title: Astrocyte to neuron reprogramming for spinal cord repair

Authors: *A. NICEFORO[1], T. A. FORTINO[2], Y. SHAH[2], L. V. ZHOLUDEVA[4], L. QIANG[3], M. A. LANE[3];
[1]Drexel University-College of Med., Philadelphia, PA; [2]Neurobio. & Anat., [3]Drexel Univ., Philadelphia, PA; [4]Gladstone Inst., San Francisco, CA

Abstract: Traumatic spinal cord injury (SCI) results in the loss of neurons and glia with accompanied reactive gliosis and tissue scarring, preventing significant endogenous repair. A potential, innovative therapeutic strategy that can be used to target these reactive astrocytes is direct cellular reprogramming by overexpression of neurogenic transcription factors (TFs) or microRNAs (miRs) that controls cellular fates. Here we used a rat model of cervical SCI to test the hypothesis that activated resident astrocytes known to partition the cavity that develops after injury, can be reprogrammed into neurons by inducing the expression of either *Ascl1,* an early expressed neurogenic TF, or a combination of *miR124* and *miR9/9**. Primary astrocyte cultures were generated from postnatal days 2-3 (P2-3) rat cortex and spinal cord, and activated with TGFβ (Transforming growth factor beta) one day prior to doxycycline-inducible lentiviral transduction. Doxycycline was added for 15 days to induce TF expression, prior to extended culture to facilitate neuronal maturation. Immunocytochemistry revealed glial-derived neurons positive for neuronal markers (e.g., MAP2, NeuN and TAUR1) and negative for the astrocytic markers (e.g., GFAP). Neuronal activity was measured using multielectrode arrays (MEAs) in reprogrammed cells compared to scramble virus-treated astrocytes. Anatomical, behavioural and electrophysiological outcome measures were used to assess the effects of the reprogramming strategies *in vivo,* post-cervical SCI. While anatomical evidence confirmed *in vivo* reprogramming of resident astrocytes into neurons, behavioural and functional outcomes showed no significant differences in respiratory function. Advances in cellular reprogramming are providing novel ways to manipulate the cytoarchitecture of the injured cervical spinal cord. This ongoing research is highlighting a novel therapeutic approach for promoting anatomical repair.

Disclosures: A. Niceforo: None. **T.A. Fortino:** None. **Y. Shah:** None. **L.V. Zholudeva:** None. **L. Qiang:** None. **M.A. Lane:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.04

Topic: B.07. Synaptic Plasticity

Title: Transplanting glial restricted progenitor cells for repair

Authors: *M. CUSIMANO;
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Abstract: *Marissa Cusimano[1,2], Alessia Niceforo[1,2], Tara Fortino[1,2], Indigo VL Rose[4], Lyandysha V. Zholudeva[3], Shane Liddelow[4,5,6], Liang Qiang[1,2], Michael A. Lane[1,2]*
1.*Department of Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, USA* 2.*Spinal Cord Research Center, Drexel University College of Medicine, Philadelphia, USA*3.*Gladstone Institutes, San Francisco, California, USA*4.*Neuroscience Institute, NYU Grossman School of Medicine, New York, NY, USA*
More than half of all spinal cord injuries (SCIs) occur at the cervical level resulting in persistent, life-threatening respiratory deficits. Respiratory compromise and associated secondary complications remain a leading cause of morbidity and mortality in patients suffering from cervical SCI. While spontaneous improvements in respiration have been reported clinically and experimentally, this spontaneous recovery alone remains insufficient to significantly improve respiratory function. Given the limited capacity for self-repair in the spinal cord, there has been a significant research effort toward promoting neural repair post-SCI. One promising approach with continued pre-clinical and clinical interest, is transplantation of neural precursor cells that have been shown to survive, integrate and even facilitate neural repair. One component of these donor cells is glial restricted progenitors (GRPs), that have been shown to reorganize the cytoarchitecture of the injured internal milieu and promote and support axonal growth. Preclinical studies have demonstrated that GRPs transplanted into SCI, migrate into host tissue, reduce glial scar formation and inflammation, while promoting axon growth post-SCI. However, several pre-clinical studies have yielded variable or only limited functional recovery. Therefore, we propose that GRPs alone require additional components, such as endothelial cells (ECs) to enhance cell survival, integration, and tissue repair. Our preliminary studies demonstrate that transplantation of ECs at the site of injury contribute to vascular repair. Phenotypic analysis (immunocytochemistry, gene expression) is used to define phenotype of donor cells prior to and following transplantation. Particular attention is given to the pro-reparative phrenotypes of these donor cells. Ongoing work tests the efficacy of transplanted cells to anatomically and functionally integrate with injured vasculature and phrenic spinal pathways, and their contribution to improved phrenic function post-SCI.

Disclosures: M. Cusimano: None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.05

Topic: B.07. Synaptic Plasticity

Support: DBT/Wellcome Trust India Alliance [Senior Fellowship No. IA/S/16/2/502727]
Department of Biotechnology through the DBT-IISc partnership program
Revati and Satya Nadham Atluri Chair Professorship

Title: Synergistic interactions among intrinsic, synaptic, and structural heterogeneities drive synaptic plasticity profiles in dentate gyrus granule cells

Authors: *S. SHRIDHAR[1], P. MISHRA[2], R. NARAYANAN[1];
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Abstract: Granule cells (GC) in the dentate gyrus exhibit pronounced heterogeneities in their intrinsic properties and synaptic connectivity, with these heterogeneities further amplified by the expression of adult neurogenesis. The impact of such heterogeneities on synaptic plasticity rules has not been quantitatively analyzed. Here, we assessed the ramifications of the expression of intrinsic, synaptic, and structural heterogeneities on synaptic plasticity profiles induced through two protocols: the BCM-like 900-pulses protocol and the theta-burst stimulation (TBS) protocol. First, we addressed the impact intrinsic heterogeneities had on plasticity profiles obtained with both induction protocols, with a fixed baseline synaptic strength across models. We found that heterogeneities in intrinsic properties resulted in heterogeneities in the modification threshold of the BCM-like protocol and the amount of plasticity induced by TBS. However, pair-wise correlations between these plasticity measurements and any of the intrinsic measurements or parameters were weak ($|r|<0.4$). Next, we examined the relationship between excitability properties and synaptic strength and showed that similar plasticity profiles could be obtained across all models with different synaptic strengths, thereby demonstrating plasticity degeneracy whereby the impact of heterogeneities in intrinsic properties could be counterbalanced by heterogeneities in synaptic strength. However, we did not find strong pair-wise correlations between synaptic strength and any intrinsic measurement or parameter governing the model. We then explored the role of neurogenesis-induced structural heterogeneity, by progressively altering the diameter of the model neurons, mimicking maturation-induced increase in GC surface area. When synaptic strengths were fixed, we found a progressive rightward shift in the plasticity profile with an increase in diameter. Importantly, in immature neurons with extremely small diameters, the plasticity profile manifested no long-term depression for a large range of baseline synaptic strength values. Finally, when the plasticity profiles were tuned to be similar by altering synaptic strengths, we found the emergence of plasticity degeneracy involving intrinsic, structural, and synaptic parameters. Together, our analyses provide a biophysical framework for understanding the role of various heterogeneities and the synergistic interactions among them in engram cell formation, in effectuating the maturation-induced switch in synaptic plasticity regimes, and in the emergence of plasticity degeneracy.
*SS & PM contributed equally to this study.

Disclosures: S. Shridhar: None. **P. Mishra:** None. **R. Narayanan:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.06

Topic: B.07. Synaptic Plasticity

Title: Hippocampal and thalamic afferents form distinct synaptic microcircuits in the mouse infralimbic frontal cortex

Authors: *K. GRAHAM[1], N. P. SPRUSTON[2], E. B. BLOSS[1];
[1]The Jackson Lab., Bar Harbor, ME; [2]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Neural circuits within the frontal cortex support the flexible selection of goal-directed behaviors by integrating input from brain regions associated with sensory, emotional, episodic, and semantic memory functions. From a connectomics perspective, determining how these disparate afferent inputs target their synapses to specific cell types in the frontal cortex may prove crucial in understanding circuit-level information processing. Here, we used monosynaptic retrograde rabies mapping to examine the distribution of afferent neurons targeting four distinct classes of local inhibitory interneurons and four distinct classes of excitatory projection neurons in mouse infralimbic cortex. Interneurons expressing parvalbumin, somatostatin, or vasoactive intestinal peptide received a large proportion of inputs from hippocampal regions, while interneurons expressing neuron-derived neurotrophic factor received a large proportion of inputs from thalamic regions. A more moderate hippocampal-thalamic dichotomy was found among the inputs targeting excitatory neurons that project to the basolateral amygdala, lateral entorhinal cortex, nucleus reuniens of the thalamus, and the periaqueductal gray. Together, these results show a prominent bias among hippocampal and thalamic afferent systems in their targeting to genetically or anatomically defined sets of frontal cortical neurons. Moreover, they suggest the presence of two distinct local microcircuits that control how different inputs govern frontal cortical information processing.

Disclosures: K. Graham: None. **N.P. Spruston:** None. **E.B. Bloss:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.07

Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH113545
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Title: Synaptic signaling networks encode experience by assuming stimulus-specific and brain-region-specific states

Authors: *J. LAUTZ[1], E. GNIFFKE[1], K. TSEGAY[1], Z. ZHU[2], J. P. WELSH[3], S. E. SMITH[4];
[2]CIBR, [3]Ctr. for Integrative Brain Res., [1]Seattle Children's Res. Inst., Seattle, WA; [4]Ctr. for Integrative Brain Res., Seattle Childrens Res. Inst., Seattle, WA

Abstract: A core network of ubiquitously expressed glutamate-synapse-associated proteins mediates activity-dependent synaptic plasticity throughout the brain, but the specific proteomic composition of synapses differs between brain regions. Here, we sought to classify the diversity of activity-dependent remodeling across brain regions using quantitative multiplex co-immunoprecipitation (QMI). This novel proteomic technique allows for the simultaneous and quantitative measurement of the amount of co-association between large numbers of proteins in shared complexes.We first compared the response of cultured neurons to distinct stimuli, and defined PIN parameters that differentiate input types. We next

compared the response of three different brain regions maintained alive in vitro to an identical stimulus, and identified three qualitatively different PIN responses. Finally, we measured the PIN response following associative learning tasks, delay and trace eyeblink conditioning, in three brain regions, and found that the two forms of associative learning are distinguished from each other using brain-region-specific network mechanisms. We conclude that although the PIN of the glutamatergic post-synapse is expressed ubiquitously, its activity-dependent dynamics show remarkable stimulus-specific and brain-region-specific diversity.

Disclosures: J. Lautz: None. **E. Gniffke:** None. **K. Tsegay:** None. **Z. Zhu:** None. **J.P. Welsh:** None. **S.E. Smith:** None.

Poster

P121. Structural Plasticity: Neurons, Glial, Microcircuits, and Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P121.08

Topic: B.07. Synaptic Plasticity

Support: Singapore Ministry of Education Academic Research Fund Tier 3 MOE2017-T3-1-002
NUSMED-FOS Joint Research Programme NUHSRO/2018/075/NUSMed-FoS/01
NUS Research Scholarship

Title: Interrogating modulatory effects of CA2 on CA1 plasticity in mice hippocampus

Authors: *M. BIN IBRAHIM, N. KOH, S. SAJIKUMAR;
Natl. Univ. of Singapore, Singapore, Singapore

Abstract: The hippocampus plays an integral role in episodic memory formation and storage, particularly by neurons in its CA1 subfield. Beyond the circuitry is the CA2 region. While not directly involved in the hippocampal loop and episodic memory, the CA2 region is implicated in social memory. There also exists monosynaptic connections from CA2 innervating CA1. The functional relevance of the CA2-CA1 connections has yet to be uncovered, suggesting possible modulation of CA1 by CA2. Unravelling this will shed light on how different forms of memory – episodic and social – interact with one another in the hippocampus. Hence, it is likely that these connections could play a role in memory persistence of episodic memory in the CA1 via activation during social interaction.We aimed to interrogate how the CA2-CA1 connections can modulate synaptic plasticity of the Schaffer collateral (SC)-CA1 synapses. Field electrophysiology of hippocampal slices from young male C57BL/6 mice was utilised to measure synaptic modification via long-term potentiation (LTP), a cellular correlate of learning and memory. Weak stimulation of SC-CA1 synapses exhibit early-LTP but not late-LTP in SC-CA1 synapses. Besides that, the weak stimulation of CA2 neurons does not lead to any modification in synaptic strength in SC-CA1 synapses. However, when preceded by a weak stimulation of CA2 neurons, SC-CA1 synapses exhibit a late phase of LTP upon weak stimulation. This ‘priming’ phenomenon is also shown to be protein synthesis-dependent and time-dependent.Following this, we investigated the associativity of the CA2-primed late-LTP via the synaptic-tagging-and-capture hypothesis (STC), a model for associative plasticity. Using field electrophysiology, CA2-primed late-LTP is unable to participate in STC. When a

second set of SC-CA1 synapses is weakly stimulated following CA2 priming, both the first and second population of SC-CA1 synapses can only exhibit early-LTP. This preliminary set of results demonstrate that CA2 connections onto CA1 can influence the synaptic plasticity of CA1, suggesting possible implications of how social behavioural states can modulate persistence of memory. Our next steps will involve analysing the molecular pathways and players involved in plasticity and signalling, and replicating the electrophysiological result using behavioural models.

Disclosures: M. Bin Ibrahim: None. **N. Koh:** None. **S. Sajikumar:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.01

Topic: B.10. Epilepsy

Support: NINDS

Title: Seizure onset is stochastic at the single neuron level

Authors: *L. A. LAU, K. P. LILLIS, K. J. STALEY;
Massachusetts Gen. Hosp., Boston, MA

Abstract: Acquired epilepsies are characterized by spontaneous, recurrent seizures that emerge following injury. The unpredictable nature of seizures is one of the most disabling features of epilepsy. Understanding seizure initiation, or ictogenesis, is critical for developing mechanistically based treatments for medically refractory epilepsy. However, ictogenesis is difficult to study, due to the spontaneous nature of seizures and poor spatial sampling available for capturing seizure onset in vivo. Here, we developed novel techniques for chronic cellular resolution imaging of neuronal activity in the hippocampal organotypic slice culture model of post-traumatic epilepsy to analyze seizure onset at the single neuron level. Hippocampal slice cultures generate spontaneous seizure-like events following slicing injury. With this preparation, it is feasible to image the entire network, ensuring that the earliest pathological activity is captured (as no outside inputs exist). Pan-neuronal GCaMP7 expression was paired with DLX-cre-targeted tdtomato labeling of interneurons to separate the calcium activity of principal cells and interneurons. We used a custom imaging system to observe undisturbed organotypic hippocampal slice cultures over several weeks to capture the calcium activity across dozens of seizures. Chronic calcium imaging of the entire hippocampal network, with paired electrophysiology, revealed 3 patterns of seizure onset: low amplitude fast activity, sentinel spike, and spike burst + low amplitude fast activity onset. These patterns recapitulate common features of human seizure onset, including low voltage fast activity and spike discharges. We also used this preparation to track the activity of individual neurons and test whether a subpopulation of neurons consistently initiates seizure activity. Our cellular level tracking revealed that neuronal onset sequences were highly variable seizure-to-seizure and lacked a repeatable population of neuronal activators at seizure onset. These results argue against seizure initiation by a small number of neuronal drivers, such as hub cells, and is rather consistent with transitions to seizures driven by state changes that allow for re-entrant seizure activity in non-stereotyped sequences.

We further explore how individual neurons contributed to the overall population signal during ictal onset and frank seizure. Interestingly, the large population signal during frank seizure is due to both synchronous re-activation of neurons that were recruited during onset and increased intra-cellular calcium amplitude.

Disclosures: L.A. Lau: None. **K.P. Lillis:** None. **K.J. Staley:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.02

Topic: B.10. Epilepsy

Support: NIH R01NS115017
NIH R01NS094596

Title: Establishing a human iPSC-derived neuron model of SLC35A2-associated epilepsy

Authors: *D. LAI[1], D. WILLIAMS[2], P. SOSICKA[3], A. K. RESSLER[2], H. H. FREEZE[3], M. BOLAND[2], E. L. HEINZEN[1];
[1]Univ. of North Carolina, Chapel Hill, NC; [2]Columbia Univ., New York, NY; [3]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: *SLC35A2* encodes a Golgi-localized UDP-galactose transporter that is essential for protein glycosylation. Variants in *SLC35A2* cause a congenital disorder of glycosylation that is associated with intractable seizures, as well as epileptic encephalopathies. Our lab was the first to identify post-zygotically acquired *de novo*, loss-of-function (LOF) variants in *SLC35A2* in 17% of individuals with intractable non-lesional focal epilepsy – a finding now corroborated by two other groups. Despite this clear association with epilepsy, it is unknown how *SLC35A2* variants contribute to epileptogenesis. In this study, we develop a human induced pluripotent stem cell (iPSC) derived neuron model to investigate how *SLC35A2* variants disrupt neural activity and neural connectivity using whole-cell patch clamp electrophysiology and multielectrode array (MEA), respectively.
We have established iPSCs (isogenic control) CRISPR-edited to harbor a pathogenic missense variant (p.Ser304Pro; SLC35A2$^{S304P/Y}$) and a frameshift indel (SLC35A2$^{-/Y}$), all of which express the pluripotent markers NANOG and SOX2 using immunofluorescent (IF) staining. Both *SLC35A2* missense and indel variants encode LOF proteins, which is validated using a MALI lectin binding assay that showed reduced binding in SLC35A2$^{S304P/Y}$ and SLC35A2$^{-/Y}$ protein lysates compared to the isogenic control. Loss of transporter activity can be attributed to reduced protein expression and loss of Golgi-localization when assessed on IF staining. To investigate the consequence of *SLC35A2* variants on neural network activity, iPSCs were differentiated into glutamatergic neurons using dual smad inhibition and plated for MEA analysis. Over six weeks of recordings, synchronous activity was only detected in isogenic control neural networks compared to those formed by SLC35A2$^{S304P/Y}$ and SLC35A2$^{-/Y}$ neurons as quantified by mutual information (P-value <0.01) and the spike train tiling coefficient (P-value <0.01). Whole-cell patch clamp electrophysiology recordings also reveal differences in excitability between *SLC35A2* variants compared

to the isogenic control when action potential (AP) characteristics (e.g., AP duration, rheobase, etc.) and passive membrane properties (e.g., resting membrane potential, capacitance, etc.) are assessed. Together, these findings demonstrate that neurons harboring *SLC35A2* variants lead to aberrant neuron function and network activity, which may be contributing to the epileptogenic phenotype. Further characterization of the underlying mechanisms of *SLC35A2*-associated epileptogenesis and evaluations across an allelic series in this model system are underway.

Disclosures: D. Lai: None. **D. Williams:** None. **P. Sosicka:** None. **A.K. Ressler:** None. **H.H. Freeze:** None. **M. Boland:** None. **E.L. Heinzen:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.03

Topic: B.10. Epilepsy

Support: Program for Research Initiated by Students and Mentors (PRISM)
American Academy of Neurology Medical Student Research Scholarhship

Title: Role of Functional Network Formation in Epilepsy

Authors: *U. BODDETI[1], M. BACHANI[1], J. OWOTADE[1], M. MOYER[1], R. SERRA[1], H. P. ZAVERI[2], K. ZAGHLOUL[3], A. KSENDZOVSKY[4];
[1]The Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Dept. of Neurol., Yale Univ., New Haven, CT; [3]NIH, Bethesda, MD; [4]Dept. of Neurosurg., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Introduction: Despite surgical resection of a defined epileptogenic focus (EF), about 50% of patients go on to have refractory seizures[1]. Recently, focal epilepsy is being redefined as a network disorder[1] and studies have demonstrated that resection of nodes outside the EF may contribute to better surgical outcomes[1]. Additionally, our group has shown higher interictal connectivity between nodes involved in seizure onset in a cohort of epilepsy patients, further suggesting the presence of an underlying distributed epileptogenic network in focal epilepsy[1].
Objective: To characterize seizure network formation in a novel *in vitro* culture model of cortical epilepsy.
Methods: Primary mixed cultures of cortical neurons from P1 rat pups were cultured on 96-well multi-electrode array (MEA) plates with eight active electrodes per well for stimulation and recording. We developed an *in vitro* stimulation model of cortical epilepsy to study epilepsy network formation using a biphasic tetanic stimulation at 50 or 100 Hz, 500 μV, 250 μA applied for one hour daily for ten days.
Results: Four-days of daily *in vitro* stimulation demonstrated significant increases in neuronal baseline bursting, modeling kindled seizures. Tetanic stimulation with 50Hz had the highest elevation in neuronal busting. In order to compare distributed network connectivity, we calculated and ranked coherences (13-32Hz) across all electrode pairs (n=24) and identified the top 15% for comparison to control. The average coherence across the top connected pairs was significantly higher in stimulated wells compared to controls (0.27 vs. 0.17, p=0.0002). Furthermore, coherence across the highest-ranking electrode pair was

strengthened with daily stimulation. This was not seen in control electrodes.
Conclusion Statement from Research Findings: Our data suggests that daily stimulation with 50Hz strengthens connectivity and increases overall neuronal bursting *in vitro* thereby potentially recapitulating *in vivo* seizure networks.
Conclusion: Similar to human data, this *in vitro* model suggests an elevated interictal coherence among electrode pairs involved in seizure formation. Next, we aim to characterize the structural nature of this network quantifying axonal boutons and dendritic spines. Ultimately, our work aims to enable a better understanding of network formation in epilepsy that will inform future epilepsy surgery decision making.
References:
1. Andrews JP, Gummadavelli A, Farooque P, et al. Association of Seizure Spread With Surgical Failure in Epilepsy. *JAMA Neurol*. 2019;76(4):462-469. doi:10.1001/jamaneurol.2018.4316

Disclosures: U. Boddeti: None. **M. Bachani:** None. **J. Owotade:** None. **M. Moyer:** None. **R. Serra:** None. **H.P. Zaveri:** None. **A. Ksendzovsky:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.04

Topic: B.10. Epilepsy

Support: CNPq
CAPES

Title: In vitro oscillation patterns of distinct areas of hippocampal formation in animal model of epilepsy

Authors: J. RIGHES MARAFIGA, M. VENDRAMIN PASQUETTI, *M. CALCAGNOTTO; Biochem., NNNESP Lab-UFRGS, Porto Alegre, Brazil

Abstract: Introduction: Hippocampal network oscillations are useful to pursue brain activity in temporal lobe epilepsy (TLE). However, the dynamics of underlying oscillation pattern during the epileptogenesis throughout the hippocampal formation in TLE is not clear. Here, we characterized the *in vitro* oscillatory patterns within the hippocampal formation of adult epileptic male rats at two different stages of epileptogenesis, 30 and 60 days after pilocarpine-induced *Status Epilepticus* (*SE*). Material and Methods: Extracellular pair recordings were performed in CA1, CA3, dentate gyrus (DG) and entorhinal cortex (EC) of hippocampal formation slices of epileptic (n = 19) and aged-matched control (n = 20) animals, under either 4-Aminopyridine (4-AP)-induced hyperexcitability or spontaneous network activity condition, without 4-AP. Local field potentials were analyzed and power spectral densities (n_{epoch} = 30-50) and phase coherence (n_{epoch} = 20-25) were computed in 5s-epochs between interictal epileptiform events (IEDs) and 5s-epochs of spontaneous network activity using MATLAB. Data were analyzed by either Student's *t*-test (parametric) or Mann-Whitney U test. (non-parametric) with significance level of $p<0.05$. All animal procedures were performed according the Ethics Committee on Animal Use-UFRGS (approval # 33274). Results: At 30 days post-*SE*, 4-AP bathed slices from epileptic animals had increased ictogenesis in CA1; higher power of slow and/or middle gamma in EC, CA1 and CA3; and high-

frequency oscillations (HFOs) in CA3. Phase coherence was higher in middle gamma between CA1-CA3 and EC-CA1, and in HFOs between EC-CA1. At 60 days post-*SE*, we observed increased ictogenesis in EC and DG; higher power of slow and/or middle gamma in CA1, CA3 and DG, HFOs in EC, CA3 and DG; and higher phase coherence in HFOs between CA1-CA3. Under spontaneous network activity at 30 days post-*SE,* slices from epileptic animals, already had higher power of slow and/or middle gamma in all recorded regions, and HFOs in EC. At 60 days post-*SE*, they had higher power of slow and/or middle gamma in EC, CA3 and DG, higher power of HFOs in DG; and higher phase coherence in fast ripples oscillations between DG-CA3, when compared to controls. Conclusion: We found, region- and stage-dependent specific changes in gamma and HFOs within the hippocampal formation of epileptic animals under a second insult of hyperexcitability and during the spontaneous network activity, without epileptiform activity. Taken altogether, our results reinforce the role of gamma and HFOs within the hippocampal formation in ongoing pathological processes of network reorganization, crucial to the epilepsy establishment.

Disclosures: J. Righes Marafiga: None. **M. Vendramin Pasquetti:** None. **M. Calcagnotto:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.05

Topic: B.10. Epilepsy

Support: NIH Grant AG055328
NIH Grant MH109305
NIH Grant NS037562
NIH Grant NS081203

Title: Use of a submerged chamber for new insights into spreading depolarization in hippocampal slices

Authors: *Y.-L. LU[1], H. E. SCHARFMAN[1,2];
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Abstract: Spreading depolarization (SD) is sudden and synchronized depolarization of principal cells followed by depression of activity, which slowly propagates across brain regions like cortex or hippocampus. SD is considered to be mechanistically relevant to migraine, epilepsy, and traumatic brain injury. Interestingly, research into SD, especially SD that occurs spontaneously, is not as common as SD using models of focal stimulation. Here we optimize an in vitro experimental model allowing us to record SD without focal stimulation. This method uses electrophysiological recordings and imaging of intrinsic optical signals in slices. The method is also relatively easy and inexpensive. Acute hippocampal slices from mice or rats were prepared and used for extracellular and whole-cell recordings in area CA3. Recordings were made in a submerged-style chamber which allowed flow of artificial cerebrospinal fluid (aCSF) above and below the slices. Flow was fast (>5ml/min), and temperature was 32°C. ACSF

containing 0 mM Mg^{2+} and 5 mM K^{+} (0 Mg^{2+}/5 K^{+} aCSF) was used. Two major types of activity were observed: SD and seizure-like events (SLEs). Although both mouse and rat slices showed SLEs, only mouse slices developed SD in the first hour of 0 Mg^{2+}/5 K^{+} aCSF exposure. Intrinsic optical imaging showed that most SDs initiated in CA3 and propagated into CA1 and dentate gyrus. In dentate gyrus, SD propagated in two separate waves: into hilus and into granule cell/molecular layers. This optimized in vitro model can be used to better understand the mechanisms and relationship between SD and SLEs. It could also be applied in preclinical drug testing.

Disclosures: Y. Lu: None. **H.E. Scharfman:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.06

Topic: B.10. Epilepsy

Support: NS082046
NS32403

Title: Selective modulation of vCA1 rescues social memory in chronic epileptic mice.

Authors: *A. M. GOODMAN[1], J. B. KAHN[3], A. M. BERNAL[4], D. A. COULTER[2];
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Abstract: Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults and is associated with high rates of comorbidities including cognitive, behavioral, and affective disruptions. These comorbidities are not only detrimental to quality of life but are not corrected - and may even be exacerbated - by existing therapies for TLE. Central to chronic TLE are dysfunctional hippocampal circuits which, when healthy are critical for appropriate function of several types of learning, memory, and related cognition, making them prime targets for therapeutic intervention. Since this epilepsy-associated behavioral dysfunction is presumably based on hyperexcitable aggregate circuit properties, our overarching goal is to modify the activity of these circuits, thereby correcting behavioral dysfunction. Our previous work used chemogenetic DREADDs in vCA1 to demonstrate that circuit-level manipulation of activity was able to rescue performance in a social memory discrimination (SMD) task in a 22q11.2 deletion syndrome mouse model of psychiatric disorders. We also showed that DREADD mediated inhibition of dentate gyrus granule cells in a pilocarpine (pilo) mouse model of TLE was sufficient to rescue spatial object recognition performance in a region-dependent manner. In this study, we first identified that epileptic (pilo) mice had deficient social memory, assessed with the SMD task. We next determined the role of vCA1 pyramidal neurons in mediating this behavioral deficiency. Inhibitory DREADDs (hM4Di/KORD) recruitment in vCA1 excitatory neurons was sufficient to rescue SMD (p=0.043, RM 1-way ANOVA). Cre-dependent vCA1 DREADDs together with CaV2-Cre infusion into the mPFC were used to selectively modulate mPFC projecting vCA1 pyramidal neurons to determine the

role of the subnetwork in SMD deficiency. Selective inhibition of mPFC projecting vCA1 pyramidal neurons was also able to rescue SMD (p=0.012, paired t-test). In summary, hyperexcitable vCA1 neurons are critical mediators of epilepsy associated deficits in social memory. These results further demonstrate that circuit-specific modulation may be a viable therapeutic strategy to correct multiple behavioral comorbidities. We extend this conclusion by showing that subnetwork specific circuit modulation may be used to provide specific, targeted correction of behavioral comorbidities.

Disclosures: A.M. Goodman: None. **J.B. Kahn:** None. **A.M. Bernal:** None. **D.A. Coulter:** None.

Poster

P144. Modeling Networks In Vitro and In Vivo

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P144.07

Topic: B.10. Epilepsy

Support: NIH/NINDS K24-NS088568
R01- 2NS062092

Title: Not all signals are created equal: spectral differences between brain regions in epilepsy

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Abstract: Intracranial EEG (iEEG) is used both clinically and increasingly for research into questions of basic neuroscience; over the last few decades, scientists have relied on iEEG recordings to study the role of different brain regions in various cognitive tasks. While the majority of this research has been performed in epileptic brain, it is unclear how such pathology affects the physiological activities of each brain region. In this study, we seek to address this question by evaluating how the epileptogenicity of a region impacts its regular neural dynamics, as measured through the spectral power estimates of the iEEG signal.
Five-minute interictal periods of awake (n=99) and asleep (n=98) data from patients (n=33) with medically refractory focal epilepsy who underwent presurgical evaluation with iEEG were analyzed. The spectral power in six frequency bands (delta, theta, alpha, beta, low gamma, and high gamma) was evaluated and compared across seven brain regions (hippocampus, lateral temporal, frontoparietal, cingulate, amygdala, occipital, and insula). The analyzed data were classified into four groups: hippocampus (n=19), lateral temporal (n=7), frontoparietal (n=5), and occipital (n=2) lobes, depending on the seizure onset zone (SOZ) of each patient. The power in each frequency band in each region was then averaged over the interictal data in each SOZ group. Within each SOZ group, the average power was compared for all region pairs within each frequency band, using Kruskal-Wallis tests to identify significance (p=0.05).
We found that for hippocampus SOZ, the hippocampus had significantly larger power compared to other regions (non-SOZ) across all bands ($p<0.05$). This trend was also apparent for frontoparietal SOZ, where the frontoparietal lobe had the largest or second to largest power across all bands compared to other

regions. Interestingly, this trend was not conserved for lateral temporal and occipital lobe seizure onsets. For lateral temporal SOZ, the occipital lobe had the largest power across all bands, and for occipital onset, the hippocampus had the largest power across bands. Furthermore, for all SOZs except lateral temporal, the hippocampus had the largest absolute power.
Our findings demonstrate that the relationship between the SOZ and spectral power magnitude is complex. In the hippocampus and frontoparietal lobes, the effect of epileptogenicity on neural dynamics is much more apparent, while less obvious in lateral temporal and occipital lobes. This variability in signals has implications for identifying SOZ for epilepsy, but also more broadly for informing how future analyses and comparisons may need to account for these differences.

Disclosures: D. Reich: None. **P. Salami:** None. **S. Cash:** None.

Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P195.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIMH MH10748
NIMH MH121102

Title: Perturbations of protein kinase signaling in Alzheimer's Disease

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Abstract: Alzheimer’s disease (AD) is the most common cause of dementia in the United States and 14 million Americans are expected to develop AD by 2060. Despite the acceleration of AD prevalence, there are no effective treatments, and many recent clinical trials have failed. To identify disease-altering targets, a deeper understanding of the pathophysiology of this devastating illness is needed. Expanding our understanding of the pathophysiology of AD requires knowledge of changes in protein kinase signaling networks. We hypothesize that changes in protein kinase signaling networks are perturbed in AD. Using the PamGene12 Kinome Array platform, we deployed a novel bioinformatics workflow where we identified kinases that are under and overrepresented in the disease using postmortem dorsolateral prefrontal cortex (DLPFC) in AD. Adenosine monophosphate activated protein kinase (AMPK) was identified as a “hit” kinase between control, Mild Cognitive Impairment (MCI), and AD subjects, suggesting that AMPK may be implicated in the transition from MCI to AD. To confirm our bioinformatic findings, we performed AMPK activity assays. AMPK activity was decreased in male and female AD DLPFC. Moreover, we found lower AMPK activity in MCI vs controls, and even lower AMPK activity in AD vs MCI. Inspired by our changes in enzyme activity, we measured changes in transcript expression. Transcript expression of the regulatory subunits of AMPK were changed.

Transcripts for canonical upstream activators of AMPK (Tak1, LKB1, and OGT) were increased. To mechanistically study the phosphorylation profile of AMPK, we knocked down AMPKα1 and AMPKα2 using siRNA (25 pmols) ± AICAR [1 mM], an allosteric activator of AMPK, in primary murine astrocytes. With the PamGene12 Kinome Array, we identified 15 peptides where the peptide phosphorylation was simultaneously increased in the activated cultures and decreased in the AMPK-KD cultures. These 15 peptides were significantly enriched for key metabolic signaling pathways. Examination of these 15 peptides in human postmortem brain as well as astrocytes derived from familial human AD iPSCs revealed differential activity of the AMPK network. Interestingly, increased phosphorylation was observed at Laminin-B1 (LMNB1), a reporter peptide of AMPK, in both male and female subjects as well as astrocytes derived from iPSCs, potentially serving as a novel biomarker of the disease. AMPK and its network represent a potential key node in the pathogenesis and pathophysiology of Alzheimer's Disease. Further work will explore the subunit-specific role of AMPK in driving the Alzheimer's phenotype.

Disclosures: N.D. Henkel: None. **X. Wu:** None. **E.S. Shedroff:** None. **A. Joyce:** None. **K. Alganem:** None. **G. Meares:** None. **Z. Wen:** None. **R.E. McCullumsmith:** None.

Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P195.02

Topic:

Support: NIMH MH10748
NIMH MH121102

Title: Measurement of PIM1 kinase activity in Alzheimer's dementia

Authors: *J. RETHMAN[1], A.-R. HAMOUD[2], R. E. MCCULLUMSMITH[3];
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Abstract: Measurement of PIM1 Kinase Activity in Alzheimer's DementiaAuthors: Jacob B. Rethman, Abdul-rizaq Hamoud, Khaled Alganem, Ali S. Imami, Elizabeth S. Shedroff, Nicholas D. Henkel, and Robert E. McCullumsmithAlzheimer's dementia (AD) is the most common cause of dementia in the United States and 14 million Americans are expected to develop AD by 2060. Despite the acceleration of AD prevalence, there are no effective treatments, and many recent clinical trials have failed. To identify disease-altering targets, a deeper understanding of the pathophysiology of this devastating illness is needed. PIM1 is a proto-oncogene serine/threonine-protein kinase involved in the mTOR signaling pathway. This kinase phosphorylates PRAS40 which regulates activity of the mTORC1 protein complex. Accumulating evidence suggests this signaling pathway intersects with AD pathophysiology. Using the PamGene12 Kinome Array, we measured protein kinase activity for the serine-threonine kinome in AD and control postmortem DLPFC. Using our novel bioinformatic pipeline, we identified PIM1 as an overrepresented kinase "hit" in AD. Furthermore, data from the platform

suggests a decrease in PIM1 activity. We will confirm these findings using a luciferase-based kinase assay for PIM1 activity. PIM1 kinase activity will be measured in dorsolateral prefrontal cortex (DLPFC) homogenates from AD (N=20) and control (N=20) samples. Additionally, PIM1 kinase activity will be measured in schizophrenia (N=20) and control (N=20) samples to access disease specificity. These experiments will be conducted with a specific PIM1 inhibitor to quantify PIM1 activity levels. This data will determine if changes in PIM1 activity are AD-specific or broadly related to disorders of cognitive dysfunction in neuropsychiatric disorders. Furthermore, these findings will validate PIM1 as a "hit" on the kinome array platform. **Keywords:** Alzheimer's Disease, Schizophrenia, PIM1, postmortem, DLPFC

Disclosures: J. Rethman: None. **A. Hamoud:** None. **R.E. McCullumsmith:** None.

Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P195.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DGAPA-UNAM Grant IA203920

Title: Transcriptomic analyses revealed conserved and divergent molecular pathways in various neurodegenerative diseases

Authors: *A. V. ISLAS BUSTAMANTE GUTIÉRREZ[1,2], A. VARELA-ECHAVARRÍA[2], V. Y. MULEY[2];
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Abstract: Neurodegeneration is any pathological condition that primarily affects neurons leading to loss of their structure and function, and ultimately death. The onset of neurodegeneration is exceptionally well associated with aging and often triggers in older adults. Neurodegeneration manifests in clinically and pathologically recognizable phenotypes referred to as neurodegenerative diseases (ND). ND represent a group of neuropathologies that affect specific neurons in certain anatomical parts of the brain. Multiple neuropathologies co-exist in older adults more often than by random chance, and each neuropathology contributes differently to the cognitive impairments and motor functions among affected individuals. Molecular mechanisms underlying such clinical features and differences among ND are largely unknown. There is still a lack of knowledge about the conserved and divergent genetic pathways among ND. In this study, we have analyzed microarray expression datasets from 18 independent studies, available through the GEO database. Each dataset represents expression in degenerative brain tissues from ND patients and healthy tissues and covers all major ND such as Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), and Frontotemporal dementia (FTD), along with rare conditions such as pick disease, progressive supranuclear palsy, and Creutzfeldt-Jakob Disease. The differential gene expression between healthy and each ND was performed and the differentially expressed genes (DEGs) were analyzed for their enrichment in Gene Ontology terms. Consistent with previous studies, DEGs in AD were heterogeneous depending on the disease stage and the tissue source from specific brain regions. Interferon-gamma

signaling pathways were up-regulated in asymptomatic, incipient, and moderate AD patients irrespective of the brain region, and also in patients with neurofibrillary tangles, FTD associated with Progranulin gene mutation. This suggests that the neuronal loss in these patients was induced by JAK/STAT signaling. In contrast, FTD without Progranulin mutation affected muscle contraction and blood pressure pathways. Many DEGs from most ND were enriched in neurotransmitter transport and synaptic organization related pathways. Overall, our results provide evidence on convergence of dysregulated inflammatory immune response and synaptic signal transmission pathways in most ND, and a highly heterogeneous functional landscape in AD patients. These results are being validated using publicly available RNA-sequencing datasets and also analyses being carried out for many rare ND.

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Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

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Program #/Poster #: P195.04

Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Proteomic lineage analysis identifies joint subtypes of autosomal dominant and sporadic Alzheimer’s disease

Authors: *B. LOGSDON[1], A. SULOVARI[1], A. BUCHIN[2], G. MERRIHEW[3], J. PARK[3], D. PLUBELL[3], C. C. WU[3], J. A. HARRIS[2], A. DERVAN[1], R. HERSHBERG[1], I. PEIKON[1], R. J. BATEMAN[4], J. P. CHHATWAL[5], M. R. FARLOW[6], C. MCLEAN[7], K. L. NEWELL[8], M. P. FROSCH[9], B. F. GHETTI[10], E. B. LARSON[11], C. KEENE[3], R. J. PERRIN[12], T. J. MONTINE[13], M. J. MACCOSS[3]; [1]Cajal Neurosci., Seattle, WA; [2]Allen Inst. For Brain Sci., Seattle, WA; [3]Univ. of Washington, Seattle, WA; [4]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [5]Brigham and Women's Hosp., Boston, MA; [6]Dept Neurol, Indiana Univ. Sch. Med., Indianapolis, IN; [7]Alfred Hosp., Melbourne, Australia; [8]Dept. of Pathology & Lab. Med. MS 3045, Univ. of Kansas Med. Ctr., Kansas City, KS; [9]Harvard Med. Sch., Boston, MA; [10]Indiana Univ. Sch. of Med., Indianapolis, IN; [11]Kaiser Permanente Washington Hlth. Res. Inst., Seattle, WA; [12]Div. of Neuropathology, Washington Univ., Saint Louis, MO; [13]Stanford Univ., Palo Alto, CA

Abstract: Motivation: Alzheimer’s disease (AD) is a devastating illness with a great need for highly effective disease modifying therapies. Determining molecular pathways that are driving disease at distinct stages of disease progression in antemortem brain samples is impractical and unethical. To identify stage

specific molecular disease drivers, we apply a machine learning approach to learn a trajectory of disease progression based on whole proteome expression variation in post mortem AD samples.
Methods: We performed whole proteome quantification via mass spectrometry using a data-independent acquisition protocol. We profiled 62 samples derived from superior medial temporal gyrus tissue from three studies (Adult Changes in Thought, University of Washington ADRC, and DIAN) for 24 autosomal dominant AD, 18 sporadic AD, 11 high AD neuropathologic change controls, and 9 low AD neuropathologic change controls. We applied a manifold learning approach (DDRTree) to the proteome data (40,346 peptides from over 5,000 genes across samples) to learn a lineage of disease progression from healthy aging to late stage disease.
Results: Based on the topology of the learned proteome disease lineage, we identify two distinct late stage disease subtypes of AD that are shared across sporadic and mutant PSEN AD cases. One subtype is characterized by loss of expression of 909 (FDR<0.05) proteins involved in intracellular trafficking (e.g. intracellular protein transport GO:0006886, adjusted P-value=$6.865x10^{-3}$) whereas the other subtype is characterized by loss of expression of 670 proteins (FDR<0.05) involved in synaptic function (e.g. synaptic vesicle exocytosis GO:0016079, adjusted P-value=$1.642x10^{-7}$). We demonstrate that genes that are predictive of these subtypes overlap with previously published subtype associated genes from RNA-seq data in sporadic AD cases ($P<1x10^{-3}$) based on a study from the Accelerating Medicine Partnership in Alzheimer's Disease consortium.
Conclusions: Molecular heterogeneity as revealed by proteome variation can help disentangle the molecular etiology of the disease at clinically relevant disease stages. The shared proteomic expression signatures across sporadic and mutant PSEN cases suggests common late stage disease mechanisms - within subtype - between autosomal dominant and sporadic disease. Our results suggest that there are common subtypes of AD characterized by either synaptic dysfunction or intracellular trafficking deficits.

Disclosures: B. Logsdon: A. Employment/Salary (full or part-time):; Cajal Neuroscience. **A. Sulovari:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **A. Buchin:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **G. Merrihew:** None. **J. Park:** None. **D. Plubell:** None. **C.C. Wu:** None. **J.A. Harris:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **A. Dervan:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **R. Hershberg:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **I. Peikon:** A. Employment/Salary (full or part-time):; Cajal Neuroscience. **R.J. Bateman:** None. **J.P. Chhatwal:** None. **M.R. Farlow:** None. **C. McLean:** None. **K.L. Newell:** None. **M.P. Frosch:** None. **B.F. Ghetti:** None. **E.B. Larson:** None. **C. Keene:** None. **R.J. Perrin:** None. **T.J. Montine:** None. **M.J. MacCoss:** None.

Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

Location: Virtual Only

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Program #/Poster #: P195.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AG005133
NIH AG066468
NIH MH116046
NIH MH107756

Title: Psychosis in Alzheimer's Disease is Associated with Increased Expression of Ubiquitin Ligases

Authors: *M. R. DECHELLIS-MARKS[1], R. SALISBURY[1], Y. WEI[3], Y. DING[3], J. KRIVINKO[1], O. LOPEZ[1], J. KOFLER[2], M. MACDONALD[1], R. SWEET[1];
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Abstract: Psychosis in Alzheimer's disease (AD+P) is a phenotypic variant that affects 40 – 60% of all AD subjects. AD+P is associated with more rapid deterioration compared to AD without psychosis (AD-P). The neurobiological basis of psychosis in AD is poorly understood. Neuroimaging studies which compared AD+P to AD-P have found decreased synaptic indices in the dorsolateral prefrontal cortex (DLPFC). Previously, we reported that the presence of multiple neuropathologies is a minor fraction of the risk of psychosis in AD. However, we found that canonical synaptic proteins levels in cortical gray matter are reduced in AD+P compared to AD-P, suggesting that vulnerability to psychosis may be, in part, driven by loss of synaptic proteins. To determine if protein level differences were driven by transcriptional changes we performed RNA sequencing, finding only a mild correlation between synaptic transcript and protein levels (DeChellis-Marks., *In Review).* We further found altered mRNA expression of genes involved in multiple posttranscriptional pathways Taken together, these results suggests that the synaptic proteome in AD+P is differentially perturbed by post-transcriptional mechanisms that alter protein availability.
In this study we asked (1) if gray matter proteins are differentially abundant and (2) which post-transcriptional pathways may be driving the synaptic protein availability differences between AD-P, AD+P, and controls. We evaluated the proteome of 129 subjects (Neuropathological Controls: 19; AD-P: 49; AD+P: 61) by lysing DLPFC tissue. We performed TMT labeling and high-pH reverse phase fractionation to increase depth and resolution of the proteome. We quantified more than 3,000 proteins at 90% present call. Our preliminary analysis also identified 186 proteins that were nominally significantly differentially expressed in AD+P compared to AD-P (uncorrected p-value < 0.05). 137 (74%) of these proteins were upregulated in AD+P relative to AD-P. Interestingly, functional annotation identified the proteins altered in AD+P to be enriched for the protein ubiquitination pathway (uncorrected p = 3.42E-10; B-H corrected p = 1.59E-7). Altered protein ubiquitination pathway activity suggests that the relative decrease in synaptic protein levels in AD+P may be a result of protein degradation.

Disclosures: M.R. DeChellis-Marks: None. **R. Salisbury:** None. **Y. Wei:** None. **Y. Ding:** None. **J. Krivinko:** None. **O. Lopez:** None. **J. Kofler:** None. **M. MacDonald:** None. **R. Sweet:** None.

Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

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Program #/Poster #: P195.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This work was supported by a grant from Tata Trust
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Title: Actin interactome analysis of differentially expressed proteins in synaptosomes of Alzheimer's disease mouse model

Authors: *H. P A[1,3], R. KOMMADDI[1], A. VERMA[2], M. CHANDRAN[4], A. JALEEL[4], V. RAVINDRANATH[1,2];
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Abstract: Dendritic spines are highly dynamic structures enriched with actin, which undergoes activity dependent modification to control the synaptic and cognitive functions. The dynamic equilibrium between globular and filamentous actin modulates the spine morphology and synaptic plasticity. The rapid turnover of actin during assembly/disassembly is finely regulated by several actin binding proteins at the synapse. We have shown that perturbation of F-actin and total dendritic spines in one month old APP/PS1 mice and primary cortical neurons. However, the molecular mechanisms involved in F-actin loss in synaptosomes, the underlying factors and the functional consequence needs to be elucidated. Thus, characterizing the actin interactome from synaptosomes of wildtype and APP/PS1 mice delineates molecular mechanisms involved in the synaptic dysfunction during AD. Here, we isolated synaptosomes, F-actin and G-actin fractions from synaptosomes, performed immunoprecipitation followed by LC-MS/MS analysis. We detected 1053 proteins in WT and 988 proteins in APP/PS1 mice at the age of six months in synaptosomes. We detected 350 common actin interacting proteins in synaptosomes of WT and APP/PS1 mice. Additionally, we found that 209 proteins in WT and 256 proteins in APP/PS1 are uniquely associated with actin. From F-actin fraction, we identified 130 proteins specific to WT and 70 proteins specific to APP/PS1. We also found 224 common proteins interacting with actin in F-actin fraction. Our proteomic analysis of actin interacting proteins in the synaptosomes isolated from six month old WT and APP/PS1 mice revealed proteins with significant differences in actin interactome with respect to proteins involved in synapse organization, protein translation and energy metabolism.

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Poster

P195. Alzheimer's Disease: Genetics, Genomics, and Other Omics Approaches IV

Location: Virtual Only

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Program #/Poster #: P195.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 733050106/ZONMW_/ZonMw/Netherlands
733050811/ZONMW_/ZonMw/Netherlands
733051076/ZONMW_/ZonMw/Netherlands

Title: Age-dependent hippocampal proteomics in the APP/PS1 alzheimer mouse model by directDIA

Authors: *S. J. F. VAN DER SPEK, M. A. GONZALEZ-LOZANO, F. KOOPMANS, S. S. M. MIEDEMA, I. PALIUKHOVICH, A. B. SMIT, K. LI;
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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder. Currently a cure is lacking, and the cause remains largely unknown. However, toxic effects of amyloid beta are believed to play a major role in AD pathogenesis. These toxic effects are in part recapitulated in the Amyloid Precursor Protein swe/Presenelin 1 dE9 (APP/PS1) mouse model of AD. In the current study, we analyzed the proteome of a hippocampal synapse enriched fraction obtained from APP/PS1 mice and their wildtype controls at 6 and 12 months of age. For the analysis, we performed label free-quantification proteomics by data independent acquisition (DIA). First, we compared the use of a classical DIA analysis with a recently improved directDIA workflow, that does not require the use of a project specific spectral library. Subsequently, directDIA was applied to the 6- and 12-months APP/PS1 datasets and differential expression analysis was performed using the Mass Spectrometry Downstream Analysis Pipeline (MS-DAP). Strongest regulation of proteins was observed at 12-moa. Especially proteins involved in amyloid beta homeostasis and microglial-dependent processes, like synaptic pruning and immunoreactivity, including APOE, CLU and C1CA-C.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P208.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG066489
2T32HD071866-06

Title: Early impairments of fear memory extinction and amygdala plasticity in the TgF344AD rat model of Alzheimer's disease are distinct from impairments in non-pathological aging

Authors: *C. M. HERNANDEZ, N. L. JACKSON, M. E. BAGLEY, L. L. MCMAHON;
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Abstract: Alzheimer's disease (AD) is accompanied by cognitive impairments affecting several memory domains. One such domain, emotional memory, is supported by a vast network of medial temporal lobe structures which are negatively impacted in AD. Human studies suggest the inability to acquire aversive emotional (fear) memories may be an early sign of AD that occurs prior to measurable cognitive impairments. The transgenic Fischer344 AD (TgF344AD) rat model recapitulates many aspects of human AD. The current study used behavioral and electrophysiological approaches in TgF344AD rats to define the contributions of genotype and age to fear memory impairments in AD. Young adult (YA, 6 mo) and middle-aged (MA, 14 mo) non-Tg (nTg) and TgF344AD (Tg) rats were trained on a contextual fear conditioning paradigm consisting of acquisition (tone, CS; shock, US), extinction (CS), retrieval (CS),

and renewal (CS) with a 24-hr delay between each test. At least 3 weeks post-testing, rats were sacrificed for *ex-vivo* slice electrophysiology to record extracellular field potentials from the basolateral amygdala. Synaptic physiology experiments included measuring the strength of basal excitatory transmission in input/output curves, and the magnitude of long-term potentiation (LTP) induced by high-frequency stimulation.In YA adult rats, there was no effect of genotype on acquisition, although, YA Tg rats showed extinction impairments that carried over to retrieval and renewal testing. These extinction impairments in YA Tg rats may be due to increased strength of basal transmission, synaptically driven hyperexcitability, and attenuated LTP magnitude. In MA nTg rats, there were acquisition and extinction impairments relative to young nTg rats. While there were no differences in the input/output relationship of peak field potential amplitudes, hyperexcitability and attenuated LTP magnitude was observed in MA nTg rats relative to nTg. Interestingly, MA Tg rats showed an enhanced ability to extinguish fear expression to the CS relative to MA nTg. However, MA Tg rats continued to show impairments in retrieval and renewal. Enhanced extinction in MA Tg rats may be associated with BLA compensatory mechanisms, as MA Tg rats showed attenuated field peak amplitudes, while having greater hyperexcitability, with no difference in LTP relative to MA nTg rats. These data recapitulate early deficits in human AD patients and further suggest deficits in AD manifest distinctly from nonpathological aging.
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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P208.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH GrantRO1AG066489

Title: Investigating the effects of increasing O-GlcNAc in the TgF344-AD Alzheimer’s disease rat model

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Abstract: Alzheimer’s disease (AD) is currently ranked as the sixth leading cause of death in the United States, with more recent estimates indicating that it may rank up to third in older populations. In 2020 alone, it is projected that AD directly cost Americans over $300 billion, with this number growing exponentially every year. This is because the greatest risk factor for developing AD is aging, and as our aging population is expected to rise, so too will the incidences of AD. Current estimates by the Center for Disease Control and Prevention (CDC) expect AD cases to reach over 14 million cases by 2060. Unfortunately, there are few advances in treatment options, and this is further complicated by limitations in rodent models that recapitulate human AD both at the level of histopathology and behavioral phenotypes. One of the earliest regions of pathological change in humans with AD is the Locus Coeruleus

(LC), with accumulationof hyperphosphorylated Tau (pTau). The LC is critically important as it is the only source of noradrenergic (NA) input into forebrain region, specifically the hippocampus. It has been known for several decades that the NA input is vital to many physiological processes, and has been shown to be required for spatial learning and memory as well as contextual fear. One treatment receiving robust attention is O-GlcNAcylation, the O-linked attachment of the β-N-acetylglucosamine (O-GlcNAc) to serine/threonine residues. Importantly O-GlcNAcylation competes with phosphorylation on Tau at key serine residues. Accordingly, pharmacologically increasing O-GlcNAcylation using an inhibitor of O-GlcNAcase, Thiamet-G, decrease pTau levels in transgenic mice (add the mouse type) as well as improve spatial learning and memory.. Currently several OGA inhibitors are in clinical trials for other tauopathies as well AD, however; it is not known how a chronic increase in O-GlcNAcylation will affect other pathology or immune systems. Our study tests the hypothesis that an increase in O-GlcNAc will decrease overall histopathological markers in a novel rat model of AD, the TgF344-AD. This model exhibits many features of early onset pathology in human AD including pTau accumulation in LC and degeneration of noradrenergic fibers in hippocampus. To test this hypothesis we will treat WT and Tg animals with Thiamet-G, an O-GlcNACase inhibitor, to chronically increase O-GlcNAcylation. We will then assess markers of AD pathology, including amyloid-beta and pTau, as well as other inflammatory markers. This novel work will investigate the possible mechanisms/pathways that are improved by increasing O-GlcNAc.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P208.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MR/M013944/1

Title: Disrupting the Dkk1-LRP6 interaction attenuates synapse loss reduces beta-amyloid production and preserves cognition

Authors: *J. D. JACKSON[1,2], C. ELLIOTT[3,4], G. WILLIAMS[4], N. ASHTON[4], J. FINDLAY[3,5], M. ULMSCHNEIDER[6], A. HYE[4], C. BALLARD[6], M. HARTE[7], R. AL-SHAWI[8], G. BAILLIE[3], P. SIMONS[8], R. KILLICK[4], W. XIA[1,2];
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Abstract: Loss of central synaptic connectivity is a central to the etiopathology of Alzheimer’s disease. The underlying mechanisms driving synapse loss remain poorly understood. However, increasingly evidence point to a disruption in Wnt signalling playing a major, if not central role. This disruption is most likely the result of the ability of β-amyloid (Aβ) to induce Dickkopf-1 (Dkk1). Dkk1 binds to LRP6,

removing it from the Frizzled co-receptor complex and, in so doing, antagonises the canonical arm of Wnt signalling, whilst concomitantly enabling activity in the non-canonical, or β-catenin-independent, arms of Wnt signalling to proceed. We have shown that in neurons this process leads not only to the loss of synapses but to further Aβ production too. We hypothesised that by disrupting the binding of Dkk1 to LRP6 synapses would be protected, and Aβ production reduced. Here we report the mapping of the Dkk1-LRP6 interaction by peptide array and the development of a disruptor peptide derived from Dkk1 which reversibly binds LRP6 with high-affinity. This disruptor peptide restores Wnt-β-catenin activity in the presence of Dkk1 in a dose dependent manner. In primary rat neuronal cultures it protects against Dkk1-driven reduction in dendritic spines and lowers the concomitant production of endogenous $A\beta_{1\text{-}38,\ 1\text{-}40}$ and $_{1\text{-}42}$. Following intracerebroventicular administration the peptide preserves cognitive performance in an acute rat model of oligomeric $A\beta_{1\text{-}42}$ mediated memory impairment. These new data further support the contention that the induction of Dkk1 and its effects on LRP6 are an important element of Alzheimer's disease neuropathogenesis, and establish Dkk1 as a therapeutic target through which one might combat this intractable disease.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R21 NS109750

Title: Axonal Aβ stress induced tau mislocalization causes retrograde synaptic defects within a compartmentalized in vitro model system.

Authors: *T. NAGENDRAN[1], J.-H. TSENG[2], T. J. COHEN[3], A. M. TAYLOR[1];
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Abstract: Tau protein tangles and brain atrophy are hallmarks of Alzheimer's Disease (AD). An early cellular event in the progression of AD is the mislocalization of pathological tau from the axon to the somatodendritic compartment of affected neurons. Following this mislocalization, pathological tau is released and taken up by adjacent neurons and cells. However, the molecular mechanisms that regulate tau mislocalization and how neuronal function is affected, remains unclear. To test whether exposure of axons to Aβ challenge regulates tau mislocalization and leads to synaptic defects, we cultured E18.5 rat hippocampal neurons in compartmentalized microfluidic chambers. Isolated axons at 9-10 days in vitro were treated with Aβ conditioned media (Aβ-CM) for 24 h. Aβ-CM, collected from Aβ oligomer-challenged microglia, contains neuroinflammatory factors that induce neuritic tau beading with exposure to non-compartmentalized neurons. Restricted exposure of Aβ-CM to axons within compartmentalized

chips for 24 h caused a redistribution of tau to the somatodendritic compartment in the absence of neuritic beading. In addition to tau mislocalization, we found that exposure of axons to Aβ-CM for 24 h was sufficient to cause a significant increase in synaptic vesicle release rate. We quantified synaptic vesicle release rate by using a FM dye based optical method in conjunction with electrical stimulation. Further we found that application of a local activity blockade (tetrodotoxin and low calcium) at the time of treatment largely inhibited the mislocalization of tau puncta and normalized the synaptic vesicle release rate. To confirm that tau mislocalization causes the change in presynaptic vesicle release, we cultured tau knock-out (KO) and wildtype (WT) neurons within compartmentalized microfluidic chambers and treated their axons with Aβ-CM for 24 h. We found that exposure of tau KO axons to Aβ-CM did not affect the proportion of responsive FM puncta in the somatodendritic compartments in contrast to WT neurons treated with Aβ-CM. These results indicate that tau mislocalization causes synaptic defects and these defects are ameliorated by pharmacological activity blockade. Together, our results provide confirmation that tau redistribution can be quantified in our *in vitro* model in advance of cell death, mirroring AD phenotype *in vivo* and providing a unique platform to identify therapeutic targets that may reduce the spread of AD pathology in the brain.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

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NUSMED-FOS Joint Research Programme (NUHSRO/2018/075/NUSMed-FoS/01)

Title: Role of Nogo-A as a plasticity suppressor in APP/PS1 mice model of Alzheimer’s Disease

Authors: *M. VAZQUEZ[1], S. NAVAKKODE[2], S. SREEDHARAN[1];
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Abstract: Nogo-A, a myelin associated protein, is long known as a neurite growth inhibitor. However, in recent years, the role of Nogo-A as a plasticity suppressor has gained more importance. Nogo-A has been shown to inhibit protein synthesis dependent long-term potentiation (late-LTP), a cellular correlate of learning and memory. Interestingly, Nogo-A has been found to be overexpressed in the hippocampus of Alzheimer’s disease (AD) patients, however its role in AD remains elusive. Alzheimer’s disease, a progressive neurodegenerative disease, is the most common type of dementia in the world. Although much research has been done, the molecular cause of the disease remains unknown and thus, till date, there are no effective treatments. Therefore, further research on the molecular basis of the disease is

needed. In our study we have focused on the role of Nogo-A as a plasticity suppressor in the hippocampus of APP/PS1 mice which is an AD mice model. Loss of synaptic plasticity has been reported in AD mice at 3 months of age, a timepoint that is earlier than the widespread neuron death observed at a later stage of the disease, which signifies that loss of synaptic plasticity is one of the first events to occur in the progression of the disease. Considering these aspects, we hypothesized that the early loss of synaptic plasticity could be reversed by inhibiting the Nogo-A protein in APP/PS1 mice. Our results showed that inhibiting the Nogo-A pathway via Nogo receptor antibody (Nogo-R ab) led to the rescue of late-LTP in APP/PS1 mice. Next, we tested whether the rescue of synaptic plasticity can be achieved in aged APP/PS1 mice, in which the pathology is more advanced. We found that inhibiting the Nogo-A pathway also led to the rescue of late-LTP in aged APP/PS1 mice. Additionally, we tested whether inhibition of the Nogo-A pathway would also rescue Synaptic Tagging and Capture (STC), a cellular model for associative plasticity and memory, which has also been found to be impaired in APP/PS1 mice. Inhibition of the Nogo-A pathway via Nogo-R ab led to the rescue of STC in APP/PS1 mice. Overall, our results revealed the beneficial role of inhibiting Nogo-A to rescue plasticity in neurodegeneration.

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Poster

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Title: Beta Amyloid-Induced Dysregulation of the Exocyst Complex Impedes Postsynaptic Receptor Trafficking and Alters Dendritic Spines

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Abstract: Synaptic dysfunction and loss are hallmarks of the early pathogenesis of Alzheimer’s disease (AD), leading to impaired cognitive function, including disruption of memory processing. Accumulation of neurotoxic oligomeric beta amyloid (Aβ) in the prodromic period leading up to AD is thought to contribute to dendrite atrophy, altered dendritic spine dynamics resulting in synaptic dysfunction and spine loss, but the molecular mechanisms for these Aβ-associated changes are still unclear. The exocyst has been studied extensively in yeast and other mammalian cell types, but little is known of role of the exocyst at the synapse. The exocyst complex is an eight-subunit complex implicated in vesicle tethering and trafficking preceding fusion facilitated by SNARE proteins. Preliminary work in our lab has found evidence of exocyst involvement in APP trafficking in murine primary neurons. This insight prompted us to investigate exocyst involvement in trafficking of certain key synaptic receptors when challenged by Aβ. Aβ oligomers may disrupt synaptic plasticity through dysregulation of postsynaptic glutamate receptor trafficking. Disruption of this balance has been found to modulate dendritic spine size, and may

prompt dendritic spine elimination. Aβ oligomers have been shown to promote AMPAR endocytosis, but the impact of Aβ on dysregulation of exocyst-dependent AMPAR exocytosis onto the postsynaptic membrane has not been explored. This study is assessing a novel role for the exocyst in Aβ-induced dysregulation of AMPAR GluA1 delivery, culminating in a decrease in dendritic spine density. Mouse primary hippocampal neurons were treated with Aβ and changes in dendritic spines were quantified via immunocytochemistry. Preliminary results show an increase in Exoc1 staining following Aβ treatment, correlating to decreased postsynaptic AMPAR GluA1 presence, diminished spine size and overall increased dendrite simplification. Live imaging will be conducted to visualize the Aβ induced modulation of the exocyst complex to further elucidate the potential consequences of these changes in exocyst function on dendritic spines.
Understanding how Aβ modulates postsynaptic receptor trafficking may reveal key events in disease pathogenesis, allowing for targeted intervention.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Research Council of (Lithuania), Agence Nationale de la Recherche (France) (Flagship ERA-NET Joint Transnational Call JTC 2019 in synergy with the Human Brain Project, No. S-FLAG-ERA-20-1/2020-PRO-28)
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Title: Rescue of the pathological effect of amyloid precursor protein intracellular domain on synaptic plasticity in hippocampal CA1 pyramidal neuron in early Alzheimer's disease: a computational modeling study

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Abstract: Alzheimer’s disease (AD) is a progressive memory loss and cognitive dysfunction brain disorder brought on by the dysfunctional amyloid precursor protein (APP) processing and clearance of APP peptides. Increased APP levels lead to the production of AD related peptides such as amyloid beta and the amyloid APP intracellular domain (AICD), and consequently modify the intrinsic excitability of the hippocampal CA1 pyramidal neuron and impair synaptic plasticity of Schaffer collateral synapses

(Pousinha et al., Cell Reports 2019).This study explores the extent of AICD effect on synaptic plasticity at Schaffer collateral synapses in early AD and the possible treatment targets. We used a detailed compartmental computational model of CA1 pyramidal neuron (Migliore et al., PLOS Comp Biology 2018) and a modified NMDA receptor-dependent voltage-based model of synaptic plasticity (Clopath et al., Front. Synaptic Neurosci., 2010) to analyse alteration in synaptic plasticity at the clustered Shaffer collateral synapses under the effect of AICD. The neuron was stimulated at 2 bursts of 100 Hz for 1 s each to induce long-term potentiation (LTP). We included the influence of the pathological AICD levels by increasing the maximal conductances of SK channels and L-type calcium channels by the factors of 4.5 and 1.3, respectively, and strenghthening the contribution of the GluN2B-containing NMDA receptor (NR2B) at a synaptic level by a factor of 4 (Pousinha et al., Elife 2017). Our simulation reproduced experimental results shutting down synaptic plasticity during LTP induction protocol (Pausinha et al., Cell Reports 2019). The possible rescue of the AICD effects on impaired synaptic plasticity was modeled by blocking the SK channel and NMDA NR2B conductances. The results show that the strength of synaptic plasticity is gradually restored as the SK channel and NMDA NR2B conductances are decreased. When both SK channel and NMDA NR2B conductances are downscaled by a factor of 0.6 or lower if compared to the pathological AICD level conditions, synaptic plasticity is restored due to the absence of the overactivation of SK channels by NMDA NR2B-mediated calcium influx. The computational model provides us with the insights into the complex interactions of intrinsic neuronal excitability and synaptic plasticity mechanisms in AD pathophysiology, and allows suggesting the conditions under which the pathological effects of AICD increase can be negated and normal function can be restored.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

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Program #/Poster #: P208.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01 AG0 62285
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R01 AG027161

Title: Synaptic density in atypical and non-Alzheimer’s dementia

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Abstract: Objectives: [^{11}C]UCB-J is a PET radioligand which specifically binds to synaptic vesicle glycoprotein SV2A and is designed to reflect synaptic density. The accumulation of beta amyloid plaques and neurofibrillary tau tangles distinguishes Alzheimer’s from other dementia-causing diseases. While

people with Alzheimer's disease typically present with cognitive impairment, there have been cases where no clinical presentation of disease is present despite a significant accumulation of plaques and tangles. In this analysis we are looking to analyze hippocampus UCB-J uptake in these participants when compared to a control group.
Methods: Thirty-one participants (67.5±6.7 years old, 18F/11M) recruited from the Wisconsin ADRC and the Wisconsin Registry for Alzheimer's Prevention study underwent [^{11}C]UCB-J dynamic PET imaging to assess synaptic density, T1w-MR imaging, and the Rey Auditory Verbal Learning Test (RAVLT). Of this group twenty are cognitively unimpaired. [^{11}C]PiB dynamic imaging was performed to assess amyloid-β plaque accumulation and [^{18}F]MK-6240 dynamic imaging to assess neurofibrillary tangle accumulation. Subject-specific hippocampus ROIs for [^{11}C]UCB-J analysis were defined using FreeSurfer (v7) segmentation of the participant's MR image. [^{11}C]UCB-J uptake was quantified by calculating the distribution volume ratio (DVR) using SRTM2. **Results**: Twenty participants were cognitively unimpaired, eighteen with no significant plaque accumulation (CU A-) with a hippocampus UCB-J distribution volume ratio DVR of 0.99±0.07. Despite their cognitively unimpaired status two participants had significant plaque and tangle accumulation (CU A+T+) and a hippocampus UCB-J DVR of 0.99±0.02. Two participants were found to have dementia but are low accumulators of plaques and tangles (Dementia A-T-) with a hippocampus UCB-J DVR of 0.77±0.11. **Conclusions:** This preliminary data suggests that [^{11}C]UCB-J uptake in the hippocampus is unchanged in participants with a significant amount of plaques and tangles in the absence of cognitive impairment. It was also observed that participants with a lack of significant plaques and tangles with dementia-level cognitive impairment show decreased uptake in the hippocampus compared to the CU A-T- control group. This shows that [^{11}C]UCB-J may be helpful in determining changes in cognition as well as determining why participants with significant amounts of plaques and tangles seem to have a resilience to clinical presentation of the disease.

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Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P208.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PAPIIT IN204519

Title: Adult hippocampal neurogenesis in a preclinical model of sporadic a Alzheimer's disease

Authors: *G. CERVANTES[1], C. CARRILLO PRADO[1], S. DIAZ-CINTRA[2], P. C. BELLO-MEDINA[2]; [1]Escuela Nacional de Estudios Superiores, Unidad León, Univ. Nacional Autónoma de México, León, Mexico; [2]Dept. de Neurobiología del Desarrollo y Neurofisiología, Inst. de Neurobiología Campus Juriquilla, Univ. Nacional Autónoma de México, Querétaro, Mexico

Abstract: Most of the cases of Alzheimer's disease in patients (95%) are sporadic (ADs). So the ADs mice model has been implemented by the administration of intracerebroventricular streptozotocin (STZ-icv), which produces a decrease in glucose in the brain, neuroinflammation, cholinergic deficit, oxidative stress, and impairment in learning and memory. It is now recognized that adult neurogenesis (AN) plays an important role in learning and declarative long-term memory. On the other hand, the overtraining (increase in training sessions number) of a spatial task produces structural changes that modify the functioning of the hippocampus network and facilitate learning and memory. The objective of this study is to evaluate the effect of overtraining in the Morris water maze (MWM) on adult neurogenesis on the dentate gyrus (DG) in an STZ-icv induced model of AD. CD1 mice were administered vehicle (VEH) or STZ-icv (3.0 mg/Kg). Body weight was recorded for 30 days, subsequently, they were subjected to the MWM task. The mice were randomly assigned in four groups: 1) STZ-Naïve, 2) STZ-swimming control without training, 3) STZ-MWM1 who were trained in one session (8 trials each), or 4) STZ-MWM3 who were trained in three sessions (8 trials each), all groups count their respective controls (VEH). The doublecortin protein (DCX) detection was realized with immunohistochemistry in the ginu, upper blade, and lower blade of DG of the dorsal hippocampus. A decrease in body weight was observed in all groups during the administration of the STZ-icv and on day 5, the weight was increased in the VEH compared to STZ groups, who presented a significant decrease from day 2 to 17. In the MWM has been observed a decrease in escape latency in the MWM1-VEH and MWM3-VEH groups. The MWM1-STZ group did not show any significant decrease, however, the MWM3-STZ decreased its latency on the third day of training similar to the MWM1-VEH group. Histological analysis of the DCX protein (AN marker) in the dorsal hippocampus GD is in progress. We thank A. Aguilar Vázquez and N. Hernández Ríos for their excellent technical support. The present work was supported by PAPIIT IN204519.

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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Multiscale and multimodal imaging of AD pathology reveals amyloid plaque-associated neuronal and mitochondrial abnormalities

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Abstract: Diseases of the brain typically exhibit pathology in various cell types and at multiple scales. Alzheimer's disease (AD), for example, involves dysfunctions of neurons, glia and vessels, with abnormalities ranging from changes at individual synapses to the dysregulated metabolism in various brain regions. Thus, understanding AD requires information about pathological changes at both macro and nano scales, preferably, in the same brain. No current technology is suitable or practical for such a purpose. We address this gap by adapting our recently reported pipeline for multiscale multimodal imaging of entire brains using MRI, micron scale synchrotron source X-ray microscopy, and automated serial electron microscopy (EM). With this pipeline, we are able to image brain pathology over six orders of magnitude in resolution in the same AD transgenic mouse. Synchrotron source X-ray microscopy clearly reveals the composition of individual plaques in various brain regions corresponding to MRI imaging. The speed of X-ray microscopy allows rapid evaluation of amyloid plaque accumulation over multiple experimental conditions including developmental ages, across different transgenic lines, and in mouse models of sleep apnea. Large volume EM reconstructions of the same brains reveal deficits of neuronal networks and mitochondrial abnormalities associated with amyloid plaque deposition. We envision that this multiscale multimodal imaging pipeline will greatly facilitate the investigation of pathogenic processes in human AD brains as well as in mouse models of AD.

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Poster

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Title: Regional amyloid burden correlates with domain-specific cognitive performance in mild cognitive impairment

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Abstract: Beta-amyloid (Aβ) deposition is the earliest pathology associated with Alzheimer's Disease (AD). However, the relationship between Aβ and cognitive decline, be it in healthy aging or preclinical AD, (i.e., in mild cognitive impairment, MCI), is not completely understood. While summary measures of total cortical Aβ deposition may be correlated with cognitive performance, few studies have identified relationships between regional Aβ and specific cognitive deficits. In-vivo imaging studies are vital to advancing our understanding of the role of Aβ in preclinical AD. In this study, we used data driven analyses of Aβ-PET to investigate the relationship between the spatial distribution of Aβ deposition and domain-specific cognitive impairment. Forty-seven participants with multi-domain amnestic MCI (md-aMCI) and thirty-seven healthy, cognitively normal comparison subjects underwent clinical and neuropsychological assessments and high-resolution positron emission tomography (PET) to measure Aβ deposition. Voxel-wise and partial least squares correlation (PLSC) analyses were conducted to identify spatial patterns of Aβ deposition that best correlated with performance on the California Verbal Learning Test (CVLT), the Brief Visual Memory Test (BVMT) and the Delis-Kaplan Executive Function System (DKEFS) measures of semantic and phonemic fluency. Statistical significance of the identified spatial patterns of amyloid was assessed using permutation testing and confidence intervals were estimated via bootstrapping. Significant clusters were defined to exceed 50 contiguous voxels correlated at a significance level of $p < 0.001$. We found that md-aMCI was associated with greater Aβ burden relative to comparison subjects. Within the md-aMCI cohort, but not comparison subjects, distinct regional patterns of Aβ correlated with impaired performance in immediate verbal recall ($R = -0.48 \pm 0.06$, $p < 0.001$), delayed verbal recall ($R = -0.39 \pm 0.08$, $p < 0.001$), immediate visual-spatial recall ($R = -0.48 \pm 0.06$, $p < 0.001$), delayed visual-spatial recall ($R = -0.54 \pm 0.06$, $p < 0.001$) and semantic fluency ($R = -0.41 \pm 0.06$, $p < 0.001$) but not in phonemic fluency. These results suggest that among those with mild cognitive impairment, regional deposition of Aβ may be correlated with the nature and degree of cognitive deficits.

Disclosures: D.A. Stevens: None. **C. Workman:** None. **H. Kuwabara:** None. **M.A. Butters:** None. **A.V. Savonenko:** None. **N. Nassery:** None. **N. Gould:** None. **M.A. Kraut:** None. **J. Joo:** None. **J. Kilgore:** None. **V. Kamath:** None. **D.P. Holt:** None. **R.F. Dannals:** None. **A. Nandi:** None. **C.U. Onyike:** None. **G.S. Smith:** None.

Poster

P208. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P208.12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS057255

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NIH Grant NS091585
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AHA Grant 0840110N

Title: NMDA receptor GluN3A subunit as a pathogenic regulator of sporadic Alzheimer's disease

Authors: *S. P. YU[1], W. ZHONG[1], K. BERGLUND[1], X. GU[1], M. Q. JIANG[1], L. WEI[2];
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Abstract: Abstract: Alzheimer's disease (AD) is a common neurodegenerative disease, evolving amyloidosis and tau protein hyperphosphorylation, synapse dysfunction, neuron degeneration, and cognitive deficits. Extensive investigations based on the Aβ/tau hypothesis have been performed in transgenic animal models expression familial/mutated AD genes. However, treatments based on this hypothesis, including the recent amyloid antibody Aduhelm, have not provided effective clinical therapies. Hyperactivity of the glutamatergic NMDA receptor (NMDAR) is a common pathophysiology of AD and has been viewed as a consequence of Aβ pathology. Among NMDAR subunits GluN1, 2, 3 (NR1, 2, 3), GluN3A is an inhibitory subunit that suppresses NMDA currents and Ca^{2+} influx. Recent evidence from rodent and human studies shows that GluN3A is widely expressed and plays important functional roles in neonatal and adult brains. Cellular Ca^{2+} overload is a trigger of excitotoxicity, while GluN3A may play a regulatory role in Ca^{2+} homeostasis. The role of GluN3A regulation in AD is unknown. We tested the novel hypothesis that chronic neuronal hyperactivity and Ca^{2+} dysregulation caused by GluN3A deficiency could lead to slowly advanced "neurodegenerative excitotoxicity", dementia and AD pathology in an age-dependent manner. Ca^{2+} imaging and MultiElectrode Array recordings in GluN3A KO brain slices revealed moderate but sustained elevation of cytosolic Ca^{2+} levels, neuronal hyperactivity, and impaired synaptic plasticity compared to age-matched controls. Aging GluN3A KO mice showed increased Ca^{2+}-dependent signals, chronic inflammation, neuronal loss and recapitulated the disease symptoms including early onset of olfactory dysfunction followed by cognitive deficits. The AD hallmarks, including β-amyloid deposition and tau protein hyperphosphorylation, were identified as a late pathology in the cortex and hippocampus. In the "gain of function" experiment, expression of GluN3A in the GluN3A KO brain prevented AD progression. Early treatment at the pre-clinical stage using the NMDAR antagonist memantine (MEM; 10 mg/kg/day, 3 months) prevented/attenuated symptoms in GluN3A KO mice. Western blot analysis of AD patient's brains showed lower levels of GluN3A in the cortex compared to normal aging subjects. Our results support the "Ca^{2+} hypothesis" of AD with the novel amyloid-independent mechanism that the deficiency of GluN3A alone causes a slight lifelong Ca^{2+} dyshomeostasis that can lead to AD pathophysiology and amyloid pathology. The long-term GluN3A modulation of NMDARs signifies new therapeutic targets and possible preventive interventions for a sporadic type of AD.

Disclosures: S.P. Yu: None. **W. Zhong:** None. **K. Berglund:** None. **X. Gu:** None. **M.Q. Jiang:** None. **L. Wei:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer's Fund
NIH NS100459
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NIH AG023084
NIH 5P01AG052350
Choi Family Therapeutic Screening Facility at USC

Title: Upregulation of endothelial Picalm with a drug identified from an FDA-approved drug screen ameliorates amyloid pathology in mice

Authors: *K. KISLER, A. P. SAGARE, D. LAZIC, S. A. BAZZI, E. J. LAWSON, C.-J. HSU, E. ZUNIGA, A. R. NELSON, Z. ZHAO, B. V. ZLOKOVIC;
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Abstract: *PICALM*, phosphatidylinositol binding clathrin assembly protein, is a known genetic risk factor in Alzheimer's disease (AD). In healthy mice and humans, PICALM is highly expressed in brain endothelial cells, and involved in clathrin-mediated endocytosis, trafficking, and clearance of amyloid-β (Aβ) from the brain across the blood-brain barrier. PICALM brain endothelial levels are reduced in AD. PICALM reduction leads to reduced Aβ clearance from brain and exacerbation of Aβ pathology, which could be reversed by increasing *Picalm* endothelial expression. This suggests that therapeutic strategies that upregulate *Picalm* expression in the vasculature could alleviate brain Aβ pathology. To identify a drug to increase *Picalm* levels, we developed a luciferase reporter assay and screened a library of 2007 FDA-approved drugs. Secondary mRNA screening revealed a lead hit compound, T-65, elevating *Picalm* mRNA and protein levels by 2-3 fold *in vitro* in a human endothelial cell line and *in vivo* in mouse brain endothelium. Treatment of *Picalm*-hemizygous 5XFAD mice with T-65 increased endothelial *Picalm* levels, reduced brain Aβ load, and improved behavior. Endothelial-specific genetic deletion of *Picalm*, however, abolished the beneficial effects of T-65, suggesting that the drug targets endothelial PICALM. Together this confirms the importance of endothelial PICALM and indicates that PICALM upregulation could be a promising new therapeutic strategy for AD.

Disclosures: K. Kisler: None. **A.P. Sagare:** None. **D. Lazic:** None. **S.A. Bazzi:** None. **E.J. Lawson:** None. **C. Hsu:** None. **E. Zuniga:** None. **A.R. Nelson:** None. **Z. Zhao:** None. **B.V. Zlokovic:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG055581

NIH Grant R01 AG056622
Alzheimer's Association Grant NIRG-15-362799
BrightFocus Foundation Grant A2017457S

Title: Memory impairments and synaptic deficits in Tg19959 and APP/PS1 AD model mice are alleviated by eEF2K inhibitor A-484954

Authors: *N. KASICA, X. ZHOU, W. YANG, X. WANG, T. MA;
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Abstract: Mounting evidence indicates synaptic failure as an early and key event in Alzheimer's Disease (AD) pathophysiology. Maintenance of long-term memory and synaptic plasticity requires *de novo* protein synthesis. Phosphorylation of mRNA translation factor eukaryotic elongation factor 2 (eEF2) by its kinase eEF2K results in inhibition of general protein synthesis. Previous studies have shown elevated levels of eEF2 phosphorylation in post mortem AD human brain tissue and in AD mouse models. Here, we investigated whether suppression of eEF2 phosphorylation via eEF2K inhibitor A-484954 can alleviate AD-associated synaptic failure and memory impairments. Aged Tg19959 mice (6-9 months), APP/PS1 (12-16 months) and age-matched controls were treated with a subcutaneous pellet containing A-484954 or vehicle. The pellet continuously releases treatment over 30 days. Starting two weeks after pellet placement, the mice underwent cognitive assessment via the Novel Object Recognition (NOR) and Morris Water Maze (MWM) tasks. Golgi-Cox Stain, Amyloid Beta immunohistochemistry, Western blots, SUnSET Assays, mass spectrometry (MS) proteomic analysis, and transmission electron microscopy (TEM) were also performed. We found that cognitive impairments displayed in aged Tg19959 and APP/PS1 mice were alleviated with treatment of A-484954. Brain tissue from these mice also underwent high performance liquid chromatography (HPLC) to assess drug concentration in the brain. In addition, Golgi-Cox stain was done to assess dendritic spine density and morphology. Spine analysis indicates a rescue in levels of mature spines in the CA1 region of the hippocampus in APP/PS1 mice treated with A-484954. TEM analysis indicated a rescue in dendritic polyribosome assembly, post-synaptic density (PSD) formation, and PSD length. Additionally, SUnSET assays revealed a rescue in translational capacity in the hippocampi of AD mice treated with A-484954. Taken together, our results suggest that treatment with a eEF2K inhibitor, A-484954, alleviates cognitive impairments, restores synaptic morphology, and rescues translational capacity in mouse models of AD.

Disclosures: N. Kasica: None. **X. Zhou:** None. **W. Yang:** None. **X. Wang:** None. **T. Ma:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Research UK RF2019A-003

Title: Chronic Pharmacological Inhibition of Glymphatic Function Exacerbates Propagation of Tau Pathology in an Animal Model

Authors: *D. M. LOPES[1], J. A. WELLS[1], Z. AHMED[2], M. F. LYTHGOE[1], I. F. HARRISON[1]; [1]Univ. Col. London, London, United Kingdom; [2]Neurosci. Next Generation Therapeut. (NGTx), Eli Lilly and Co., Cambridge, MA

Abstract: The glymphatic system describes the exchange of peri-arterial cerebrospinal fluid (CSF) with interstitial fluid in the parenchymal extracellular space, and peri-venous clearance out of the brain. Facilitated by astrocytic aquaporin-4 channels, this pathway has been shown to effectively clear proteins prone to aggregation in neurodegenerative diseases, such as amyloid-β, tau, and α-synuclein. Many of these proteins have been the focus of intense research efforts in recent years following the discovery of their 'prion-like' mechanism of propagation throughout the brain. The extracellular space, that which is cleared by the glymphatic system, defines the major conduit for cell-to-cell propagation of such proteins in the brain, positioning the glymphatic system as a candidate for therapeutic enhancement for neurodegenerative disease. Here, we tested proof-of-principle, that modulation of glymphatic function affects propagation of tau pathology in an animal model of such pathological aetiology. Tau propagation was initiated in young (2 m.o.) Thy1-hTau.P301S mice (P301S mice), by injection of aged P301S mouse brain homogenate (or wildtype control), into the hippocampus and overlying cortex. Following recovery, animals received chronic treatment with the pharmacological aquaporin-4 inhibitor, TGN-020 (50mg/kg, i.p., 3 times/week) or vehicle for 10 weeks. Behavioural performance was accessed at baseline, 2, 4 and 10 weeks post-injection. At the end of the study, in vivo structural brain MRI scans were acquired for quantification of regional volumetric changes, and CSF and brains were collected for quantification of the extent of tau propagation, aggregation and resultant neurodegeneration following chronic impairment of glymphatic function. Mice chronically treated with TGN-020 exhibited exacerbated outcomes in hippocampal dependent cognitive memory tasks compared to vehicle treated controls. This was accompanied by intensified atrophy in treated brains, and a greater extent of tau aggregation and neurodegeneration following chronic drug treatment.These data suggest that modulation of the function of the water channel aquaporin-4, and by extension the function of the glymphatic system, is capable of altering the extent to which tau is able to propagate throughout the brain. These findings provide hope for therapeutic development against neurodegenerative disorders defined by 'prion-like' propagation, and rationale for further study of the involvement of the glymphatic system in neurodegenerative proteinopathies.

Disclosures: D.M. Lopes: None. **J.A. Wells:** None. **Z. Ahmed:** None. **M.F. Lythgoe:** None. **I.F. Harrison:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KHIDI grant HI18C1801
Genuv Inc.

Title: Trametinib restores memory deficits by activating endogenous neurogenesis in mouse model of Alzheimer's disease

Authors: *M.-Y. KIM[1], M. KIM[1], H. KIM[1], K.-J. YOON[2], S. HAN[1];
[1]Genuv Inc., Seoul, Korea, Republic of; [2]Korea Advanced Inst. of Sci. and Technol. (KAIST), Daejeon, Korea, Republic of

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by dementia due to synaptic loss and neuronal death, among many other causes. Proposed treatments based on neurotoxic protein elimination, however, have brought disappointing results until recent controversial approval of Aduhelm™, suggesting that new approaches should be explored. Here, we suggest that encouraging adult neurogenesis from endogenous neural stem cells (NSCs) in patient's brain can be a potential therapeutic for Alzheimer's disease. To develop regenerative CNS drug discovery, we established a phenotype-based drug discovery platform, ATRIVIEW®, aiming to identify agents that induce neuronal differentiation of adult NSCs of AD model mice. Using a FDA-approved drug library, we identified the most potent hit, SNR1611 (Trametinib), a selective MEK1/2 inhibitor. Trametinib induced neuronal differentiation of adult NSCs dose-dependently. MEK1/2 knock-down by shRNA, as trametinib did, induced neuronal differentiation and reduced apoptosis of NSCs derived even from the brain of AD model mouse, 5XFAD. When administered orally, trametinib recuperated neurogenesis in hippocampal dentate gyrus (DG) and subventricular zone (SVZ). Especially, we found evidence of NSCs' existence in the brain cortex and trametinib enhanced neurogenesis from these cortical NSCs. Trametinib administration also rescued cognitive deficits in 5XFAD mice. Altogether, these observations provide evidence that MEK inhibition by trametinib induces endogenous neurogenesis in the brain cortex as well as in the DG/SVZ and is a potential therapeutic approach for the recovery from neurodegeneration. Therefore, we are suggesting that trametinib is a new therapeutic candidate for AD.

Disclosures: M. Kim: None. **M. Kim:** None. **H. Kim:** None. **K. Yoon:** None. **S. Han:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant T32GM135095

Title: Inhibition of G9a ameliorates reactive gliosis in Alzheimer's Disease

Authors: *R. N. SHEEHY[1], L. XIE[2], Y. LI[1], L. J. QUINTANILLA[1], X. CHEN[2], J. SONG[1];
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Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease that characterized by progressive cognitive failure. A prominent feature of AD pathology is the extracellular accumulation of amyloid-beta (Aβ) peptides that aberrantly activates astrocytes and microglia, inducing neuroinflammation. The histone/lysine methyltransferase G9a (EHMT2) has recently been implicated in AD. A recent study

showed that enzymatic inhibition of G9a with a partially brain penetrant inhibitor rescued synaptic and cognitive functions in AD mice, implicating constitutively active G9a and G9a-associated pathways in AD etiology. Despite the established role of G9a in synaptic functions, it remains unknown whether G9a regulates glial-mediated neuroinflammation and the transition to reactive gliosis in AD pathology. Our recent data demonstrated that Aβ induces G9a hyperactivity. We hypothesized that a brain penetrant G9a inhibitor would significantly ameliorate reactive gliosis in AD. To test this hypothesis, we treated an Aβ AD mouse model, 5xFAD mice, with a brain penetrant G9a inhibitor. After 3 days of treatment, the hippocampi of treated and control mice were isolated for proteomic analysis. G9a inhibitor treated mice showed a significant decrease in protein abundance of many hallmark AD risk genes, including amyloid precursor protein (APP), Presenilin 1 (Psen1), and Apolipoprotein E (Apoe), as well as a significant reduction in glial fibrillary acidic protein (GFAP), a characteristic marker of astrocytes. Furthermore, immunofluorescence analysis in G9a inhibitor treated detected decreased reactive astrocytes, increased association of microglia with Aβ plaques, and a trending decrease in Aβ plaque abundance. These results suggest that G9a inhibition ameliorates reactive gliosis and may decrease Aβ plaque formation by improving microglia clearance. Overall, our data suggest that G9a is a novel therapeutic target in the treatment of AD and possibly other neuroinflammatory disorders.

Disclosures: R.N. Sheehy: None. **L. Xie:** None. **Y. Li:** None. **L.J. Quintanilla:** None. **X. Chen:** None. **J. Song:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Kir6.2-containing KATP channels are necessary for hyperglycemic dependent increases in amyloid-β

Authors: *J. GRIZZANTI[1], M. PAIT[1], L. DEITZELWEIG[1], W. MORITZ[2], M. STANLEY[4], C. M. CARROLL[1], J. A. SNIPES[1], D. M. HOLTZMAN[3], C. NICHOLS[2], S. L. MACAULEY[1]; [1]Gerontology, Wake Forest Sch. of Med., Winston Salem, NC; [2]Dept Neurol., Washington Univ., St. Louis, MO; [3]Dept Neurol., Washington Univ., Saint Louis, MO; [4]Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Aberrant excitability contributes to the production and deposition of Aβ in the Alzheimer's disease brain. Previous work from our lab demonstrated that hyperglycemia, or elevated blood glucose levels, increased brain excitability and Aβ levels potentially through inward rectifying, ATP-sensitive potassium (K_{ATP}) channels. K_{ATP} channels are present on several different cell types and help to maintain excitatory thresholds throughout the brain. K_{ATP} channels are sensitive to changes in the metabolic environment, which are coupled to changes in cellular excitability. Therefore, we hypothesize that neuronal K_{ATP} channels are necessary for the hyperglycemic-dependent increases in extracellular Aβ and knocking out these channels will uncouple the relationship between metabolism, excitability, and Aβ pathology. Kir6.2, the pore forming subunit, and SUR1, the sulfonylurea receptor, heterodimerize to form

K_{ATP} channels preferentially expressed on neurons. To determine the relationship between these channels, Aβ, and hyperglycemia, we crossed APP/PS1 mice with mice lacking neuronal K_{ATP} channels, the Kir6.2 -/- mice. Acutely, we utilized in vivo microdialysis under normal and hyperglycemic conditions to monitor Aβ release into the hippocampal interstitial fluid (ISF) in APP/PS1 mice, with or without K_{ATP} channels. Chronically, we exposed Kir6.2-/-, APP/PS1 mice to high sugar water for 3 months to determine the effects of chronic hyperglycemia on amyloid plaque burden in these mice. We found no difference in steady state ISF Aβ levels in APP/PS1 mice with or without Kir6.2-containing K_{ATP} channels. However, in the presence of a hyperglycemic clamp, Kir6.2+/+, APP/PS1 mice showed a significant increase in ISF Aβ levels compared to Kir6.2-/- mice. This was accompanied by increases in ISF lactate, a marker of neuronal activity. Chronically, Aβ plaque load was comparable between APP/PS1 mice with or without Kir6.2-K_{ATP} channels. When APP/PS1 mice with or without K_{ATP} channels were given a chronic hyperglycemic challenge, Kir6.2+/+, APP/PS1 mice showed a significant increase in cortical and hippocampal plaque deposition, while no increase in plaque load was observed in Kir6.2-/-, APP/PS1 mice. This demonstrates that Kir6.2-containing K_{ATP} channels are necessary for hyperglycemia dependent increases in Aβ levels and amyloid plaque formation and, under hyperglycemic conditions, the absence of Kir6.2 affords protection against further increases in Aβ production and deposition. These data suggest that pharmacological antagonism of Kir6.2-K_{ATP} channels holds therapeutic benefit in reducing Aβ pathology for diabetic and prediabetic patients.

Disclosures: J. Grizzanti: None. **M. Pait:** None. **L. Deitzelweig:** None. **W. Moritz:** None. **M. Stanley:** None. **C.M. Carroll:** None. **J.A. Snipes:** None. **D.M. Holtzman:** None. **C. Nichols:** None. **S.L. Macauley:** None.

Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Alzheimer's disease preclinical efficacy database: improving the scientific rigor, reproducibility, and predictive value of preclinical research for alzheimer’s disease

Authors: *S. CHAKROBORTY, A. SHARMA, Z. MARTIN, J. YUAN, S. PETANCESKA, L. REFOLO;
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Abstract: The Alzheimer’s Disease Preclinical Efficacy Database (AlzPED) is a publicly available data repository created by the National Institute on Aging (NIA) to address the poor scientific rigor, predictive value, and translatability of preclinical efficacy studies in Alzheimer’s disease (AD) animal models. The database is designed to house published and unpublished preclinical therapeutic studies incorporating experimental details of both positive and negative data. AlzPED specifically incentivizes the submission of unpublished negative data by providing a platform to create citable reports of these data. Studies are submitted to AlzPED through a curator and obtained from multiple sources. Prior to publication in the database, each study is carefully curated by two experts for data on authors, AD animal models,

therapeutic targets and agents, outcomes and most importantly evaluated for rigor in study design and methodology with a Rigor Report Card consisting of a standardized set of expert-recommended study design elements. AlzPED currently hosts curated summaries for nearly 1200 published therapeutic studies in AD animal models. The database provides easy access to information on study design, 195 animal models, 1019 therapeutic agents, 225 therapeutic targets, more than 2000 AD-related outcomes, principal findings, funding sources, patents, and related clinical trials. Evaluation of Rigor Report Cards from each study demonstrates significant under-reporting of critical elements of methodology such as power/sample size calculation, blinding for treatment, blinding for outcomes, randomization, balancing for sex, animal genetic background, and inclusion/exclusion criteria, these being reported by fewer than 30% of the nearly 1200 curated studies. Our analysis of curated studies demonstrates serious deficiencies in reporting critical elements of methodology. These deficiencies diminish the scientific rigor, reproducibility, and translational value of the preclinical studies. Adopting a standardized set of best practices like those proposed by AlzPED can improve the predictive power of preclinical studies in AD animal models and promote the effective translation of preclinical drug testing data to the clinic.

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Poster

P235. Therapeutic Strategies: Preclinical Animal Models and Small Molecule Therapeutics V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P235.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant UL1TR002736

Title: Low-dose radiotherapy and HDAC inhibition in the 3xTg-AD model of Alzheimer's disease

Authors: *N. RICCIARDI[1], F. MODARRESI[2], I. LOHSE[3], I. NEWMAN[2], M. BROWN[2], C.-H. VOLMAR[2], C. WAHLESTEDT[2], B. MARPLES[4];
[1]Dept. Biochem. and Mol. Biol., [2]Dept. of Psychiatry & Behavioral Sci., [3]Univ. of Miami Miller Sch. of Medicine, Ctr. For Therapeut. Innovation, Miami, FL; [4]Dept. of Radiation Oncology, Univ. of Rochester, Rochester, NY

Abstract: Rationale: Single-target therapeutic approaches for Alzheimer’s disease (AD) have yielded suboptimal results over the last 2 decades in efforts to slow or reverse cognitive decline. Previous work has shown that the epigenetic histone deacetylase 3 (HDAC3) inhibitor RGFP966 can improve memory and hold disease modifying potential. Additionally, our collaborators have shown that cranial radiotherapy is a plausible, noninvasive therapy in pre-clinical AD models. These two multifactorial treatments act by independent mechanisms that complement each other however their historically known side effects at high doses have kept them from clinical exploration. **Objective:** Explore the synergistic potential of low-dose RGFP966 and radiation therapy on AD hallmarks and memory *in vitro* and *in vivo.* **Methods:** *In vitro* studies of innate immune modulation and amyloid precursor protein (APP) processing were performed in cell lines (SIM-A9 and HEKAPP$_{Swe}$) and primary microglia cells via ELISA, Western

blotting, confocal imaging, and RT-qPCR. *In vivo* experiments were performed in 3xTg-AD mice (male and female, n= 6-9/group). Vehicle (V), 3 mg/kg RGFP966 (RGFP), 2 Gy/wk radiotherapy (RT), and low-dose combination therapy (LDCT) animals were treated for 2 months and then behavioral assessment of spatial memory (Y-maze, Barnes maze) and recognition memory (novel object recognition) was performed. Molecular analysis included hippocampal gene expression evaluation by NanoString neuropathology panel, confirmatory RT-qPCR, Western blotting, ELISA assessment of amyloid and tau processing, and blood and hippocampal Luminex panel for cytokine production. All *in vitro* studies were replicated 2-3 times. **Results:** LDCT elicits a tolerant microglial response evidenced by downregulation of master regulator genes (*Spi.1, Iba1*, and *Trem2*) and cytokine gene expression (*Il6* and *Il10*). These genes remain downregulated after stimulation with oligomeric $A\beta_{42}$ compared to control treated cells or individual treatments. LDCT also increases $A\beta_{42}$ uptake in primary microglia and promotes non-amyloidogenic APP processing and neurotrophic gene expression in $HEKAPP_{Swe}$ cells. *In vivo* studies supported the immune down regulation (*Csfr1*) and neurotrophic gene (*Npas4, Bdnf, Fos*) upregulation of LDCT. We also observed modest improvements in memory in the Barnes maze in both RT and LDCT treated animals compared to V treated mice. **Conclusions:** LDCT elicits a unique anti-AD gene expression profile *in vitro* and *in vivo* that does not occur in single-treatment animals. The synergistic potential of LDCT was further supported by modest spatial memory improvements and decreased cytokine production

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Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

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Program #/Poster #: P263.01

Topic: C.03. Parkinson's Disease

Support: Ministry of Health-Open Fund Large Collaborative Grant / MOH-OFLCG18May-0002
Ministry of Health Tier 3 Academic Research Fund / MOE2016-T3-1-004
Clinician Scientist Residency Seed Fund / CSSDFD19OCT-0007
ExxonMobil-NUS Research Fellowship for Clinicians
NUS Research Scholarship

Title: Near-infrared light stimulation confers neuroprotection against α-synuclein toxicity by activating PGC-1α mediated mitochondrial biogenesis

Authors: *A. S. C. FOO[1,4,5], G. G. Y. LIM[5], H.-J. KIM[2], W. TANG[5], H. C. CHOONG[6], H. Y. CHAN[3], J. S. Y. HO[2], T. W. SOONG[1], K. L. LIM[7,5];
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Abstract: There is presently no treatment capable of preventing neuronal death in Parkinson's Disease (PD), a progressive neurodegenerative disorder characterized by the presence of intracellular aggregates containing misfolded α-synuclein. In this study, we examine the neuroprotective and mitochondrial modulatory effects of near-infrared (NIR) light stimulation in in-vitro Parkinsonian models. Using monochromatic light of 680nm wavelength, we treated α-synuclein preformed fibril (α-synPFF) seeded cortical neuronal cultures derived from E16-17 mice embryos and determined the extent of intraneuronal phosphoserine-129 α-synuclein (pS129 α-syn) propagation. Concurrently, we also assessed treated neurons for apoptotic marker expression levels and changes in mitochondrial morphology. To assess the effects of NIR on mitochondrial status, we stimulated monolayer HeLa cell cultures with 680nm monochromatic light and 1) measured cellular adenosine triphosphate (ATP) levels using a bioluminescence assay, 2) quantified mitochondrial membrane potential changes and 3) examined expression levels of fission/fusion and mitobiogenesis-inducing proteins. We observe in cultured cortical neurons that chronic NIR stimulation mitigates intracellular accumulation of pS129 α-syn and reduces expression of the apoptosis driver cleaved caspase-3. Concomitantly, NIR stimulation also reverses mitochondrial elongation induced by α-synPFF seeding in cultured neurons. In HeLa cell cultures, NIR stimulation upregulates the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional co-activator with a central role in the regulation of mitochondrial biogenesis. This is observed in conjunction with increases in cellular ATP levels as well as transcription factor A mitochondria (TFAM) expression; TFAM being a downstream effector molecule of PGC-1α essential for mitochondrial DNA transcription. In addition, we also observe that an upstream promoter of PGC-1α transcription, phosphoserine133-cAMP response element binding protein, is increased in HeLa cells with NIR stimulation. Collectively, these results suggest that PGC-1α mediated mitochondrial biogenesis, triggered by exposure to NIR light, may confer cytoprotection against α-synuclein induced toxicity.

Disclosures: A.S.C. Foo: None. **G.G.Y. Lim:** None. **H. Kim:** None. **W. Tang:** None. **H.C. Choong:** None. **H.Y. Chan:** None. **J.S.Y. Ho:** None. **T.W. Soong:** None. **K.L. Lim:** None.

Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.02

Topic: C.03. Parkinson's Disease

Support: DAE-ICT-1060

Title: Mitochondrial targeted triphenyl phosphonium ethyl ferulate improved rotenone-induced behavioral deficits, oxidative changes, and mitochondrial dysfunction in rotenone induced rat model of parkinson's disease.

Authors: *A. S. PATIL, M. K.I, S. SATHAYE, M. DEGANI;
Dept. of Pharmaceut. Sci. and Technol., Inst. of Chem. Technol., Matunga, India

Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Pathological changes in PD leads to degeneration of dopaminergic neurons in the Substantia nigra area of the brain responsible for controlled movement of the muscles. Ethyl ferulate (ethyl 4-hydroxy-3-methoxycinnamate, EF), an alkyl ester derivative of ferulic acid, has been shown to possess various biological activities like anti-cancer, anti-oxidant, protecting mitochondrial dysfunction, neuroprotective activity etc. In this exploratory work, based on above data suggestive of neuroprotective potential of EF; we decided to explore EF for its anti-Parkinson's potential. Mitochondrial dysfunction is implicated in PD. To address this, we decided to synthesize mitochondrial targeted ethyl ferulate (M-EF) to increase its efficacy. This was done by substituting hydroxyl groups of EF and with a propyl linker and TPP+ moiety. The coupling to TPP+ results in targeting the mitochondrial matrix. The objective of the present study was to evaluate the comparative neuroprotective effect of EF and M-EF against pathological alterations induced by rotenone in rat brain. Rotenone is a known mitochondrial toxicant leading to its dysfunction. In the present study rats were injected bilaterally with rotenone (12 μg) in Substantia nigra and further treated orally with EF (10, 20 and 50mg/kg) and M-EF (1,5 and 10 mg/kg) for 30 days. During the study behavioural tests such as the Rota-rod, open field, and Barnes maze test were performed. At the conclusion of the study, antioxidant (reduced glutathione, superoxide dismutase, catalase, and lipid peroxidation) and proinflammatory (TNF-α) as well as mitochondrial (complex I) characteristics were assessed in mid-brain homogenates. EF and M-EF significantly improved the locomotor activity and the muscle strength as compared to the negative control group. A significant attenuation in the cognitive dysfunction by EF and M-EF was observed in barnes maze test. The effects of EF and M-EF treatment on oxidative stress and inflammation produced by rotenone poisoning were dramatically reduced. Rotenone inhibition of mitochondrial complex I was likewise significantly reduced by EF and M-EF. The preliminary findings show that EF and M-EF have neuroprotective properties against rotenone-induced neurotoxicity in rats. A tenfold higher activity was seen with M-EF as compared to EF. Further confirmation of the activity will be assessed using immunohistochemistry for dopaminergic activity along with mitochondrial function and health.

Disclosures: A.S. Patil: None. **M. K.i:** None. **S. Sathaye:** None. **M. Degani:** None.

Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.03

Topic: C.03. Parkinson's Disease

Title: Profiling MCC-950 as a potent and selective Nod-like receptor family pyrin domain containing 3 (NLRP3) inhibitor for Parkinson's Disease (PD)

Authors: *M. PAPAKOSTA, H. SUN, N. ENGLISH, P. ROLZIN, J. BLIESATH, Y. CHEN, U. BANERJEE, D.-A. HARRIS, C. WRIGHT, A. GREEN, J. MCLAUGHLIN, A. HOLLAND, N. BROADBENT, H. ZOU, M. BAKSH, J. SCHACHTER, T. WOLINSKY, H. ESTRELLA, M. VILKHOVOY, C. ROTTER, T. NISHI, E. CHANG, H. MONENSCHEIN, R. HODGSON;
Takeda Develop. Ctr. Americas, Inc., San Diego, CA

Abstract: PD patients show chronic neuroinflammation, α-synuclein inclusions in the form of Lewy bodies in neurons and substantial loss of dopaminergic neurons projecting from the substantia nigra pars compacta (SNc) to the corpus striatum (Jiang and Dickson 2018). Despite huge advances in understanding PD, safe, effective treatments elude patients. The central nervous system (CNS) inflammatory component in PD is mainly due to chronically activated microglial cells, sensed by the NLRP3 inflammasome, an important component of the innate immune system expressed in the cytosol (Sawada et al 2006; Poewe et al 2017). NLRP3, upon activation by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) such as misfolded proteins, ATP, nigericin, assembles and oligomerizes with adaptor apoptosis-associated speck-like protein (ASC) and pro-caspase-1 to form multiprotein intracellular complexes, which activate the caspase-1 cascade. Proinflammatory cytokines (interleukin (IL)-1β and IL-18) are released, inducing a lytic cell death (pyroptosis), which induces inflammation leading to dopaminergic neuronal death (Guo et al. 2015). Postmortem brains from PD patients show elevated levels of NLRP3, ASC and caspase-1 and PBMCs and serum from PD patients show increased NLRP3 activation and higher levels of IL-1β, that correlate with severity and progression of PD (Gordon et al 2018; Chaterjee et al. 2020; Fan et al 2020; Anderson et al 2021). Thus, the NLRP3 inflammasome may be an effective therapeutic target for PD. We have conducted *in vitro* and *in vivo* studies to characterize the NLRP3 small molecule inhibitor, MCC-950 (Perregaux et al., 2001; Collet al., 2015) and assess its utility in PD preclinical *in vivo* studies. In agreement with the literature, we show that MCC-950 directly and selectively binds NLRP3 with high affinity and potently inhibits cytokine release in activated microglia/macrophages *in vitro* across a variety of assays. MCC-950 inhibits NLRP3 *in vivo* in a pharmacokinetic/pharmacodynamic (PK/PD) model in the periphery with high potency (IC_{50} = ~17 nM free plasma) and efficacy. However, MCC-950 has no significant efficacy in brain PK/PD assays, possibly due to poor pharmacokinetic characteristics exemplified by a very low unbound relative, Kp,uu value (0.07; mouse) which is a measure of the extent of the distribution equilibrium of a compound between the unbound fractions in brain and in blood plasma. Therefore, MCC950 is not a suitable tool compound for investigating the role of NLRP3 in central neurodegenerative activity in vivo.

Disclosures: M. Papakosta: None. **H. Sun:** None. **N. English:** None. **P. Rolzin:** None. **J. Bliesath:** None. **Y. Chen:** None. **U. Banerjee:** None. **D. Harris:** None. **C. Wright:** None. **A. Green:** None. **J. McLaughlin:** None. **A. Holland:** None. **N. Broadbent:** None. **H. Zou:** None. **M. Baksh:** None. **J. Schachter:** None. **T. Wolinsky:** None. **H. Estrella:** None. **M. Vilkhovoy:** None. **C. Rotter:** None. **T. Nishi:** None. **E. Chang:** None. **H. Monenschein:** None. **R. Hodgson:** None.

Poster

P263. Neuroprotective Mechanisms I

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Program #/Poster #: P263.04

Topic: C.03. Parkinson's Disease

Support: NIH F31HL136047
NIH R21NS084158
NIH P51OD011106
American Parkinson Disease Association PF-APDA-SFW-1854

Title: Myelination in a nonhuman primate model of Parkinson's disease cardiac sympathetic neurodegeneration

Authors: *J. M. METZGER[1], H. N. MATSOFF[1,2], D. VU[1], A. D. ZINNEN[1], K. M. JONES[1], V. BONDARENKO[1], H. A. SIMMONS[1], C. F. MOORE[3], M. E. EMBORG[1,4];
[1]Wisconsin Natl. Primate Res. Ctr., [2]Occup. Therapy Program, [3]Dept. of Psychology, [4]Dept. of Med. Physics, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Minimal myelination is proposed to be a contributing factor to the preferential nigral neuronal loss in Parkinson's disease (PD). Similar to nigral dopaminergic neurons, sympathetic neurons innervating the heart have long, thin axons which are unmyelinated or minimally myelinated. Interestingly, cardiac sympathetic loss in PD is heterogeneous across the heart, yet the spatial relationship between myelination and neurodegeneration is unknown. Here we report the mapping of myelin basic protein (MBP) expression across the left ventricle of normal rhesus macaques (n=5) and animals intoxicated with systemic 6-OHDA (50 mg/kg iv) to model parkinsonian cardiac neurodegeneration (n=10). A subset of 6-OHDA-treated rhesus received daily dosing of pioglitazone (5 mg/kg po; n=5), a PPARγ agonist with neuroprotective properties. In normal animals, MBP-immunoreactivity (-ir) was identified surrounding approximately 14% of axonal fibers within nerve bundles of the left ventricle, with more myelinated nerve fibers at the base level of the left ventricle than the apex ($p < 0.014$). Greater MBP-ir at the base was related to greater number of nerve bundles at that level relative to the apex ($p<0.05$), as the percent of myelinated nerve fibers in bundles was not significantly different between levels of the heart. Cardiac sympathetic loss following 6-OHDA was associated with decreased MBP-ir in cardiac nerve bundles, with the percent decrease of MBP-ir greater in the apex (84.5%) than the base (52.0%). Interestingly, cardiac regions and levels with more MBP-ir in normal animals showed attenuated sympathetic loss relative to areas with less MBP-ir in 6-OHDA + placebo ($r = -0.7$, $p < 0.014$), but not in 6-OHDA + pioglitazone ($r = -0.1$) subjects. Our results demonstrate that myelination is present around a minority of left ventricle nerve bundle fibers, is heterogeneously distributed in the heart of rhesus macaques, and has a complex relationship with cardiac sympathetic neurodegeneration and neuroprotection.

Disclosures: J.M. Metzger: None. **H.N. Matsoff:** None. **D. Vu:** None. **A.D. Zinnen:** None. **K.M. Jones:** None. **V. Bondarenko:** None. **H.A. Simmons:** None. **C.F. Moore:** None. **M.E. Emborg:** None.

Poster

P263. Neuroprotective Mechanisms I

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Program #/Poster #: P263.05

Topic: C.03. Parkinson's Disease

Support: DoD Grant W81XWH-19-1-0757 (Awarded to MFS)

Title: Glial cell line-derived neurotrophic factor signaling: a new mechanistic perspective in exercise-mediated recovery of motor impairment in a rat hemi-parkinson's model

Authors: *E. A. KASANGA[1], M. K. SHIFFLET[1], V. A. NEJTEK[1], M. F. SALVATORE[2];
[1]Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; [2]Inst. for Healthy Aging, Univ. of North Texas Hlth. Sci. Ctr., Ft Worth, TX

Abstract: Identifying the CNS mechanisms driving beneficial motor effects of exercise in Parkinson's disease (PD) can yield viable molecular targets for genetic or pharmacological approaches. By targeting these exercise-responsive mechanisms, the likelihood of mitigating disease progression is increased, given the yet unknown CNS mechanisms that are driving the motor benefits already established in PD patients. Rodent PD models can yield insight into exercise-driven CNS mechanisms, but arguably studies must be tethered in practicable limits of exercise intensity for a PD patient for optimal translation to the patient. In our study, we used this guideline to investigate exercise-responsivity of glial cell line-derived neurotrophic factor (GDNF) signaling in a treadmill exercise paradigm initiated after establishing motor impairment in the 6-hydroxydopamine (6-OHDA) hemi-Parkinson's rat model. Rats that were later assigned to the exercise (EX) or non-exercise (NE) groups were first acclimated to our established treadmill exercise protocol. Seven days after nigrostriatal lesion induction by 6-OHDA, motor impairment was verified by at least 25% reduction in the use of the forepaw associated with lesion and rats were assigned into the EX or NE groups with similar forepaw use deficits. Rats exercised three times per week at a final treadmill speed of 10 m per min for 40 min. Forepaw use was evaluated on a weekly basis on the day following the third exercise session each week for three weeks. Our treadmill regimen was associated with a highly significant recovery (~50% increase) of forepaw use by the third week of exercise. However, we did not observe any difference in striatal GDNF protein expression between the lesioned NE or EX groups. In contrast, we observed significant increases in the GDNF family receptor, GFR-alpha1, and receptor tyrosine kinase, RET protein expression in the lesioned hemisphere of the striatum of the EX group. These results shed new light on the plausibility that increased GDNF signaling plays a role in recovery of motor function following loss of nigrostriatal neurons, as seen in PD. As such, it is plausible that these receptors may be targeted to maintain exercise benefits, given the progressive nature of PD and the known barriers faced by PD patients to exercise.

Disclosures: E.A. Kasanga: None. **M.K. Shifflet:** None. **V.A. Nejtek:** None. **M.F. Salvatore:** None.

Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.06

Topic: C.03. Parkinson's Disease

Support: NIH grant AG048918

Title: A proteomic survey of sex- and age-differences in the striatum and substantia nigra of non-human primate brain to identify novel treatment targets in Parkinson's disease

Authors: *J. K. BLACKBURN, R. WILSON, A. WONG, T. LAM, J. D. ELSWORTH;
Yale Univ., New Haven, CT

Abstract: Oxidative stress is a major contributor to the damage and death of dopamine neurons in Parkinson's disease (PD). Current PD treatments only temporally alleviate symptoms, thus there is a dire need for new, effective therapies that target underlying causes. So we have conducted a high-throughput proteomic survey in non-human primate (NHP) brain to identify novel neuroprotective targets. We based this exploratory study on two phenomena: (1) dopamine neurons in the infant NHP brain are resilient against oxidative stress (Morrow et al. 2012) and (2) the male sex is a significant risk factor for PD (Pinares-Garcia et al. 2018). Thus, we sought to identify age- and sex-dependent proteins in substantia nigra and striatum of NHPs with neuroprotective potential. We exploited label-free quantitative tandem mass-spectrometry to perform deep proteomic profiling of substantia nigra (SN) and striatum (STR) in St Kitts green monkeys. Whole tissue samples were dissected from 20 monkeys (5 male and 5 female of two ages: infant (11-28 days) and adult (4.5-6 KG) We detected a total of 3824 proteins, with 992 and 1263 showing age-dependent expression in SN and STR, respectively. Just over half (59%) were down regulated in adults compared to infants, and about half of down-and up-regulated proteins were shared between SN and STR, thus a substantial number of differentially expressed proteins are region specific. Functional analysis revealed that differentially expressed proteins are involved in mechanisms associated with PD, such as glutathione metabolism and intracellular transport in SN, and mitochondria function, protein catalysis, and vitamin B6 in STR. Principal component analysis revealed that only adult SN proteomes have an overall sex difference. 36 proteins in SN and 2 proteins in STR had sex-dependent expression. Several proteins that had higher expression in females were associated with neuroprotective mechanism, such as SLC6A3 and PGAM5, whereas proteins that were expressed higher in males included GPR37 and EIF4G1, which are associated with PD. Together these results indicate that some sex-dependent proteins align with sex-dependent risk of PD and they warrant further investigation. In summary, this exploration of age- and sex-differences in NHP brain provides an unprecedented opportunity for identifying new therapeutic targets in PD. REFERENCES Morrow BA, RH Roth, S Diano, and JD Elsworth 2012 'Susceptibility to a parkinsonian toxin varies during primate development', *Exp Neurol*, 235:273-81.Pinares-Garcia, PM Stratikopoulos,Zagato,Loke, and J Lee 2018. 'Sex:A Significant Risk Factor for Neurodevelopmental and Neurodegenerative Disorders', *Brain Sci* 8.

Disclosures: J.K. Blackburn: None. **R. Wilson:** None. **A. Wong:** None. **T. Lam:** None. **J.D. Elsworth:** None.

Poster

P263. Neuroprotective Mechanisms I

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Program #/Poster #: P263.07

Topic: C.03. Parkinson’s Disease

Support: NIH T32GM067795
NIH R21 AG057006
NIH R01 ES029035
NIH P30 ES005605
University of Iowa Graduate College

Title: A dopamine-derived biomarker produced via neurotoxicants

Authors: *R. CRAWFORD[1], E. GILARDONI[2], K. BOWMAN[1], J. DOORN[1];
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Abstract: Background. Parkinson's disease is a neurodegenerative disorder characterized by disruption of dopamine homeostasis and oxidative stress. The aldehyde metabolite of dopamine, 3,4-dihydroxyphenylacetaldehyde (DOPAL), is implicated in dopaminergic cell death due to its ability to modify proteins and cause oxidative stress. Aberrant DOPAL production may be caused by exposure to certain pesticides that disrupt the dopamine homeostatic pathway. This research has identified a DOPAL conjugate that is produced in SH-SY5Y neurons after supplementation with dopamine and exposure to the pesticide rotenone. Specifically, the amino acid L-cysteine scavenges DOPAL to form a putative thiazolidine ring that is identifiable and quantifiable via mass spectrometric methods. This has implications in neuroprotection as well as the potential for a novel biomarker for dopamine dyshomeostasis. **Methods.** SH-SY5Y neurons were supplemented with dopamine and exposed to 1μM of the PD-correlated pesticide rotenone. Both intracellular and extracellular components were evaluated at intermittent time points from 0 to 24 hours. Controls included cells that were also supplemented with N-acetyl cysteine (i.e., the precursor to L-cysteine) and cells that were treated with only dopamine. L-cysteine was also evaluated for its protective abilities by observing modification of proteins (i.e., glutathione S-transferase or bovine serum albumin) by DOPAL in the presence of absence of this scavenger. Mass spectrometric methods were employed to assess the mechanism of action of protection by L-cysteine and elucidate the formation of an L-cysteine-DOPAL conjugate. **Results.** L-cysteine fully protected glutathione S-transferase activity from modification by dopamine and DOPAL. L-cysteine was also found to form a putative thiazolidine conjugate with DOPAL via LC-MS. This conjugate was also found to form in SH-SY5Y neurons after treatment with dopamine and n-acetyl cysteine, or when cells were treated with dopamine and exposed to rotenone. The DOPAL-L-cysteine conjugate is exported to the extracellular matrix. **Conclusions.** Because aberrant DOPAL production is a hallmark of the etiopathology of Parkinson's disease, an identifiable DOPAL derivative may help diagnose disease earlier. We propose that the observed DOPAL-L-cysteine production is a novel pathway of neuroprotection and that it is relevant to diseases that are marked by dopamine disruption, such as Parkinson's disease.

Disclosures: R. Crawford: None. **E. Gilardoni:** None. **K. Bowman:** None. **J. Doorn:** None.

Poster

P263. Neuroprotective Mechanisms I

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.08

Topic: C.03. Parkinson's Disease

Support: Department of Education: #P031S150199

Title: High-intensity, short-term exercise protects against 6-OHDA in an animal model of Parkinson's Disease

Authors: *M. HANNA, A. PEREZ, J. ROSALES;
Vanguard Univ., Costa Mesa, CA

Abstract: Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by the degeneration of the dopaminergic neurons of the nigrostriatal pathway. Patients with PD typically experience motor symptoms, including tremors, rigidity, slowness of movement, and postural instability. Lewy Body pathology from misfolded α-synuclein aggregates is another major hallmark of the disease. In animal models of PD, increased oxidative stress, reactive oxygen species, inflammatory cytokines, and microglial activation have been reported to play a significant role in mediating PD pathology. In this study, we tested if five weeks of high-intensity treadwheel exercise before administering the dopaminergic neurotoxin 6-hydroxydopamine exerts a neuroprotective effect in an animal model of Parkinson's disease. After injection of 6-OHDA, behavioral tests were assessed within one week of the injection through examining apomorphine-induced rotation, methamphetamine-induced rotation, and sensory neglect. Apomorphine and methamphetamine-induced rotation are used to assess the extent of impairment caused by 6-OHDA and directly correlate to the degree of dopaminergic loss. Results showed that in 6-OHDA injected rats, prior exercise training reduced apomorphine-induced contralateral rotation and methamphetamine-induced ipsilateral rotation compared to the non-exercised 6-OHDA group. Exercised and non-exercised rats in the 6-OHDA groups showed reduced sensory neglect on the contralateral side of the body compared to saline groups; however, prior exercise training did not significantly improve sensory neglect compared to the non-exercise 6-OHDA group. The data suggest that high-intensity, short-term exercise can act as a neuroprotectant factor by reducing the extent of dopaminergic neurodegeneration. 5-weeks of prior exercise training was not sufficient to improve sensory neglect.

Disclosures: M. Hanna: None. **A. Perez:** None. **J. Rosales:** None.

Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.09

Topic: C.03. Parkinson's Disease

Support: NIH-R56NS109608
ABRC ADHS18-198846

Title: Analysis of neuroprotective and anti-inflammatory activity of sub-anesthetic ketamine-treatment in the progressive unilateral 6-OHDA-lesion rat model

Authors: *C. J. STOPERA[1], M. J. BARTLETT[3], M. R. SEXAUER[1], K. BERNARD[1], J. A. STANCATI[5], S. J. SHERMAN[1], K. STEECE-COLLIER[6], H. W. MORRISON[2], T. FALK[4];
[2]Col. of Nursing, [1]The Univ. of Arizona, Tucson, AZ; [3]Dept. of Pharmacol., [4]Dept. Of Neurol., Univ. of Arizona Col. of Med., Tucson, AZ; [5]Dept. of Translational Neurosci., [6]Michigan State Univ., Grand Rapids, MI

Abstract: Low-dose, sub-anesthetic ketamine has been shown to be neuroprotective in rodent models of cerebral ischemia and traumatic brain injury, with anti-inflammatory effects contributing to ketamine's neuroprotective actions. Our lab has shown prior that sub-anesthetic ketamine reduces L-DOPA-induced dyskinesia in a rat 6-hydroxydopamine (6-OHDA) Parkinson's disease (PD) model, is acutely anti-parkinsonian, and ketamine's long-term anti-dyskinetic effects were identified as brain-derived neurotrophic factor (BDNF)-dependent. We have also shown sub-anesthetic ketamine may exhibit neuroprotective effects in a progressive 6-OHDA rat model of PD. Here, male Sprague-Dawley rats were treated with either ketamine or vehicle via the following protocol (6-hr treatment; 3 x 20 mg/kg; *i.p.*; 2-hrs apart) beginning 6-hrs prior to a unilateral intrastriatal 6-OHDA lesion. Rats were then treated daily with the 6-hr protocol for 7 days post-lesion. Using the amphetamine-induced rotation test, as an estimate of lesion severity, rats were injected with D-amphetamine (5 mg/kg; *i.p.*) and rotational asymmetry was assessed by counting the net ipsilateral rotations (mean ± SEM) over 90-minutes. On Day 28 post-lesion, rats treated with ketamine (211 ± 116) showed a significantly decreased number of net ipsilateral rotations compared to the vehicle (666 ± 187) group (Two-tailed t-test; $p < 0.05$; n=15), suggesting a neuroprotective effect of ketamine. To investigate anti-inflammatory action via activation of microglia, we have stained the substantia nigra (SN) and striatum (STR) with the microglia marker, IBA1, and analyzed branch length/cell and end points/cell. We found no effects in the SN, but there was a significant reduction of branch length/cell by 6-OHDA, compared to the intact STR (Two-way ANOVA; $p < 0.001$; n=8). Ketamine further significantly reduced branch length/cell in the intact STR ($p < 0.05$). The number of end points/cell was also significantly reduced by 6-OHDA in vehicle treated rats ($p < 0.001$), but not in those treated by ketamine. These data provide the first indicator of ketamine's effects on microglial morphology. Additional morphological analyses and assessment of a functional marker of microglia (CD68) are ongoing. We are also currently analyzing astrocyte activity using GFAP as a marker of activation. Unbiased stereology of dopaminergic neurons in the SN is ongoing and we are investigating the role of BDNF in ketamine's neuroprotective effects via *in situ* hybridization for RNA of both BDNF and its receptor, TrkB. In conclusion, an acute neuroprotective activity of ketamine is further supporting the ongoing clinical evaluation in individuals with PD.

Disclosures: C.J. Stopera: None. **M.J. Bartlett:** None. **M.R. Sexauer:** None. **K. Bernard:** None. **J.A. Stancati:** None. **S.J. Sherman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SJS and TF have a pending patent application for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease.. **K. Steece-Collier:** None. **H.W. Morrison:** None. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SJS and TF have a pending patent application for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease..

Poster

P263. Neuroprotective Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P263.10

Topic:

Title: Maternal nutritional oral supplementation with Nano-emulsified punicic acid (Nano-PSO) during gestation and lactation, protects against fetal and early life rotenone neurotoxicity to their adult offspring

Authors: *M. GÓMEZ-CHAVARÍN[1], J. SÁNCHEZ-CAMACHO[2], P. PADILLA-CORTES[3], A. RAMIREZ[4], G. ROLDÁN[1], J. RAMIREZ-SANTOS[4], G. GUTIERREZ-OSPINA[4];
[1]Lab. de Neurobiología Conductual, Depto. Fisiología, Facultad de Medicina, Univ. Nacional Autónoma de México (UNAM), México., Ciudad de Mexico, Mexico; [2]Escuela Superior de Medicina, Inst. Politécnico Nacional, México, Mexico; [3]Unidad de Cromatografía de Alta Resolución, Inst. de Investigaciones Biomédicas. UNAM, México., Ciudad de Mexico, Mexico; [4]Lab. de Biología de Sistemas, Depto. de Biología Celular y Fisiología, Inst. de Investigaciones Biomédicas. UNAM. México, Ciudad de Mexico, Mexico

Abstract: The fetal origin of adult disease's hypothesis predicts that adult neurodegenerative diseases may arise as a result of gestational insults. Parkinson's disease (PD) is now recognized to be induced by exposure to environmental neurotoxins that impair mitochondrial oxidative metabolism. Hence, mothers exposed to such neurotoxins during gestation and/or lactation might give rise to adult offspring offended by PD. In this work we tested this prediction by first exposing pregnant and/or lactating mother rats to daily subcutaneous injections of rotenone during gestation and/or lactation. As expected, their adult offspring displayed motor behavior disturbances, nigral dopaminergic neurodegeneration, and reduced dopamine and increased lipid peroxidation, α-synuclein availability and senescent cell number in the substantia *nigra*. All these disturbances were prevented or greatly attenuated in adult offspring by supplementing the diet of ROT exposed pregnant and/or lactating rats with a daily oral dose of Nano-PSO. Hence, our results show that adult Parkinsonism can indeed be acquired after being exposed to environmental neurotoxins during the prenatal and early postnatal life. The condition may be fully or partly avoided by facilitating the access and promoting the consumption of potent antioxidant agents such as Nano-PSO during gestation and lactation. This work was funded by the yearly stipend provided GGO by the Instituto de Investigaciones Biomédicas, UNAM.

Disclosures: M. Gómez-Chavarín: None. **J. Sánchez-Camacho:** Other; Student Ph D. **P. Padilla-Cortes:** None. **A. Ramirez:** None. **G. Roldán:** None. **J. Ramirez-Santos:** None. **G. Gutierrez-Ospina:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIEHS T32 ES007326
NIEHS P01 ES002848-Project 3

Title: Developmental cell death in the hippocampus and related cognitive behaviors are altered by perinatal exposure to phthalates

Authors: *E. P. SELLINGER[1], H. FENTON[2], A. BRINKS[1], J. M. JURASKA[3];
[1]Neurosci. Program, [2]Vet. Med., [3]Psychology, Univ. of Illinois, Champaign, IL

Abstract: The plasticity of the perinatal period leads to increased susceptibility to environmental insult from endocrine-disrupting chemicals such as the plasticizers known as phthalates. There is an association between developmental phthalate exposure and impaired cognitive and emotional processing outcomes in children (Radke et al., 2020), however their mechanism of action remains unclear. Using a rat model, our lab has demonstrated exposure to an environmentally relevant mixture and dose of phthalates during the perinatal period results in fewer neurons in the adult medial prefrontal cortex that correlates with impaired cognitive flexibility (Kougias et al. 2018). More recently, we have shown this reduction in neurons is due, at least in part, to elevated cell death both pre- and postnatally (unpublished observations). The mPFC forms connections with the hippocampus, a brain region that also undergoes protracted development. The present study aims to investigate how phthalates alter the normal course of cell death in the dorsal and ventral hippocampus and to assess whether early exposure results in immediate cognitive behavioral changes.To expose developing pups to the phthalate mixture, dams were fed 0, 0.2, or 1 mg/kg/day on a cookie from gestational day 2 through 25 days post-partum. One male and one female pair per litter were sacrificed on P5 and another on P10 for analysis of cell death using a TUNEL label. A third male/female pair from each litter was tested on the elevated plus maze (EPM) on P27 followed by the Morris Water Maze (MWM) beginning on P29. A preliminary analysis (n=4-6/group) reveals a significant increase in cell death in dorsal CA1 ($p=0.045$) in both sexes on P5 after phthalate exposure and a similar, though non-significant, increase in the dentate. A significant effect of phthalate exposure is also seen in males only (n=5-6/group) on the percent of open arm entries measured on the EPM ($p = 0.04$). Males exposed to 1mg/kg also show a decreased latency to enter the open arm compared to controls ($p = 0.02$). Finally, no apparent effects of phthalate exposure were seen in preliminary analyses (n=5-6/group) of the MWM. Increased N and more sampled days for apoptosis and behavior will be added.

Disclosures: E.P. Sellinger: None. **H. Fenton:** None. **A. Brinks:** None. **J.M. Juraska:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Internal Bowling Green State University Funds

Title: Effects of corn grown on dredge-amended soil on hippocampal development and behavior

Authors: *K. A. S. FLANIGAN[1], A. N. JULIAN[2], V. R. RIESGO[1], M. A. RÚA[2], J. WILLING[1];
[1]Bowling Green State Univ., Bowling Green, OH; [2]Wright State Univ., Dayton, OH

Abstract: Agricultural practices designed to improve environmental health may be exposing developing mammals to compounds that can alter fundamental facets of neurodevelopment. In an effort to mitigate soil degradation, natural and synthetic amendments are administered to avoid yield losses, including the use of dredged sediment removed from local waterways (‘dredged sediment’). This sediment contains

nutrients necessary for crop production but also contains contaminants of concern (COC) including heavy metals, bisphenol-A, and polyaromatic hydrocarbons. These compounds can negatively impact neurodevelopment and behavior in mammals, particularly following perinatal exposure. Because COC can bioaccumulate in crops grown on amended soils, mammals consuming these crops, including both livestock and humans, may be impacted. The current study investigates the neurodevelopmental and behavioral impact of corn grown on dredged sediment amended fields in Long Evans rats. Female rats were exposed to corn grown on dredged sediment (or a non-dredge amended source of corn) during pregnancy and lactation. Progeny of control and exposed females were behaviorally tested in the elevated plus maze, open field, and novel object recognition tasks in young adulthood. Perinatal exposure to dredge-grown corn resulted in mild increases in anxiety-like behavior on the elevated plus maze and open field tests. In addition, we assessed the long-term effects of corn grown with dredged sediment on body weight, brain weight and hippocampal volume. These results suggest caution and further study to determine the safety of specific agricultural practices on mammalian brain development.

Disclosures: K.A.S. Flanigan: None. **A.N. Julian:** None. **V.R. Riesgo:** None. **M.A. Rúa:** None. **J. Willing:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AR160055
P30ES025128
R01ES016099

Title: The Impact of Perinatal Exposure to a Flame Retardant Mixture on Microglial Density, Reactivity, and Morphology in Adult Prairie Vole Brain

Authors: *W. P. MARINELLO, S. A. GILLERA, B. M. HORMAN, H. B. PATISAUL;
Biol. Sci., North Carolina State Univ., Raleigh, NC

Abstract: Microglia are known to shape brain sex differences critical for social behaviors. Chemicals, including flame retardants, can disrupt brain sexual differentiation but there is limited data regarding how they impact microglia distribution and function. We focused on the prevalent flame retardant mixture Firemaster 550 (FM550) which is used in foam-based furniture and infant products including strollers and nursing pillows. We hypothesized FM550 exposure would disrupt microglial density and reactivity in brain regions known to be highly sexually dimorphic or associated with social disorders in humans. We used prairie voles (*Microtus ochrogaster*) because they display spontaneous prosocial behaviors not seen in rats or mice, and thus are a useful model for studying chemical exposure-related impacts on social behavior and the underlying neurobiological systems. We have previously demonstrated that perinatal FM 550 exposure sex-specifically impacts socioemotional behaviors in prairie voles. Vole dams were exposed to FM550 (0, 500, 1000, 2000 µg/day) via subcutaneous injections through gestation, and pups were

directly exposed beginning the day after birth until postnatal day 21. Adult offspring's brains were assessed for ionized calcium-binding adapter molecule 1 (Iba-1)-positive microglia using unbiased stereology in the medial prefrontal cortex (mPFC) and the cerebellum (lobules VI-VII) and thresholding method in the amygdala. For stereology, microglia were classified based on reactivity (ramified, intermediate, ameboid). To further quantify the differences in microglia morphology after FM550 exposure, Sholl and skeleton analysis was carried out on individual microglia. Effects were sex- and dose-specific in the regions of interest. Our studies demonstrate the utility of the prairie vole for investigating the impact of chemical exposures on the developing brain, particularly regions essential for pro-social behavior.

Disclosures: W.P. Marinello: None. **S.A. Gillera:** None. **B.M. Horman:** None. **H.B. Patisaul:** None.

Poster

P299. Mechanisms of Neurotoxicity III

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Program #/Poster #: P299.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: VA Merit BX004632

Title: Correlations between neuronal damage and epileptic EEG discharges from diisopropylfluorophosphate in the rat

Authors: K.-C. HSIEH[1,2], K.-T. CHEW[1], S. RAI[1], S. KUMAR[1,4], *D. G. FUJIKAWA[1,3];
[1]VA Greater Los Angeles Healthcare Syst., North Hills, CA; [2]Med., [3]Neurol., UCLA, Los Angeles, CA; [4]California Hlth. Sci. Univ., Clovis, CA

Abstract: Introduction: Organophosphate nerve agents cause irreversible inhibition of acetylcholinesterase, which leads to prolonged seizures and neuronal damage. It is unclear if the damage resulted from seizures. In the current study, we analyzed the relationship between the severity of neuronal damage and the intensity/duration of EEG seizure discharges in the rat model of acute diisopropylfluorophosphate (DFP) exposure. Methods: Male Sprague-Dawley rats weighing 240-300g were used for experiments after being implanted with EEG electrodes on the skull and a telemetric temperature sensor intraperitoneally. The DFP was administered at 3-4 mg/kg s.c., 30 min after pyridostigmine and shortly after methylatropine and pralidoxime injections i.m., which were given to enhance the survival rate of the animals. Standard treatment for organophosphate poisoning in humans, or Chempack (the triple antidotes of diazepam, atropine sulfate, and pralidoxime), was administered 60 min after the onset of status epilepticus. The animals were monitored for 24 h and sacrificed for histological evaluation with hematoxylin and eosin (H&E) staining (n=12). The severity of brain damage was rated visually on a 7-point scale by the approximate percentage of damaged neurons in the total neuronal population in 23 brain regions. Seizure discharges were quantified by variables derived from spectral power analysis in the frequency band of 20-70Hz. Results: All animals exposed to the DFP displayed stereotypical epileptic behavioral signs and hours of continuous EEG spike discharges to varying degrees. The Chempack treatment tended to reduce the seizures temporarily but was ineffective in stopping them.

A wide range of neuronal damage was found with H&E histology, most consistently in the piriform cortex and entorhinal cortex. Correlations between the severity of neuronal damage and variables in EEG seizure discharges were found mainly in the ventral hippocampus, especially CA2 (24-h total discharge duration, $R=0.939$, $p<0.001$), and in the cerebral cortex (total spectral power of 20-70Hz in the first hour after DFP injection, $R=0.757$, $p<0.005$). Damage in other brain regions with more severe neuronal loss was not correlated with the intensity or duration of the seizure discharges. Conclusion: These results suggest that neuronal damage after DFP exposure may be induced by a more complex mechanism than excitotoxicity alone.

Disclosures: K. Hsieh: None. **K. Chew:** None. **S. Rai:** None. **S. Kumar:** None. **D.G. Fujikawa:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 2021M3H1A1048922
2021R1A2C2006110
2021M3E5D9021364
2019R1A5A2026045

Title: Phenotypic alteration of macrophages contributing to regeneration or degeneration in PNS and CNS

Authors: *Y. SEO[1], M. J. KWON[2], B. G. KIM[1,3];
[1]Neurosci. Grad. Program, Dept. of Biomed. Sci., Ajou Univ. Grad. Sch. of Med., Suwon-Si, Korea, Republic of; [2]Dept. of Brain Sci., Ajou Univ. Grad. Sch. of Med., Suwon, Korea, Republic of; [3]Dept. of Neurol., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: Macrophages dynamically change their molecular characteristics following injuries and their distinct phenotypes can have consequential effects on the outcome of neural injuries. Therefore, it would be important to understand the spectrum of phenotypic diversity of post-injury macrophages and how to regulate their phenotypes to drive regeneration while curbing secondary degeneration concurrently. The present study sought to replicate the phenotypic diversity in cultured macrophages and to examine functional influence of different macrophage phenotypes on regeneration or degeneration of PNS and CNS neurons. Cultured bone marrow-derived macrophages (BMDMs) were treated with factors that are known to induce regeneration or degeneration phenotype: lipopolysaccharide (LPS)/IFN-γ (M1), IL-4 (M2), zymosan, CCL2, and curdlan, a dectin-1 receptor agonist. Zymosan treatment induced both M1 and M2 genotypes, whereas CCL2 imparted strong and curdlan weak M2 genotype. When conditioned medium (CM) from the polarized BMDMs were treated to cultured dorsal root ganglion (DRG) neurons, M2 and CCL2-treated CMs increased DRG neurite outgrowth, and zymosan-treated CM exhibited the strongest neurite-outgrowth activity. CMs collected from all the conditions did not show evidence of toxicity to DRG neurons. When BMDM CMs were treated to cultured cortical neurons, CNS neurites

showed degeneration regardless of treatments, indicating macrophage-derived CM is inherently toxic to CNS neurons. We previously reported that neuron-macrophage interaction can drive pro-regenerative macrophage activation. When BMDMs were co-cultured with neurons and treated with cAMP, which mimics injury signals, collected CM exhibited robust neurite-outgrowth activity without any sign of toxicity for DRG neurons. Surprisingly, the CNS neurotoxicity by macrophage-derived CMs were sharply reduced by the CM from BMDM + neuron cocultures. Chemokine array revealed a significant decrease in CCL5 in the coculture CM and blocking CCL5 significantly reduced the toxicity of macrophage-derived CM for CNS neurites. Our study showed that diverse macrophage phenotypes can influence regeneration or degeneration in PNS and CNS. Blood-derived macrophages may be prone to cause degeneration for CNS neurons, and the interaction with neurons could reduce the toxicity via a CCL5-dependent mechanism.

Disclosures: Y. Seo: None. **M.J. Kwon:** None. **B.G. Kim:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FRC Grant 00125484211015121105000000000000000 5254

Title: Hippocampal neuroinflammatory and neurogenesis perturbations in diabetic male rats treated with combined antiretroviral therapy (cART)

Authors: *J. E. ASOUZU JOHNSON[1], R. NDOU[2], F. E. MBAJIORGU[1];
[1]Univ. of the Witwatersrand, johannesburg, South Africa; [2]Sefako Makgatho Hlth. Sci. Univ., Pretoria, South Africa

Abstract: Diabetes is associated with inducing hippocampal atrophy by disrupting hippocampal cytokines and neurogenesis. The diabetic condition is further burdened in Sub-Saharan Africa by the scourge of HIV and prevalent management with Combined antiretroviral therapy(cART). While cART is an efficient treatment, its potential to induce metabolic syndrome and type 2 diabetes may compound the neuropathological effects of diabetes. Therefore, this study aims to investigate the effects of cART within the type 2 diabetes model on body weight, pro-inflammatory cytokines, histomorphology, and neurogenesis in the hippocampus. MaleSprague Dawley rats were divided into 4 groups of six rats each including, NC (untreated group), AV (normal rats treated with cART composed of efavirenz, emtricitabine, and tenofovir disoproxil fumarate), DB (diabetic rats), and DAV (diabetic rats treated with cART). After ninety days of treatment, the rats were terminated, the brains were excised for immunoassay (IL-1α, IL-6, and TNFα), immunohistochemical (Ki67 and DCX), and Nissl stain histomorphology analysis in the brain homogenate and brain sections, respectively. All animal handling protocols were performed according to the standard protocol set forth by the University of the Witwatersrand Animal Research Ethics Committee approval number AREC 2018/011/58/C. Our results show that cART insignificantly increased body weight and cytokines but significantly reduced the number of neurons in

the dentate gyrus only (Bonferroni post hoc test $p = 0.001$). Diabetes significantly reduces body weight, pro-inflammatory cytokines, neuronal density (CA1 and dentate gyrus), expression of Ki67 and DCX, and significantly increased neuronal nuclei area (all hippocampal regions) at $p \leq 0.034$ Bonferroni post hoc test. However, the concurrent presence of cART in the diabetic condition significantly reduces body weight, IL-6, neuronal density (all hippocampal regions), Ki67, and DCXexpression in the hippocampus compared to the control only (Bonferroni post hoc test $p \leq 0.002$). These findings indicate that cART in diabetes can reduce neuronal density and neurogenesis in the hippocampus even in the absence of TNFα and IL-1α response.

Disclosures: J.E. Asouzu Johnson: None. **R. Ndou:** None. **F.E. Mbajiorgu:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Estradiol and 3βdiol protect cortical astrocytes from oxidative stress by regulating connexin 43-containing Gap Junctions

Authors: *S. KIM[1], N. K. KUBELKA[2], V. KRISHNAMOORTHY[1], H. LAPORTE[1], M. SINGH[1]; [1]Loyola Univ. Chicago Stritch Sch. of Medici, Maywood, IL; [2]Ctr. for Neurosci. Discovery, Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

Abstract: Cx43 is a transmembrane protein, expressed highly in astrocytes, that can comprise either hemichannels or gap junctions. Cx43 plays an important role in regulating inter-cellular communication influencing cell viability and has also been implicated in the regulation of oxidative load within a cell. Since gonadal androgens and estrogens are known to protect against oxidative stress, we wanted to determine if Cx43 expression and/or function (either as hemichannels or gap junctions) are a downstream target/mediator of the cytoprotective effects of either estrogens (estradiol, E2 and 3β-diol) or androgens (dihydrotestosterone, DHT). To validate this hypothesis, we assessed changes in Cx43 mRNA expression, Cx43 permeability in response to 100 nM E2, DHT, or the DHT metabolite, 5-α-androstane-3,17-β-diol (3βdiol), and correlated it with cell protection (against iodoacetic acid-induced metabolic/oxidative insult) afforded by these same hormones. We conducted these studies in cortical astrocytes derived from neonatal female C57/Bl6 mice. MTT viability assays were conducted to assess cell viability/health, and determining the contribution of Cx43 hemichannels versus gap junctions in hormone-induced protection against the oxidative stress was facilitated using the pharmacological agents, Gap19 (hemichannel blocker) and Gap26 (gap junction blocker). We also used 10Panx (Pannexin 1 blocker) to discern the possible involvement of the Pannexin 1 channel. Moreover, we complemented these studies with an analysis of Cx43 hemichannel and gap junction permeability, using ethidium bromide (EtBr) and lucifer yellow dye uptake assays, respectively. While all three steroids transiently increased astrocyte Gap26 mRNA expression, Cx43 mRNA expression was unaltered. Either opening or closing Cx43 hemichannels or Pannexin 1 channels exacerbated IAA induced cell death, an effect not prevented by any hormone, indicating altered Cx43 hemichannel and Pannexin 1 channel permeability may not play a significant role

in hormone protection against oxidative stress. However, E2 and 3βdiol-mediated inhibition of Cx43 gap junction permeability (as determined by dye uptake studies) were correlated with E2 and 3βdiol induced cytoprotection. Taken together, these data are the first to suggest Cx43-containing gap junctions as a mediator of E2 or 3βdiol induced protection of cortical astrocytes

Disclosures: S. Kim: None. **N.K. Kubelka:** None. **V. Krishnamoorthy:** None. **H. LaPorte:** None. **M. Singh:** None.

Poster

P299. Mechanisms of Neurotoxicity III

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P299.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Multiplexed structure-function assay for neurotoxicity and disease modeling

Authors: *D. MILLARD, D. SULLIVAN, H. HAYES;
Axion Biosystems, Atlanta, GA

Abstract: The flexibility and accessibility of induced pluripotent stem cell technology has allowed complex human biology to be reproduced in vitro at high throughput scales. Indeed, rapid advances in stem cell technology have led to widespread adoption for the development of in vitro models of neuron electrophysiology to be used in screening applications in drug discovery and safety. Furthermore, advanced cells preparations, such as spheroids or organoids, are under intense investigation with aims towards establishing mature human phenotypes in vitro. For the development and validation of in vitro neuronal models, it is critical to evaluate the structure and function of neurons, synapses, and networks. The objective of this work is to develop and validate a multiplexed structure-function assay as an efficient approach for evaluating neuronal models in vitro. A planar grid of microelectrodes embedded in the substrate of each well interfaces with cultured cellular networks to continuously monitor both the electrophysiological function and structural viability of cells. The electrodes detect the raw electrical activity from the cells to identify changes in function, while structural effects, such as morphological changes and cell viability, are detected as changes in impedance at the cell-electrode interface. Here, we characterized and validated this multiplexed assay using known control compounds that differentially affected the cell structure and function. All compounds tested (GABA, glutamate, tributyltin, and Triton X-100) altered functional spiking activity relative to a vehicle control (DMSO). Tributyltin, glutamate, and Triton X-100 also affected neuronal viability, as measured through the microelectrode-based impedance, with Triton X-100 serving as the positive control for complete loss of membrane integrity. These results support the continued development and use of human iPSC-derived neural assays on the Maestro Pro for high throughput drug discovery and safety assessment.

Disclosures: D. Millard: A. Employment/Salary (full or part-time):; Axion BioSystems, Inc. **D. Sullivan:** A. Employment/Salary (full or part-time):; Axion BioSystems, Inc. **H. Hayes:** A. Employment/Salary (full or part-time):; Axion BioSystems, Inc..

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Research Foundation Flanders: PhD fellowship 1S18618N

Title: Chronic chemogenetic stimulation of the superior colliculus as a neuroprotective strategy in glaucoma: comparative transcriptome analysis of isolated retinal ganglion cells and collicular lysates

Authors: M. CLAES, C. VAN DEN HAUTE, V. BAEKELANDT, L. H. ARCKENS, L. DE GROEF, *L. MOONS;
KU Leuven, Leuven, Belgium

Abstract: Abstract Glaucoma is a neurodegenerative eye disease characterized by a progressive loss of retinal ganglion cells (RGCs), whose axons shape the direct linkage between the retina and visual processing centers in the brain. RGCs might be prone to die due to a deficiency of target-derived neurotrophic factors after perturbed axonal transport, one of the major glaucoma hallmarks. Based on the established linkage between neuronal activation and the release of neurotropic factors, we hypothesize that chemogenetic stimulation of neurons in the superior colliculus might increase the production and secretion of target-derived neurotropic factors and, upon retrograde transport of those factors to the retina, might aid the RGCs in their struggle for survival in an experimental glaucoma model. To explore this hypothesis, a bulk RNA sequencing experiment was performed on FACS sorted RGCs and collicular lysates from mice subjected to sham, glaucoma, chemogenetic stimulation and glaucoma + chemogenetic stimulation. Chemogenetic activation of the neurons in the superior colliculus was achieved via injection of an adeno-associated viral vector (AAV2/7-CaMKIIα) coding for the hM3Dq receptor. Starting one day before glaucoma induction (the microbead occlusion model), mice received a systemic injection of 3 mg/kg body weight clozapine-N-oxide (CNO). During the following 5 weeks, mice received three CNO injections per week. We evaluated the differentially expressed genes in the RGCs of all aforementioned goups; and studied how these retinal transcriptomic changes related to the altered transcriptome in the superior colliculus. These results provided interesting insights on how retinal neurons rely on their target connections in the brain for vitality, together with novel cues to fuel future treatment routes in glaucoma and other optic neuropathies.

Disclosures: M. Claes: None. **C. Van den Haute:** None. **V. Baekelandt:** None. **L.H. Arckens:** None. **L. De Groef:** None. **L. Moons:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR Grant MOP-130282

Title: TRPM3 agonists activate AMPK and enhance mitochondrial function to augment neurite outgrowth in adult sensory neurons

Authors: *S. CHAUHAN, P. FERNYHOUGH;
Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Peripheral neuropathy affects approximately 50% of the population with diabetes mellitus depending on age and disease severity. It is associated with substantial morbidity and is characterized by induction of pain and loss of sensory function beginning distally in the lower extremities. Recent studies suggest that molecular cascades maintaining mitochondrial function and calcium homeostasis are effective therapeutic targets for diabetic peripheral neuropathy. Interestingly, our lab has recently reported that muscarinic acetylcholine type 1 receptor (M1R) antagonists stimulated neurite outgrowth, in part, by activating Ca^{2+}/calmodulin-dependent protein kinase kinase II (CaMKKII) and mobilization of AMP-activated protein kinase (AMPK). This further augmented mitochondrial function in sensory neurons imparting protection against small and large fiber neuropathy in various rodent models of peripheral neuropathy (including diabetes). Transient receptor potential melastatin receptor 3 (TRPM3) is a TRP type cation channel that triggers Ca^{2+} influx. TRPM3 is quite unique in that it binds calmodulin and is open under high phosphoinositide levels (the latter would be predicted during blockade of the M1R). We hypothesized that opening of TRPM3 could activate CaMKKII and induce neurite outgrowth and may mimic antimuscarinic drug effects. Dorsal root ganglion (DRG) neurons were isolated from adult control and streptozotocin-induced type 1 diabetic male Sprague–Dawley rats. Assessment of neurite outgrowth was performed in response to pregnenolone sulphate (PS) or CIM0216 (selective and specific TRPM3 agonists, respectively). A significant dose-dependent elevation of neurite outgrowth was observed. These TRPM3 agonists also increased AMPK activation and extracellular signal-regulated kinases (ERK) signaling in control and diabetic DRG neuron cultures. There was also a significant augmentation of mitochondrial activity. Specifically, TRPM3 agonists elevated maximal respiration in diabetic DRG neuronal cultures. Our investigations towards understanding of TRPM3 activation and its downstream molecular cascade will hopefully lead to potential therapeutic targets for impeding detrimental effects of peripheral neuropathy.

Disclosures: S. Chauhan: None. **P. Fernyhough:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

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The Robert A. Welch Foundation (F-0652)
The Dell Medical School’s Texas Health Catalyst program

Title: Neuroprotective Effects of σ2R/TMEM97 Modulators in Neuronal Model of Huntington's Disease

Authors: *J. JIN[1], N. ARBEZ[1,3], J. J. SAHN[4], Y. LU[4], K. T. LINKENS[4], T. R. HODGES[4], A. TANG[1], R. WISEMAN[1], S. F. MARTIN[4], C. A. ROSS[1,2];
[1]Div. of Neurobiology, Dept. of Psychiatry, [2]Departments of Neurology, Neurosci. and Pharmacol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Cell. Sci. Dept., IdRS, Croissy-sur-Seine, France; [4]Dept. of Chem., The Univ. of Texas at Austin, Austin, TX

Abstract: Huntington's disease (HD) is a genetic neurodegenerative disease caused by an expanded CAG repeat in the human Huntingtin gene (*HTT*), yielding and expanded polyglutamine (polyQ) repeat in the exon-1 of the human mutant huntingtin (mHTT) protein, which results in neuronal degeneration with no cure nor treatment that modifies disease progression. Small molecules that bind selectively to the recently-cloned sigma 2 receptor (σ_2R), which is identical to TMEM97, have been shown to have neuroprotective effects in Alzheimer's disease, traumatic brain injury and other neurological disorders. To assess whether modulating pathways involving σ_2R/TMEM97 can provide protection in HD, we used an HD cell model to evaluate the effects of σ_2R/TMEM97 ligands on mHTT induced neuronal toxicity. We first synthesized a set of compounds designed to bind to σ_2R/TMEM97, and binding profiles (K_i) of these ligands were determined. Modulators with high selectivity for σ_2R/TMEM97 relative to σ_1R were then tested in our HD cell models. Primary cortical neurons were cultured in vitro for 7 days and then co-transfected with either normal HTT construct (Htt N-586-22Q/GFP) or mHTT construct (Htt-N586-82Q/GFP). Transfected neurons were treated with σ_2R/TMEM97 or σ_1R modulators for 48 hours. After treatment, neurons were fixed and stained with Hoechst. Condensed nuclei were quantified to assess cell death in transfected neurons. Significantly, σ_2R/TMEM97 modulators reduced the neuronal toxicity induced by mHTT, and their neuroprotective effects were not blocked by NE-100, a selective σ_1R antagonist. These results indicate for the first time that σ_2R/TMEM97 modulators can protect neurons from mHTT induced neuronal toxicity, suggesting that targeting σ_2R/TMEM97 may provide a novel therapeutic approach to treat HD patients.

Disclosures: J. Jin: None. **N. Arbez:** None. **J.J. Sahn:** Other; NuvoNuro, Inc. **Y. Lu:** None. **K.T. Linkens:** None. **T.R. Hodges:** None. **A. Tang:** None. **R. Wiseman:** None. **S.F. Martin:** Other; NuvoNuro, Inc. **C.A. Ross:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

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Program #/Poster #: P316.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

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Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Medical Research Program under Award No. W81XWH2010199

NIH grant UL1TR001876
NIH grant KL2TR001877

Title: Mesenchymal Stromal Cells Delivered through Cardiopulmonary Bypass Improve Reperfusion/Reoxygenation Injury in Neonatal Brain by Reducing Microglial Activation-Mediated Neurotoxicity

Authors: *K. KOBAYASHI[1,2,3], K. SARKISLALI[1,2], T. MAEDA[1,2,3], N. SARIC[1,2,3], F. A. SOMAA[1,2], C.-H. HSU[6], J. LI[1,2,3], S. TU[1,2,3], M. A. AYODEJI[1,2,3], C. LEONETTI[1,2,3], P. VYAS[4], Y. IMAMURA KAWAHARA[7], K. HASHIMOTO-TORII[1,8,9], T.-W. TU[6], P. C. WANG[6,10], P. J. HANLEY[5,8], J. A. FRANK[11,12], R. A. JONAS[1,2,3,8], N. ISHIBASHI[1,2,3,8,9];
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Abstract: Background: Neurodevelopmental impairment is one the most important current challenges for survivors after neonatal cardiac surgery. Cardiopulmonary bypass (CPB) can cause substantial oxidative/inflammatory stress and microglial activation. Bone marrow-derived mesenchymal stromal cells (BM-MSCs) have significant immunomodulatory properties and regulate microglial activation. We hypothesize that BM-MSC delivery to the neonatal brain at the time of cardiac surgery limits inflammation and microglial activation caused by CPB.**Methods:** Two-week old piglets were randomly assigned to one of three groups: (1) Control, (2) CPB, (3) CPB followed by BM-MSC administration. BM-MSCs ($10x10^6$/kg) were delivered through CPB during the rewarming period.**Results:** In the developing cortex, caspase-3 was activated at 3hrs post CPB-induced insult and normalized by postoperative day 1. During this time window, we identified a significant link between oxidative/inflammatory stress and the activation of JAK-STAT3 pathway, suggesting JAK-STAT3 signaling as a potential therapeutic target. Positron emission tomography indicated that intra-arterial BM-MSC delivery through CPB uniformly distributed the cells to most of the organs analyzed. *T2**-weighted brain imaging and immunohistochemistry showed an even distribution of BM-MSCs between right and left hemispheres and within the cortex and white matter. At 3hrs post surgery, 46 and 44% of BM-MSCs were localized to the cortical and white matter parenchyma, respectively. No evidence of micro-embolic events or detrimental effects was observed. CPB caused acute microglial expansion and activation. BM-MSC treatment suppressed CPB-induced STAT3 activation and inhibited microglial STAT3-phosphorylation, thereby switching the microglial phenotype to a less pro-inflammatory state. In addition to an increase in circulating anti-inflammatory cytokines, genome-wide RNA profiling identified inhibition of pro-apoptotic transcriptional signatures, likely resulting due to the reduction of reactive-oxygen species following BM-MSC treatment. BM-MSC delivery through CPB inhibited acute caspase-3 activation in cortical neurons and limited the induction of apoptotic signals caused by cardiac surgery. Neuronal capase-3 activation was correlated with microglia activation, indicating BM-MSC-involvement in suppression of microglia-mediated neurotoxicity.**Conclusions:** BM-MSC delivery through CPB has a significant translational potential for minimizing oxidative/inflammation stress during CPB and subsequent inhibition of microglia-mediated neurotoxicity in children undergoing cardiac surgery.

Disclosures: K. Kobayashi: None. **K. Sarkislali:** None. **T. Maeda:** None. **N. Saric:** None. **F.A. Somaa:** None. **C. Hsu:** None. **J. Li:** None. **S. Tu:** None. **M.A. Ayodeji:** None. **C. Leonetti:** None. **P. Vyas:** None. **Y. Imamura Kawahara:** None. **K. Hashimoto-Torii:** None. **T. Tu:** None. **P.C. Wang:** None. **P.J. Hanley:** None. **J.A. Frank:** None. **R.A. Jonas:** None. **N. Ishibashi:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIBIB R01EB016629-01
ANR-17-CE14-0005

Title: Vegf-c confers neuroprotection and ameliorates ischemic stroke outcomes

Authors: L. S. BRAGA BOISSERAND[1], J. BOUCHART[3], H. BENVENISTE[2], F. HYDER[4], L. H. SANSING[1], A. C. EICHMANN[5], J. L. THOMAS[6];
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Abstract: Meningeal lymphatic vessels promote tissue clearance and immune surveillance in the central nervous system (CNS). Vascular Endothelium Growth Factor-C (VEGF-C) regulates meningeal lymphatic growth and has therapeutic potential for neurological disorders such as cognitive aging and brain tumors, and might be beneficial in stroke injury repair. Here, we investigated effects of VEGF-C overexpression on brain fluid drainage, gene expression and stroke outcome. Intra-cerebrospinal administration of an adeno-associated virus expressing VEGF-C (AAV-VEGF-C) and post-contrast T1 mapping of the head and neck showed that VEGF-C increased the size of collecting lymph nodes and their drainage by CNS-derived fluids. Single nuclei RNA sequencing of forebrain cells isolated from VEGF-C pretreated and control mice revealed that VEGF-C inhibited microglia proliferation and increased the DNA damage response in subsets of neural cells. Using a mouse model of ischemic stroke induced by transient middle cerebral artery occlusion, we found that AAV-VEGF-C pretreatment, but not post-injury treatment with recombinant VEGF-C, reduced ischemic stroke injury, ameliorated motor performances in the subacute stage and increased expression of BDNF and NGF in the forebrain. VEGF-C pretreatment thus promotes CNS-derived fluid and solute drainage, confers neuroprotection to brain tissues and protects against ischemic stroke damages.

Disclosures: L.S. Braga Boisserand: None. **J. Bouchart:** None. **H. Benveniste:** None. **F. Hyder:** None. **L.H. Sansing:** None. **A.C. Eichmann:** None. **J.L. Thomas:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

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Program #/Poster #: P316.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: European Union (transMed, MSCA-ITN-2017-765441)
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Stiftelsen för Synskadade i f.d. Malmöhus län

Title: The rap guanine exchange factor 4, EPAC2, may have a neuroprotective effect on degenerating photoreceptors

Authors: M. RASMUSSEN[1], J. ZHOU[1], F. SCHWEDE[2], *P. EKSTRÖM[1];
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Abstract: The eye disease Retinitis Pigmentosa (RP) leads to severe vision loss due to neuroretinal degeneration with photoreceptor death, but the mechanisms are still unknown. Therefore, to develop therapies to prevent disease progression in RP, there is a dire need to reveal the underlying pathology. During RP in mice (i.e., *rd* models) detrimental high cyclic GMP (cGMP) levels are observed in photoreceptors. cGMP is a common second messenger, which interacts with various proteins and a recent study showed that the protein rap guanine exchange factor 4 (EPAC2) is a cGMP interactor in the neuroretina. EPAC2 is activated by cAMP and is an accepted cGMP-interacting protein, albeit cGMP has almost no activatory effect *in vitro*. However, whether EPAC2 may be affected by cGMP and thus play a role in RP remains unclear.
To decipher this, we collected retinas from RP mouse models at different ages (postnatal day = PN); *rd1* (PN11-19), *rd10* (PN17-22), *rd2* (PN19-22), and corresponding wild-type (wt, controls) and quantified the EPAC2 expression using immunofluorescence. Proximity Ligation Assay (PLA) was applied to verify if cGMP or cAMP and EPAC2 were in proximity in the photoreceptor layer (outer nuclear layer = ONL). Lastly, *rd10* and wt (PN12-PN24) retinal explant cultures were used to pharmacologically manipulate retinal EPAC2 activity. The results were analyzed using 2-way ANOVA.
Our results show significantly increased EPAC2 expression in the ONL during degeneration in *rd1* and *rd10* retinas, but not in the *rd2* model, as compared to wt. Moreover, the PLA indicated that the number of cGMP:EPAC2 interactions increased significantly over time in *rd1* and to some extent in *rd10*, but not in the *rd2* model. In comparison to cGMP:EPAC2, the cAMP:EPAC2 interactions were fewer in *rd10* and *rd2* and again increasing over time in *rd1*. Manipulation of EPAC2 activity in the *rd10* retina revealed that EPAC2 inhibition reduced ONL thickness and significantly elevated EPAC2 expression compared to *rd10* retinas treated with an EPAC2 activator. The decreasing ONL did not correspond with an increased number of TUNEL positive cells, probably because the *rd10* photoreceptor death peaked before PN24.
In summary, we showed that EPAC2 expression and the number of cGMP:EPAC2 interactions in the ONL increased during retinal degeneration in the *rd1* and *rd10* models, although not in *rd2*. This is compatible with that high cGMP levels may negatively affect EPAC2's yet undefined, but perhaps neuroprotective, role in the RP photoreceptors, and that the retina tries to compensate for this by increasing the EPAC2 expression. This is as such supported by that EPAC2 inhibition decreased the ONL thickness and increased the EPAC2 level.

Disclosures: M. Rasmussen: None. **J. Zhou:** None. **F. Schwede:** A. Employment/Salary (full or part-time):; BIOLOG Life Science Institute GmbH & Co. KG, Bremen, Germany. **P. Ekström:** None.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Beneficial effects of a plasma fraction on processes induced in a mouse model of inflammaging

Authors: *C. THADANI, J. TORRES, R. ALCANTARA-LEE, E. CZIRR, I. GALLAGER; Alkahest, Inc., a subsidiary of Grifols, San Carlos, CA

Abstract: We previously identified that a plasma fraction (PF), derived from human plasma donations (average age 32-years-old), contains beneficial factors which have been shown to ameliorate multiple age-related deficits across varied organ systems, including the brain, in aged mice. We are now characterizing high-fat diet (HFD) fed mice as a model of inflammaging in younger mice to test the effects of PF. Providing HFD chow in mice from 6 weeks of age until the time of tissue collection at 7.5 or 13.5 months results in CNS changes including decreased cell proliferation and neurogenesis, increased inflammation, increased anxiety and depressive phenotypes, and decreased synaptic connectivity within the hippocampal region in the CNS when compared to normal diet (NC) controls. Importantly, all these are characteristics observed to be exacerbated in aged brains. We evaluated intravenous administration of PF daily for 7 days for alleviation of neurological and histopathological phenotypes observed in 7.5-month-old and 13.5-month-old male C57/Bl6 mice on HFD. Through these studies, we confirmed that PF ameliorated HFD-induced anxiety and depression and improved neural progenitor cell survival. In addition, we observed a decrease in circulating inflammatory plasma cytokines and an increase in anti-inflammatory plasma cytokines without impacting the underlying metabolic changes induced by HFD. In summary, we demonstrate that PF is a multifactorial and multimodal intervention for changes induced through inflammaging.

Disclosures: C. Thadani: A. Employment/Salary (full or part-time):; Alkahest, Inc., a subsidiary of Grifols. **J. Torres:** A. Employment/Salary (full or part-time):; Alkahest, Inc., a subsidiary of Grifols. **R. Alcantara-Lee:** A. Employment/Salary (full or part-time):; Alkahest, Inc., a subsidiary of Grifols. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest, Inc., a subsidiary of Grifols. **I. Gallager:** A. Employment/Salary (full or part-time):; Alkahest, Inc., a subsidiary of Grifols.

Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P316.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Nano PSO administration attenuates cognitive and neuronal deficits before and after a traumatic brain injury

Authors: *D. QUBTY[1], K. FRID[2,3], V. RUBOVITCH[1], M. HAR-EVEN[1], R. GABIZON[2], C. G. PICK[1]; [1]Dept. of Anat. and Anthropology, Sackler school of medicine, Tel Aviv Univ., Tel aviv, Israel; [2]Dept. of Neurology, The Agnes Ginges center for Human Neurogenetics, [3]Med. school, The Hebrew university, Jeruslalem, Israel

Abstract: Traumatic Brain Injury (TBI), one of the most common causes of neurological damage in young populations, is widely considered as a risk factor for neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's (PD) disease. These diseases are characterized in part by the accumulation of disease-specific misfolded proteins, and share common pathological features, such as neuronal death, as well as inflammatory and oxidative damage. We have recently shown that a novel Nano formulation of Pomegranate seed oil (Nano-PSO) can target its active ingredient to the brain and thereafter inhibit memory decline and neuronal death in mice models of AD and genetic Creutzfeldt Jacob disease (gCJD).PSO is comprised of large levels of Punicic Acid (Omega 5), one of the strongest natural lipid antioxidants, which is metabolized *in-vivo* into CLA (conjugated linoleic acid), both an antioxidant and a calpain inhibitor. In this study, we show that administration of Nano-PSO to normal mice whether before or post TBI application prevents cognitive and behavioral decline, as measured by behavioral tests, such as novel object recognition, Y maze, elevated plus maze, open field, and staircase. In addition, immuno-histochemical staining of brain slices at the end of the experiments indicate that the preventive Nano-PSO treatment significantly decreased neuronal death and reduced gliosis. As shown for other models of neurological disease, Nano-PSO administration prevented mitochondrial damage in the affected cells, demonstrated by COXIV1 immunostaining in the brains. Finally, to clarify the effect of our TBI model and different treatment approaches of Nano-PSO on the expression of neuroprotective proteins. We examined levels of Sirtuin1 (SIRT1) and Synaptophysin (SYP) in the cortex using western blotting. SYP, a major integral transmembrane protein of synaptic vesicles, provides a molecular marker for the synapse and serves as a functional marker of the brain. Nano-PSO consumption showed a higher level of SYP protein post-injury. Several studies have shown that SIRT1 plays a significant role in inducing neuroprotection following dietary restriction. We found a significant reduction of SIRT1 levels in the cortex, using a mouse model of TBI. This reduction was prevented in mice that consumed Nano PSO after TBI. Taken together, our results indicate that Nano PSO, as a natural brain targeted antioxidant, can prevent at least part of TBI-induced damage.

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Poster

P316. Neuroprotective Mechanisms: Preclinical: Other Therapeutics I

Location: Virtual Only

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Program #/Poster #: P316.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Saint Louis University start-up fund

Title: Progranulin preserves autophagy function in neurons under high-glucose stress through modulation of glia

Authors: *C. DEDERT, F. XU, V. MISHRA;
Dept. of Biol., St. Louis Univ. Dept. of Biol., Saint Louis, MO

Abstract: Hyperglycemia, or elevated blood glucose, is prevalent in type II diabetes and causes neural pathology through impaired autophagy and accumulation of protein aggregates in brain tissue. Progranulin is an endogenous neurotrophic factor whose mutation is implicated in the neurodegenerative disease frontotemporal dementia (FTLD), characterized by aggregation of the protein TAR DNA-binding protein 43 (TDP43). However, while progranulin is known to function in the lysosome, its mechanism of neuroprotection is not known. In this study, we investigated whether progranulin restores autophagic function in neurons under hyperglycemic stress. Primary cell cultures from E18 rat cortex were incubated in high glucose medium and treated with recombinant progranulin for 72 hours, and cellular health and function were assessed. We found that while high glucose treatment decreased macroautophagy and chaperone-mediated autophagy (CMA) activity, pre-treatment with progranulin significantly attenuated downregulation. Specifically, we assessed autophagy flux as an increase in LC3B lipidation in western blot and puncta formation in immunofluorescent imaging; we found that autophagy flux was significantly decreased in high glucose conditions and progranulin pre-treatment prevented this decrease. To assess the CMA function, we measured LAMP2A expression and perinuclear puncta formation in immunocytochemistry imaging. Our results showed that although total LAMP2A levels were unaffected, localization to the perinuclear region was decreased in high glucose-treated cells, but preserved with progranulin treatment. Intriguingly, immunofluorescence images indicated that modulation of autophagy occurred largely in the glia as opposed to neurons, indicating a role of this cell type in regulating neuronal well-being through autophagy. These novel findings implicate glial involvement both in the neuronal autophagy process and in progranulin's mechanism of effect. Our findings showcase a potential for progranulin as a promoter of autophagy under harmful stress conditions through glial activation.

Disclosures: C. Dedert: None. **F. Xu:** None. **V. Mishra:** None.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P326.01

Topic: C.08. Ischemia

Support: ISSSTE supported this work under Grant E015-233.2017.

Title: Effect of Cerebrolysin treatment on HDAC gene family expression in a rat model of neonatal hypoxic-ischemic encephalopathy

Authors: *E. BARRIENTOS ZAVALZA[1], C. PIÑA-LEYVA[2], M. LARA-LOZANO[3], G. FLORES[4], D. MARTINEZ-FONG[5], B. LEON CHAVEZ[6], A. JIMENEZ-ANGUIANO[7], J. A. GONZALEZ-BARRIOS[8];
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Abstract: Hypoxic-ischemic encephalopathy (HIE) is one of the main causes of neonatal death, and in survivors it generates long-term neurological sequelae that include learning and memory deficits, motor damage and cerebral palsy. Among the mechanisms that contribute to neurological dysfunction are excitotoxicity, apoptosis, necrosis and inflammatory process; all associated with epigenetic modifications that maintain control of gene expression during HIE. Histone deacetylases (HDAC) are enzymes that catalyze the deacetylation of histone lysine residues and their activity is related to gene repression. Furthermore, changes in HDAC gene expression have been described after hypoxia-ischemia injury. Previous studies in our laboratory have shown that Cerebrolysin administration in rats with HIE improves motor skills, learning and memory. This study aimed to evaluate the effect of Cerebrolysin administration on the HDAC gene family expression in neonatal rat model of HIE. We analyzed cerebral cortex and hippocampal samples obtained from HIE rats, 24 hours and 21 days after cerebral injury. Total RNA extraction and reverse transcription were performed; subsequently, the expression of the HDAC family genes were evaluated by q-PCR. The expression of HDAC genes family after 24 hours of hypoxia-ischemia injury, did not show statistical differences between experimental groups. Whereas, at 21 days after the brain injury, we found an increase in expression of HDAC2 and HDAC3 genes in the cortex compared to HIE (0.75±0.05 and 0.79±0.03 fold change, respectively; $p < 0.01$); and increase in expression of HDAC2, HDAC3 and HDAC7 genes in the ipsilateral hippocampus of HIE animals treated with Cerebrolysin compared to HIE (1.6±0.14, 2.37±0.21 and 5.35±0.13 fold change, respectively; $p < 0.01$). Gene expression of HDAC4, HDAC5, HDAC6, HDAC8, HDAC10 and HDAC11 were not modified. Our findings demonstrate that Cerebrolysin administration in neonatal rats with HIE exerts its epigenetic effect on learning, memory and motor system by up-regulation of HDAC2, HDAC3 and HDAC7 genes.

Disclosures: E. Barrientos Zavalza: None. **C. Piña-Leyva:** None. **M. Lara-Lozano:** None. **G. Flores:** None. **D. Martinez-Fong:** None. **B. Leon Chavez:** None. **A. Jimenez-Anguiano:** None. **J.A. Gonzalez-Barrios:** None.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P326.02

Topic: C.08. Ischemia

Support: NIH Grant R21NS109838

Title: Effect of intestinal microbiota composition on neuroinflammatory response after neonatal hypoxia-ischemia

Authors: *A. DROBYSHEVSKY, I. GOUSSAKOV, S. SYNOWIEC;
NorthShore Univ. HealthSystem, Evanston, IL

Abstract: Premature infants are often lacking normal microbial community in their intestines that naturally should have come from mothers. Premature infants are also often at risk of perinatal hypoxic-ischemic (HI) brain injury, considered as one of the major factors leading to motor, sensory and cognitive deficits. We hypothesize that neonatal gut microbiota composition can modulate immune reaction of the neonatal brain to hypoxic brain injury. C57BL/6 mouse pups were exposed to HI protocol at P10 (Vanucci model) consisting of permanent left carotid artery ligation and 8% oxygen exposure for 60 min at 37C. Microbial manipulation groups consisted of 1) naïve pups, 2) triple-antibiotic treated from E18 (maternal) to P5, 3) antibiotic treatment E18-P5 + *E.coli* gavage, 4) antibiotic treatment E18-P5 + *B. infantis* gavage. Extent of initial injury (edema) and recovery was measured on T2 weighted MRI at 24 and 72 hours after HI. Brain and gut tissue was collected for cytokine expression RT-PCR measurements. Mean extent of initial (24h) and delayed (72h) edematous HI injury was not different between microbiota groups. Injury volume decreased by 72h, with the smallest decrease in antibiotic+E.coli group. Proportion of pups with no decrease or increase of injury at 72h was largest in naïve + HI group. Significantly elevated expression of pro- (IL1b, IL6, IL2, TNF-a) and anti-inflammatory cytokines (TGF-b, IL10) was found on HI group relative to naïve and sham controls. This increase was less pronounced in HI + antibiotic group and H-I + gavage groups. Pro-inflammatory cytokines expression increased with the extent of HI injury but the slopes were not different between microbiota groups. We conclude that neuroinflammatory response after neonatal hypoxia-ischemia is affected by intestinal microbial composition, providing opportunities for therapeutic intervention through targeted nutritional supplementation.

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Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

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Program #/Poster #: P326.03

Topic: C.08. Ischemia

Support: NIH Grant R01NS111021
K08 Grant NS088563
Department of Pediatrics R and D Grant
NIH Grant U54 HD090256

Title: Role of estrogen receptor alpha in mediating normal fear response following perinatal hypoxic ischemic encephalopathy

Authors: M. HACKETT[1], B. OZAYDIN[1], N. AYCAN[1], S. YAPICI[1], N. KARAHAN KELES[2], E. BICKI[1], O. TAPARLI[1], K. CORCORAN[1], C. LAGOA-MIGUEL[1], T. Z. SHEIKH[1], P. FERRAZZANO[1],

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Abstract: Background: Perinatal hypoxic ischemic (HI) encephalopathy is one of the major causes of learning disabilities and memory deficits in children. The learning disabilities and memory deficits might be related to the increased fear or hyperactivity behavior following perinatal HI. We have previously showed that estrogen receptor (ER) alpha is upregulated in the female neonatal mice hippocampi following HI, leading to tyrosine kinase B (TrkB) mediated neuroprotection. To test the role of ER alpha on fear response and anxiety behavior in neonatal mice following HI, we performed elevated plus maze (EPM) and MRI 3 months post HI with and without TrkB agonist (7,8-dihydroxyflavone) in ER alpha wild type (WT) and complete knock-out (ERKO) mice.**Methods:** HI was induced in postnatal (P) day 9 C57BL/6J mice by using Vannucci's HI model in WT and ERKO mice. Mice were treated with 7,8 DHF (5mg/kg, i.p.) or vehicle control starting at 10 min post-HI for 7 days. At P 90+, mice underwent elevated plus maze (EPM) testing for 15 minutes. Video recordings of the EPM were analyzed using AnyMaze software. Percent (%) time spent in open arm is reported in mean ± SEM. ANOVA was used to analyze the EPM data. MRI was performed under anesthesia following EPM testing using 4.7-tesla small animal MRI. Masks of ipsilateral and contralateral hemispheres were created using ImageJ. Hemispheric areas were calculated from 8-11 slices/brain and averaged. The data is presented as the difference in CL area versus IL area for each brain as (CL−IL)/CL×100 and reported as IL hemispheric area loss. Percent time in open arm (EPM) and IL hemispheric area loss is fitted with linear regression. **Results:** Significant differences in % time spent in open arm of the EPM test indicated differing fear response between treatment groups (p= 0.013). HI mice exhibited abnormal fear response and TrkB agonist treatment rescued abnormal fear response only in female mice (%19±1) versus the male mice (%25±3) (p=0.034) in an ER alpha dependent manner. Hemispheric area loss positively correlated with % time spent in open arm (p=0.002). % open arm time for sham ER alpha KO mice was 50% less than sham WT mice. **Conclusion:** HI mice preferred the open arms of the testing apparatus indicating an abnormal fear response compared to sham mice. 7,8-DHF recovered the fear response in female mice to the sham levels but not in male mice 90 days post-HI in an ER alpha dependent way. This data suggests that TrkB agonist therapy restores the normal fear response and decreases hyperactivity in female mice in an ER alpha dependent way. Lack of ER alpha predisposes both male and female mice to have exaggerated fear response with possibly through different mechanisms.

Disclosures: M. Hackett: A. Employment/Salary (full or part-time):; university of Wisconsin-Madison. **B. Ozaydin:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **N. Aycan:** None. **S. Yapici:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **N. Karahan Keles:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **E. Bicki:** None. **O. Taparli:** None. **K. Corcoran:** None. **C. Lagoa-Miguel:** None. **T.Z. Sheikh:** None. **P. Ferrazzano:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **J.E. Levine:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **P. Cengiz:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

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Program #/Poster #: P326.04

Topic: C.08. Ischemia

Support: NIH 1K08N5121599-01

Title: Chronic real-time calcium imaging of seizures and neuronal death tracking after perinatal oxygen-glucose deprivation

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Abstract: Rationale: Neonatal seizures after hypoxia-ischemia (HI) are common in newborns and associated with significant mortality and chronic morbidity. However, definitive data indicating whether they are independently harmful or not after HI is a critical gap in the field. Our central hypothesis is that neonatal seizures independently worsen brain injury after HI. To address this question, we developed a system to track neuronal survival and seizures after oxygen-glucose deprivation (OGD). We used sustained emission of transgenically-expressed fluorescent proteins as a robust biomarker of neuronal viability (Arrasate *et al.* Nature 2004) and genetically encoded calcium indicators to follow seizure activity for 2 weeks post-OGD. **Methods:** Organotypic hippocampal slices prepared from neonatal mice expressing a neuronal red fluorescent protein and green calcium indicator (GCaMP6s) underwent 20 min of OGD. Chronic high resolution two-photon imaging of the pyramidal cell layer was performed. Neuronal death was quantified using the fluorophore quenching assay (Balena *et al. in prep*). To assess for caspase activation, slices were incubated with Biotracker NucView 405 Blue Caspase-3 Dye (Sigma-Aldrich). All analyses were performed in ImageJ. **Results**: 1) After OGD, calcium imaging demonstrated recurrent seizures (duration 23±1 sec (mean±SE)). 2) OGD induced an excess of acute (<24 hours) and chronic (1-14 days) neuronal death compared to controls (n=5 slices per group). 3) Neurons that died after OGD participated in seizure activity, did not activate caspase acutely post-injury, and exhibited robust fluorescence emission up to the time of death. 4) Neurons that died after OGD had lower ictal calcium burdens immediately post-OGD compared to neurons that survived. 1-3 days post-OGD, the ictal calcium activity was indistinguishable between groups. 5) No differences in interictal calcium activity were seen between neurons that died early or late versus those that survived. **Conclusions:** This is the first study to longitudinally measure neuronal death and seizures in real-time after perinatal acute injury. We found that neurons died with time courses consistent with both early necrotic and later apoptotic deaths. Neurons that eventually underwent apoptosis participated in seizure activity after OGD, albeit to a lesser degree than neurons that survived. This demonstrates, for the first time, a calcium activity signature immediately post-OGD that predicts which neurons will die and which neurons will survive. Critically, these data also support the hypothesis that acute post-injury seizures are a potentially treatable cause of late neuronal death after OGD.

Disclosures: M.A. McNally: None. **K.P. Lillis:** None. **T. Balena:** None. **L.A. Lau:** None. **V.I. Dzhala:** None. **K.J. Staley:** None.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P326.05

Topic: C.09.Stroke

Support: Maryland Stem Cell Research Fund

Title: Tunable biomaterial guided stroke repairs by endogenous & exogenous stem cells

Authors: *X. RONG[1,2], J. ZHU[1,2], J. XU[1,2], X. YIN[1,2], W. ZHOU[6], S. ANDRABI[1,2], R. CHEN[1,2,2], L. CHEN[1,2], I. GUAN[1,3], H. JI[6], X. LIU[7], T. DAWSON[1,2,3,4], V. DAWSON[1,2,3,5];
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Abstract: Abstract Chronic stroke is a disease of immense public health importance with serious economic andsocial consequences. By integrating multidisciplinary expertise unique to the researchenvironment at Johns Hopkins Medicine, we are focusing on chronic ischemic stroke becausethere is no treatment for the large and growing stroke survivors living with the long-termconsequences of stroke.We propose combinational reparative approaches to promote neural repair following chronicstroke: using the biodegradable hydrogel guided and supported (1) endogenous stem cellstimulation and (2) exogenous stem cell transplantation to promote the functional integrationand recovery of chronic stroke. We specifically proposed these streams together because thedevastation of stroke is phenomenal and previous clinical trials have demonstrated that thereis no silver bullet: multiple parallel strategies are required for success.First, to take advantage of our resident stem cells to restore function, we will implore abioengineering-driven idea to develop tissue-like viscoelastic biomaterials to activate theseendogenous stem cells to promote repair. We have now developed neural tissue-likebiomaterial with brain tissue compatible properties. We will use these materials to boost theendogenous stem cell repairing.Second, with this neural tissue-like biomaterial, we will achieve safe delivery of authentichuman brain cells to the stroke-injured area in a minimally-invasive way. Using human ES/iPS,we have developed a high-efficiency rosette-type neural stem cell-derived aggregates(RONA)-method for generating authentic human cortical neural cells that containrepresentative excitatory and inhibitory precursors as well as oligodendrocytes. We are able totransplant every CNS cell type thought important for recovery post-stroke. Using this strategy,we will employ dynamic observation of survival, proliferation, migration, differentiation, andfunctional integration of grafted cells to optimize cell delivery interventions to providebehaviorally measurable recovery after stroke. The long-term goal is to responsibly translatecell-based therapies into novel therapies for stroke.Building on the combined expertise in neural stem cell biology and regenerative medicine,bioengineering, and neurosurgery and stroke, we will create and test a novel combinatorialstem cell strategy for chronic stroke treatment that will pave the way for clinical trials andstrengthen our position as an international leader in the stem cell field.

Disclosures: X. Rong: None.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P326.06

Topic: C.09.Stroke

Support: NIGMS 1P20GM13497
NIEHS R21 ES031211-01A1

Title: Human Placenta Stem Cells Derived Cerebral Organoids as a Disease-Modifying Therapy for Neuropsychiatric Disorders

Authors: *C. HAACKER, X. TIAN, K. KEYS, H. LI, J. ALEXANDER, Y. WANG, X.-H. LU; LSU Hlth. Sci. Ctr., shreveport, LA

Abstract: Human Placenta Stem Cells Derived Cerebral Organoids as a Disease-Modifying Therapy for Neuropsychiatric Disorders

*Clifton Haacker[1], Xinli Tian[1], Kelsea Keys[1], Hanna Li[1], Jonathan S. Alexander[3], Yuping Wang[2], *Xiao-Hong Lu[1]*

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Basal ganglia-related neurodegenerative and psychiatric disorders are debilitating and lack disease-modifying therapy. In the last decade, stem cell therapies have come to the forefront of research as a promising therapy. The lack of ethical considerations, pluripotency, availability in nearly unlimited supply, and low immunogenicity and tumorgenicity make human Placental derived Stem Cells (hPSCs) a "New Hope" for clinical application. Major obstacles include the limited capability to differentiate stem cells into neurons, poor tracking/ control over transplant cell differentiation and survival, and poor evaluation of preclinical efficacy in animal models. We have tested different serotypes and transgene promoters that achieved more than 80% transduction efficiency with long-term stable transgene expression. We have performed transplantation of hPSCs into the striatum and substantia nigra of mice. We identified engrafted hPSCs with fully differentiated neurons in multiple brain regions, suggesting functional connections. In order to achieve a higher cell survival rate, multilineage neurodifferentiation, and robust vascularization, we grew cerebral organoids from the hPSCs using a modified protocol, yielding organoids with validated morphology and composition. The hPSCs derived brain organoids are transplanted into the striatum of a murine middle cerebral artery occlusion (MCAO) model. Efficacy is evaluated using a single-neuron genetic labeling method together with volume imaging to gain unprecedented temporal and spatial profiling of neurodegeneration and neuroinflammation after stroke. A series of neurological, motor, cognitive, and psychiatric behavioral are used across various time points to examine the efficacy of transplantation. Our study provides crucial insights for clinical translation of human brain organoid-based stem cell therapy for stroke, neurodegenerative, and psychiatric disorders.

Disclosures: C. Haacker: None. **X. Tian:** None. **K. Keys:** None. **H. Li:** None. **J. Alexander:** None. **Y. Wang:** None. **X. Lu:** None.

Poster

P326. Perinatal Ischemia and Stem Cells as Therapeutics

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Program #/Poster #: P326.07

Topic: C.09.Stroke

Support: NIH Grant R01NS058784

Title: Glial response to paracrine factors secreted by transplanted stem cells in a rodent model of stroke

Authors: S. S. TIGCHELAAR, *C. DONG, R. L. AZEVEDO-PEREIRA, X. LIANG, T. M. BLISS, G. K. STEINBERG;
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Abstract: Background: Human neural stem cell (hNSC) transplantation shows great potential as a therapy for ischemic stroke. A paracrine signaling mechanism of action is favored with stem cell-secreted factors signaling to the host brain. However, what stem cell-secreted factors are important for recovery is not known, and how the brain responds to these factors remains to be investigated. We recently made a major step towards answering these critical questions by identifying paracrine factors expressed by transplanted human neural stem cells (hNSCs) in the stroke-injured brain. The expression of several of these factors positively correlated with functional recovery. In this study, we focus on one of these paracrine factors that correlated best with stroke recovery, matrilin-2, and investigate how the brain responds to this paracrine factor with particular emphasis on the glial cell response as they are major players in brain recovery.
Method: Adult male nude rats underwent stroke using the distal middle cerebral artery occlusion (dMCAo) model. One week later, recombinant matrilin-2 was infused into the peri-infarct region, using ALZET® osmotic pumps, for 5 days. Animals were assessed for functional recovery for 5 weeks using both the Montoya staircase test and the whisker-paw reflex test. Four weeks post-treatment, brains were stained for GFAP and IBA1 to visualize astrocytes and microglia/macrophages, respectively. Images were taken and glial morphology analyzed using the Bitplane Imaris image analysis software. Output measurements of the number of cells/mm^2, cell volume, cell branching, and process length and thickness were obtained to characterize the changes in astrocytic and microglial response to injury and paracrine factor treatment.
Results: Matrilin-2 treatment significantly enhanced functional recovery compared to the vehicle group. Preliminary analyses revealed that astrocytes in the cortex of stroke rats receiving matrilin had significantly greater volume and surface area in both the ipsi- and contra-lesional hemispheres, compared to animals that received vehicle. Analysis of microglia is ongoing.
Conclusion: Matrilin-2 infusion promotes stroke recovery and modulates the glia response in the ischemic brain. Identifying paracrine factors involved in recovery following implantation of hNSCs in stroke brain, and understanding how the brain responds to these factors, is an important step in elucidating molecular pathways important for brain recovery and may ultimately identify novel therapeutic targets for stroke.

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Poster

P395. Inflammatory Pain

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Program #/Poster #: P395.01

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01NS100788
NIH Grant R01NS114018

Title: S6 Kinase Controls c-Fos Abundance and Contributes to Inflammatory Pain

Authors: *J. DE LA PENA[1], N. KUNDER[1], T.-F. LOU[1], R. CHASE[1], A. STANOWICK[1], P. BARRAGAN-IGLESIAS[3], J. PANCRAZIO[2], Z. CAMPBELL[1];
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Abstract: Translational controls permeate pain. One class of sensory neurons, nociceptors, plays an integral role in the detection and propagation of pain signals. Nociceptors can undergo persistent changes in their intrinsic excitability. Pharmacologic disruption of nascent protein synthesis diminishes acute and chronic forms of pain-associated behaviors. Yet, the targets of translational controls that facilitate plasticity in nociceptors are unclear. Here, we used ribosome profiling to probe the translational landscape in DRG neurons after treatment of the inflammatory mediators, NGF and IL-6. We found that the transcription factor, c-Fos, is preferentially translated after treatment of inflammatory mediators. We demonstrate that c-Fos is expressed in sensory neurons. We also confirmed that inflammatory mediators that promote pain in both humans and rodents increase the accumulation of c-Fos protein. Given that inflammation is known to stimulate mTOR signaling, we reasoned that downstream factors might control c-Fos levels. We found that the ribosomal protein S6 kinase 1 (S6K1) is essential for c-Fos biosynthesis. We next asked if c-Fos or S6K1 play a role in inflammatory pain using the hyperalgesic priming model. We found that inhibition of S6K1s or c-Fos with small molecules diminish mechanical and thermal hypersensitivity in response to inflammatory cues. Additionally, both inhibitors reduce evoked nociceptor activity *in vitro*. Collectively, our data reveal a novel role of S6K1 in modulating rapid response to inflammatory mediators, with c-Fos being one key downstream target.

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Poster

P395. Inflammatory Pain

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P395.02

Topic: D.03. Somatosensation – Pain

Support: R01NS109936

Title: Rapgef Family Members Expressed In Mouse Dorsal Root Ganglion Neurons Contribute To Erk Phosphorylation Downstream Of G_s-coupled Receptors

Authors: *Z. AL-ABBASI[1,2], R. GEGUCHADZE[1], D. C. MOLLIVER[1];
[1]Biomed. Sci., UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME; [2]Grad. Sch. of Biomed. Sci. and Engin., Univ. of Maine, Orono, ME

Abstract: Members of the Rap guanine nucleotide exchange factor (Rapgef) family activate Rap/Ras signaling pathways by exchanging GTP for GDP. Four of the 6 Rapgefs have been identified as effectors of cAMP signaling: Rapgef2, Rapgef3/Epac1, Rapgef4/Epac2, and Rapgef6. Rapgef1(C3G) does not bind cAMP, but has been implicated in Protein Kinase A (PKA)-dependent ERK activation. ERK signaling is required for some components of nociceptor sensitization, therefore cAMP signaling to ERK may represent an important pathway in the induction of inflammatory hyperalgesia by G_s-coupled receptors (G_sPCRs). We recently identified a role for Epac2 in nociceptor sensitization and behavioral hyperalgesia evoked by prostaglandin E2 (PGE2). Epac signaling has been reported to be mediated by both Protein Kinase C (PKC) and ERK1/2. However, studies in heterologous systems suggest that activation of ERK downstream of G_sPCRs is mediated by Rapgef2, either alone or in combination with PKA. To examine these divergent signaling pathways downstream of G_sPCRs, we first tested the distribution of Rapgef family members in dorsal root ganglia (DRG) of male mice by qPCR. We found that all 6 Rapgefs are expressed in DRG, to varying degrees. Next, we examined the relative contributions of PKA and Rapgef2 in the activation (phosphorylation) of ERK (pERK) downstream of cAMP. Application of the cAMP analog 8-Br-cAMP to dissociated DRG neurons induced pERK. The Rapgef2-selective cAMP analog N^6-Phe-cAMP also showed a dose-dependent (150-1000 micromolar) induction of pERK. Co-application of 1mM SQ22356 (an inhibitor of Rapgef2) reversed the effect of N^6-Phe-cAMP, supporting the activation of ERK by Rapgef2. Next, we examined whether activation of endogenous receptors was capable of inducing pERK. To identify G_sPCRs highly expressed in DRG, we examined published RNA-seq data and then confirmed expression of beta-adrenergic receptors Adrb1-3 and dopamine receptors Drd1, 5 by quantitative PCR. Of these receptors, Adrb2 and Drd1 were the most highly expressed. Application of 10 micromolar isoproterenol (Adrb2) or 1 micromolar SKF38393 (Drd1/5), induced pERK by 360% or 160% above baseline, respectively. While PKA inhibitor peptide PKI reduced the effect of isoproterenol by ~50%, it only slightly reduced the effect of SKF38393. These results suggest that different G_sPCRs may be differentially coupled to Rapgef2. In conclusion, Rapgef1, 2, and 6 are expressed in DRG and may contribute to cAMP signaling to ERK downstream of G_sPCRs.

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Poster

P395. Inflammatory Pain

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Program #/Poster #: P395.03

Topic: D.03. Somatosensation – Pain

Support: NIH Grant AR072230

Title: Mir-544-3p mediates arthritis pain through regulation of fcγri

Authors: *Y. LIU, S.-M. JEON, M. J. CATERINA, L. QU;
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Abstract: Chronic or episodic joint pain is a major symptom in rheumatoid arthritis (RA) and its adequate treatment represents an unmet medical need. However, the cellular and molecular mechanisms underlying RA pain remain elusive. Non-coding microRNAs (miRNAs) have been implicated in the pathogenesis of RA as negative regulators of the stability or translation of specific target mRNAs. Yet, their significance in RA pain is still not well defined. We and other groups recently identified neuronally expressed FcγRI as a key driver of arthritis pain in mouse RA models. Thus, we tested the hypothesis that miRNAs that target and regulate neuronal FcγRI attenuate RA pain. Here, qPCR analysis revealed that miR-544-3p was robustly downregulated whereas FcγRI was significantly upregulated in the dorsal root ganglion (DRG) in two mouse RA models, namely collagen II-induced arthritis (CIA) and antigen-induced arthritis (AIA). In situ hybridization showed a downregulation of miR-544-3p expression in joint-innervating DRG of mice with CIA. Rescuing miR-544-3p downregulation by intrathecal injection of miR-544-3p mimic (3 µg; 10 µl) significantly attenuated established arthritis pain in the CIA model. Moreover, this effect was likely mediated, at least in part, by FcγRI since miR-544-3p mimic downregulated FcγRI in the DRG under arthritis conditions and genetic deletion of FcγRI produced similar antihyperalgesic effects in the CIA model. Using the dual-luciferase assay, we found that miR-544-3p mimic reduced luciferase reporter activity in HEK293 cells transfected with a construct containing the full length of 3'UTR sequence of Fcgr1 but not one containing a mutant Fcgr1-3'UTR. These findings further confirmed that miR-544-3p directly targets the 3'UTR of Fcgr1 to downregulate Fcgr1 mRNA expression. In addition, Fcgr1 mRNA expression in dissociated DRG neurons in vitro was downregulated by miR-544-3p mimic and upregulated by miR-544-3p inhibitor. In naïve mice, in vivo transfection of either miR-544-3p mimic or miR-544-3p inhibitor had no effects on basal mechanical and thermal sensitivity. Yet, miR-544-3p mimic alleviated acute joint pain hypersensitivity induced by IgG immune complex (IgG-IC), whereas miR-544-3p inhibitor potentiated the pro-nociceptive behavioral effect of IgG-IC. These findings suggest that miR-544-3p causally participates in the maintenance of arthritis pain by targeting neuronal FcγRI, and thus define miR-544-3p as a new potential therapeutic target for treating RA pain.

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Poster

P395. Inflammatory Pain

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P395.04

Topic: D.03. Somatosensation – Pain

Title: Role of Cathepsin K in Chronic Inflammatory Pain

Authors: *A. THAKAR[1], M. PARACHA[2], R. A. DARLING[2], T. E. BROWN[1];
[1]IPN, Washington State Univ., Pullman, WA; [2]Univ. of Wyoming, Laramie, WY

Abstract: Chronic inflammatory pain involves various underlying pathophysiological mechanisms and is far more complex than acute pain. Current therapeutics for chronic inflammatory pain are often not effective because the etiology responsible for the pain is not addressed by traditional pharmacological treatments. There is a need to find novel targets that not only alleviate the symptomology associated with chronic pain but address the underlying mechanisms responsible for pain. Cathepsin K is a cysteine protease that has traditionally been studied in the context of bone and joint disorders. Previous work by others has shown that inhibition of cathepsin K activity reduces osteoarthritis-associated nociception in joints. However, the role of cathepsin K in models of cutaneous inflammation is understudied. We assessed the effectiveness of genetic deletion or pharmacological inhibition of cathepsin K activity in male mice on the expression of nocifensive behaviors after formalin injection or mechanical and thermal hypersensitivity after injection of complete Freund's adjuvant (CFA) into the mouse hind paw. Our data demonstrates that cathepsin K knockout mice (*Ctsk*$^{-/-}$) have an attenuation in the longer-lasting, more persistent phase of the formalin test (WT=48.1s ± 7.3s, n=8; *Ctsk*$^{-/-}$=7.1 s± 2.9s, n=8). In addition, *Ctsk*$^{-/-}$ mice do not develop mechanical or thermal hypersensitivity after CFA injection for up to 7 days. Specifically, paw withdrawal threshold (PWT) was measured with von Frey filaments, which showed a significant attenuation in CFA-induced mechanical hypersensitivity in *Ctsk*$^{-/-}$ mice (day 1=1.5 g and day 7=1.7 g, n=8) compared to WT mice (day 1=0.75 g and day 7= 1.2 g, n=8). Moreover, inhibition of cathepsin K activity was effective at reducing the expression of mechanical hypersensitivity (day 1-DMSO=0.63 g ± 0.10 g, n=12; cKi=1.23 g ± 0.15 g, n=13; and day 7- DMSO=0.52 g ± 0.08 g, n=13; cKi=1.04 g ± 0.13 g, n=13) and thermal hypersensitivity (day 1-DMSO=5.74 s ± 0.39 s, n=11; cKi=7.87 s ± 0.76 s, n=12; and day 7- DMSO=4.88 ± 0.41 s, n=11; cKi=6.58 ± 0.55 s, n=12] after CFA injection. In addition, 1 day after CFA injection the mRNA levels (3.77 fold, n=8) and cathepsin K activity levels (2.6 fold, n=8) were elevated and persisted for 7 days (mRNA- 5.24 fold, n=8 and activity- 2.96 fold, n=7). Based upon our data we demonstrate that cathepsin K plays a key role in the expression of chemically induced cutaneous hypersensitivity as Ctsk$^{-/-}$ mice and pharmacological reduction of cathepsin K activity in WT mice attenuated nocifensive behaviors.

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Poster

P395. Inflammatory Pain

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Program #/Poster #: P395.05

Topic: D.03. Somatosensation – Pain

Title: The role of Transient Receptor Potential ankyrin 1 in the Knee osteoarthritis of rat

Authors: *H. TAMAI[1], M. YAMANAKA[1], W. TANIGUCHI[1], N. NISHIO[1], D. FUKUI[1], M. SONEKATSU[1], R. TAIJI[1], Y. MATSUYAMA[1], T. UENO[1], R. MIYAKE[1], T. NAKATSUKA[2], H. YAMADA[1];
[1]Wakayama Med. Univ., Wakayama, Japan; [2]Pain Res. Ctr., Kansai Univ. of Hlth. Sci., Kumatori, Japan

Abstract: Knee osteoarthritis (knee OA) is a leading cause of impaired mobility in the elderly, and is one of the most common diseases that are often treated in clinical practice. It is thought that the pain due to knee OA is caused by the bones hitting each other due to the worn cartilage, but X-ray changes and pain do not necessarily correlate. Despite its widespread prevalence, pathogenesis of pain due to knee OA is unknown and various studies are being conducted. The Transient Receptor Potential (TRP) channels that have been attracting attention in recent years are ion channels that are expressed in various tissues throughout the body, and among them, TRP ankyrin receptor subtype 1 (TRPA1) and TRP vanilloid receptor subtype1 (TRPV1) have been reported to be associated with intraspinal pain previously. However, the little is known about the role of TRPA1 involved in chronic pain such as knee OA. Therefore, we investigated the effect of intra-articular TRPA1 on glutamatergic excitatory synaptic transmission in substantia gelatinosa (SG) neurons of knee OA model rats by using *in vivo* patch-clamp technique. We also assessed gait parameters and pain threshold with CatWalk and Pressure application measurement (PAM). In the knee OA models, excitatory postsynaptic current in SG neurons significantly increased by intra-articular administration of allyl isothiocyanate, a TRPA1 agonist. On the other hand, application of HC-030031, a TRPA1 antagonist, induced significant decrease of that. Next, we found that pain-related gait and pain threshold improved with CatWalk and PAM test by intra-articular administration of HC-030031. These results indicate that TRPA1 is expressed in the knee OA model rat, and the activation enhances the pain due to knee OA. In this study, we demonstrated that TRPA1 was critical channel for the pain caused by Knee OA.

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Poster

P395. Inflammatory Pain

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01NS116759
NIH Grant R01CA249939

Title: Long-lasting pain and profound changes in the transcriptome are caused by the disruption of mitochondrial pyruvate oxidation in dorsal root ganglia

Authors: *O. MELEMEDJIAN, T. LUDMAN;
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Abstract: Metabolism is inextricably linked to every aspect of cellular function and defects in metabolic pathways are associated with a variety of neoplastic, cardiovascular, and neurodegenerative diseases. Additionally, polymorphisms and inborn errors in metabolic genes are associated with a multitude of chronic pain conditions. Similarly, nerve growth factor (NGF) is associated with a multitude of chronic pain conditions, but its potential role in regulating the metabolism of sensory neurons is largely unknown.

Hence, we explored whether intraplantar NGF injection in mice alters the metabolism of sensory neurons. We determined that intraplantar NGF injection disrupts mitochondrial pyruvate oxidation leading to an increased extrusion of lactate and protons. These changes were driven by the enhanced expression of pyruvate dehydrogenase kinase 1 (PDHK1) and lactate dehydrogenase A (LDHA). Moreover, pharmacological and genetic blockade of PDHK1 and LDHA attenuated NGF-induced tactile allodynia. Direct disruption of mitochondrial pyruvate oxidation in dorsal root ganglia was sufficient to cause tactile allodynia that lasted at least 3 months - unlike NGF-induced allodynia which resolves within 72 hours. Full-length transcript analysis revealed that the disruption of mitochondrial pyruvate oxidation significantly altered the transcription of over 400 genes, reduced the poly-A tail length of mRNAs, and modified the alternative splicing of hundreds of transcripts. These findings demonstrate that aberrant mitochondrial pyruvate oxidation is a crucial mechanism for the development and maintenance of chronic pain.

Disclosures: O. Melemedjian: None. **T. Ludman:** None.

Poster

P395. Inflammatory Pain

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Topic: D.03. Somatosensation – Pain

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McCormick-Gabilan Faculty Fellowship
Department of Anesthesiology, Perioperative & Pain Medicine at Stanford University
University of Toyama
University of Soochow

Title: Sex-specific patterns of spinal cord neuroinflammation in a mouse model of complex regional pain syndrome.

Authors: *G. P. B. MUWANGA, H. SHEN, N. A. HUCK, C. E. JORDAN, T. E. FORMAN, S. A. CORDONNIER, E. S. HAIGHT, F. DALE-HUANG, Y. TAKEMURA, V. L. TAWFIK;
Stanford Univ., Stanford, CA

Abstract: Chronic pain is a major physical, emotional, and financial burden affecting 100 million Americans. Understanding the molecular mechanisms underlying pain is essential for developing safe and effective therapies. Microglial activation mediates chronic pain, according to numerous preclinical studies. However, translational efforts using known glial modulators have largely failed, possibly due to poor specificity of the compounds studied or an incomplete understanding of microglial reactivity. To better understand the contributions of microglia to chronic pain, we used a clinically relevant mouse model of complex regional pain syndrome (CRPS) and monitored microglial activation throughout disease progression in both males and females. We found that while both sexes exhibit spinal cord microglial activation evidenced by increases in Iba1, this activation was attenuated and delayed in

females. We also sought to evaluate the expression of the newly identified microglia-specific marker, TMEM119. We found two distinct populations of myeloid cells in the spinal cord based on the relative expression of TMEM119 and morphology: TMEM119+ microglia and TMEM119- infiltrating myeloid lineage cells, which comprised of Ly6G+ neutrophils and Ly6G- macrophages. Further studies to uncover glial-targeted therapies need to consider sex, timing after injury, and exact target population to achieve the specificity needed for translation. This is especially important because mixed myeloid populations infiltrate the spinal cord after peripheral injury and may have varying functions in pain progression or resolution.

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Poster

P395. Inflammatory Pain

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Topic: D.03. Somatosensation – Pain

Support: CIHR Foundation Grant 154281

Title: Inhibition of acute inflammation leads to chronification of inflammatory pain

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Abstract: Introduction: Recent data from a human genetics study suggests that pain resolution is coordinated by inflammatory cells during the acute phase of an inflammatory response. Thus, we hypothesized that inhibition of inflammatory response might lead to pain chronification. **Methods**: CD-1 male and female mice were treated with dexamethasone (a corticosteroid) or vehicle for seven consecutive days (0.5 mg/kg/day). On the second day of treatment, mice received either a unilateral nerve injury (chronic constriction injury; CCI) or inflammatory injury (complete Freund's adjuvant; CFA). Mechanical paw-withdrawal threshold (PWT) was measured prior to treatment (baseline) and at regular intervals until average PWTs returned to baseline values. To assess whether the phenomena is due to anti-inflammatory effects rather than analgesic action, the NSAID, diclofenac, and two analgesics with no known anti-inflammatory action (systemically administered gabapentin and peripherally administered lidocaine) were tested in the CFA model. The involvement of neutrophils was examined by depletion using anti-Ly6G or direct injection of isolated neutrophils into the hind paw. Finally, we tested whether cryotherapy (application of ice) would have similar effects after CFA injury.**Results**: Dexamethasone produced an acute anti-allodynic effect in the CFA but not CCI injured mice, but significantly delayed PWT recovery to baseline in both groups. CFA allodynia in mice receiving dexamethasone took twice as long to recover to baseline compared to vehicle. Diclofenac, gabapentin, lidocaine, and cryotherapy all reduced allodynia during the treatment period, but only diclofenac and cryotherapy prolonged the

duration of CFA-induced allodynia, suggesting that the delay in recovery is, in fact, due to the reduction of inflammation. Finally, treatment with anti-Ly6G antibody reduced acute allodynia but prologued its duration whereas neutrophil injection entirely prevented the allodynia-prolonging effect of dexamethasone, suggesting that neutrophils are involved in the resolution of pain after injury and that dexamethasone delays allodynia recovery by directly affecting neutrophils.**Conclusions**: Our observations suggest that interfering with the inflammatory response taking place immediately after injury with a corticosteroid (dexamethasone), NSAID (diclofenac) or cryotherapy, although producing the acute relief of pain, might simultaneously lead to pain chronification. If this phenomenon is also seen in humans, it could have dramatic implications for the treatment of acute pain.

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Poster

P395. Inflammatory Pain

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P395.09

Topic: D.03. Somatosensation – Pain

Support: NIH/NINDS R01 NS109541
NIGMS 5T32GM007105

Title: Expression of ectopic heat shock protein 90 (eHsp90) in male and female primary afferent nociceptors regulates inflammatory pain

Authors: *Y. WANG[1], S. SCARNEO[1,2], S. KIM[1,4], X. ZHANG[1], K. W. YANG[2], P. HUGHES[2], T. HAYSTEAD[2], A. G. NACKLEY[3,2];
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Abstract: Expression of ectopic heat shock protein 90 (eHsp90) in male and female primary afferent nociceptors regulates inflammatory pain

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Heat shock protein 90 (Hsp90) is a ubiquitously expressed integral cellular protein essential toregulating proteomic stress. Previous research has shown that Hsp90 regulates critical signalingpathways underlying chronic pain and inflammation. Recent discovery of membrane bound ectopic Hsp90 (eHsp90) on tumor cells has shown that Hsp90 induction to the plasma membrane can stabilize disease-relevant proteins. Here, we characterize eHsp90 expression in a mouse model of inflammation and demonstrate its role in nociception and pain. We found that intraplantar complete Freund's adjuvant (CFA) induced robust

expression of eHsp90 on the cell membranes of primary afferent nociceptors located in the L3-L5 dorsal root ganglia (DRG), bilaterally, with minimal to no expression in other tissues. CFA-induced increases in eHsp90 expression on lumbar DRG were significantly greater in females compared to males. Furthermore, exogenous Hsp90 applied to primary Pirt-GCaMP3 nociceptors induced increases in calcium responses. Responses were estrogen-dependent such that greater activity was observed in female or estrogen-primed male nociceptors compared to unprimed male nociceptors. Treatment of mice with the selective eHsp90 inhibitor HS-131 (10 nmol) significantly reversed CFA-induced mechanical pain, thermal heat pain, and hindpaw edema. Notably, a higher dose (20 nmol) of HS-131 was required to achieve analgesic and anti-inflammatory effects in females. Here, we provide the first demonstration that inflammation leads to an upregulation of eHsp90 on DRG nociceptors in a sex-dependent manner, and that inhibition of eHsp90 reduces nociceptor activity, pain, and inflammation. Thus, eHsp90 represents a novel therapeutic axis for the development of gender-tailored treatments for inflammatory pain. This work was supported by NIH/NINDS R01 NS109541 to AN and 5T32GM007105 from NIGMS to SS.

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Poster

P395. Inflammatory Pain

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Program #/Poster #: P395.10

Topic: D.03. Somatosensation – Pain

Support: NIH NICDR grant DE025970
Texas Woman's University Research Enhancement Program Grant
Texas Woman's University Center for Student Research Small Grant

Title: Estrogen and serotonin synergistically enhance the release of interleukin-6 and fractalkine from murine macrophages: a potential mechanism underlying sex differences in pain

Authors: *T. M. HICKMAN, S. KAUR, E. H. SIMMONS, L. K. HANSON, D. L. AVERITT; Texas Woman's Univ., Denton, TX

Abstract: Sex differences in the immune system could contribute to pain conditions more prevalent in women. In the peripheral nervous system, serotonin (5HT) can be released by immune cells, including macrophages. Peripheral 5HT can bind to excitatory 5HT receptors, including $5HT_{2A}$, expressed on nociceptors to initiate and sensitize pain signaling. Macrophages reportedly express estrogen receptors and may be sensitive to the gonadal hormone levels in females. We previously reported 5HT content in the rat vibrissal pad to be higher in female rats compared to males and that 5HT evokes significantly greater pain sensitivity when gonadal hormone levels are in flux. Further, 17β-estradiol (E2) enhances 5HT's nociceptive effects on sensory neurons. While it is clear that E2 modulates 5HT-evoked pain signaling in sensory neurons, it remains unclear if E2 can modulate the release of 5HT or other peripheral proinflammatory mediators from immune cells to contribute to pain. Here we hypothesized that E2 triggers the release of 5HT and/or proinflammatory cytokines and chemokines from cultured male and

female murine macrophages. Supernatant from IC-21 (male C57BL/6) or J774A.1 (female BALB/cN) cultures was collected before and after 1-hour treatment with 150 pM, 1 nM, or 50 nM E2 or vehicle and 5HT release was quantified by ELISA. These concentrations were used to mimic the high and low E2 levels observed during diestrus and proestrus of the rat estrous cycle. In separate cultures, supernatant was collected before and after 1-hour treatment with 100 μM 5HT, 50 nM E2, 5HT + E2, or vehicle and the release of cytokines and chemokines were quantified using a Proteome Profiler Cytokine Array. Macrophages were then fixed in 10% formalin and ERα, ERβ, and $5HT_{2A}$ receptor expression was detected by immunocytochemistry. A separate group of macrophage cultures were treated with 50 nM capsaicin (nociceptive stimulus), 10 μM 5HT + 50 nM capsaicin, 50 nM E2 + capsaicin, or 5HT + E2 + capsaicin and cell lysates were analyzed by Phospho-Kinase Array. We report that proestrus-level E2 triggers release of 5HT from macrophages which co-express ERα and $5HT_{2A}$. While E2 triggered the release of many cytokines and chemokines, E2 + 5HT synergistically increased the release of IL-6 and fractalkine, which are known to trigger allodynia. Further, we report that E2 + 5HT increased phosphorylation of p38, JNK, and Src kinases, while reducing RSK phosphorylation, implicating an intracellular interaction between ERα and $5HT_{2A}$. Together, our data suggest that E2 modulates release of proinflammatory mediators from macrophages which is exacerbated by 5HT, providing a novel mechanism underlying sex differences in pain.

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Poster

P395. Inflammatory Pain

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Program #/Poster #: P395.11

Topic: C.11. Spinal Cord Injury and Plasticity

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NeurANO Bioscience, a company that is involved in research and development of nanotherapeutics for neurological disorders (EM)

Title: Exclusive blockade of extrasynaptic NMDA receptors ameliorates chronic pain

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Abstract: Chronic pain is associated with glutamatergic excitotoxicity due to tonic overactivation of NMDA receptors at extrasynaptic sites (eNMDAR). Therefore, chronic pain can be treated by blocking eNMDARs. To test this hypothesis, we developed AuM, a first-in-class exclusive antagonist of eNMDARs, by attaching memantine (M) to a gold (Au) nanoparticle, so that the resulting nanotherapeutic

is too large to gain access to the synaptic cleft. We studied the effect of eNMDAR blockade on pain sensitivity in two experimental models: right-side spared nerve injury (SNI, mice) or left-paw chronic inflammation inducted with CFA (Complete Freund's Adjuvant, 0,1 ml emulsion, subcutaneously, rats). We stereotaxically injected 0.5 µl of 25 nM AuM or saline into the right spinal dorsal horn (mice) or epidurally injected 20 µl of 25 nM AuM or saline into the spinal canal under the foramen between L5-L6 vertebrae (rats). In the SNI model, mice were subjected to mechanical sensitivity testing by von Fray filaments starting from 3 to 25 day after injury. Our data revealed that SNI mice treated with AuM right after the injury show significant slowing down of allodynia compared to saline-injected SNI mice. Post-SNI (5 days) treatment display significant reduction of hypersensitivity. In the CFA model, rats were subjected to mechanical sensitivity testing and thermal sensitivity testing by Hargreaves starting from 1 hour to 14 days after CFA administration. CFA-inflamed animals treated with AuM right after the injury shows significant slowing down of allodynia progressing compared to saline-injected animals. In summary, our findings indicate the involvement of eNMDAR at different stages of chronic pain development and offer the opportunity to develop novel therapeutics to ameliorate the impact of nerve injury.

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Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P415.01

Topic: D.04. Somatosensation – Touch

Support: JSPS-JP16H06566

Title: Parietal contributions to illusory tactile pulling sensations

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Abstract: The sensation of directional forces and their associated sensorimotor commands are inextricably intertwined, complicating the identification of brain circuits responsible for tactile pulling sensations. One hypothesis is that, like tactile frequency discrimination, pulling sensations are generated by early sensory-frontal activity. Alternatively, they may be generated later in the somatosensory association cortex. To dissociate these accounts and uncouple the pulling sensation from unrelated but correlated sensory and motor processing, we combined high-density EEG with an oddball paradigm and asymmetric vibration at the fingertips in 15 human participants (5 females, mean age = 33.33yrs). Asymmetric vibration reliably created an illusory sensation of the hand being directionally pulled either leftwards or rightwards (left/right discrimination accuracy = 94%). Oddballs that created a pulling sensation in the opposite direction to common stimuli were compared to the same oddballs in the context of neutral common stimuli (symmetric vibration) and to neutral oddballs. Brain responses to having

directional pulling expectations violated by directional stimuli were therefore isolated. Contrary to the sensory-frontal account, sensory P50 amplitude did not differ across conditions and frontal N140 brain activity was actually larger for neutral than pulling oddballs. Instead, puling sensations were associated with amplitude and latency modulations of midline P200 and P3b potentials, and specifically, to contralateral parietal lobe activity 264-320ms post-stimulus. Source localization showed this latter activity to be from the postcentral sulcus, superior parietal lobule and intraparietal sulcus, supporting the somatosensory association cortex account of the pulling sensation. Our results show that illusory tactile pulling sensations can uniquely disambiguate the role of complex tactile sensations from their associated low-level sensorimotor processing. Pure pulling sensations depend on activity in somatosensory association cortex responsible for processing body position, tactile orientation and peripersonal space. This first step towards a spatiotemporally precise account of the pulling sensation elucidates parietal lobe function during tactile processing.

Disclosures: J. De Havas: None. **S. Ito:** None. **S. Bestmann:** None. **H. Gomi:** None.

Poster

P415. Stimulus Feature Neural Coding: Humans

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Program #/Poster #: P415.02

Topic: D.04. Somatosensation – Touch

Support: JSPS KAKENHI Grant JP20H05957

Title: Slow binding of paired stimulus features in tactile perception

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Abstract: When we touch an object, we can extract its features such as texture, shape, and direction. Previous studies have shown remarkable human's abilities to detect and discriminate individual features. For correct perception of the object by touch, not only detection of specific features, but also that of the correct combination of features is necessary. To better understand how and at what stage of information processing in the brain the tactile feature binding takes place, we psychophysically measured temporal limit of feature binding. In the experiment, the observer touched a tactile stimulator (Latero, Tactile Lab) with a single finger. The stimulator has an array of 64 pins that constructs a 10 x 10 mm contact surface, and each pin can independently produce lateral movements of the contacted surface of the skin. In the experiment, we combined pin-vibration frequency (temporal texture) and orientation as a feature pair. In a trial, two patterns were alternatively presented for four seconds. In half of the trials, the patterns were a 45-deg (right-upward) diagonal line produced by a low-frequency (20 Hz) vibration, and a -45-deg (right-downward) diagonal line produced by a higher-frequency (30, 40, 80 or 160Hz) vibration. In the other half, the two patterns were the reversed combinations of frequency and orientation. We changed the duration of each pattern presentation, and asked observers to report whether the low-frequency vibration was paired with the 45-deg or -45-deg tilt. The performance dropped with decreasing the duration of each pattern (increasing the alternation rate) or with reducing the difference in vibration frequency between the

two pairs. Critically, observers could not report the correct paring of vibration frequency with orientation unless slowing down the presentation rate (< 4 Hz, corresponded to > 125 ms for each feature pair). This poor performance cannot be explained solely by the short duration of each pattern, since the performance was greatly improved when the two patterns were presented with more-than-one-second temporal gaps. We observed same trend when the vibration frequency and motion direction were combined as a pair. Observed temporal limit was as slow as that of multimodal binding (visuo-tactile, audio-tactile), and much slower than that of visual feature pairings of color or luminance with orientation. Since fast pairing rates suggest the processing of feature binding at early stages, no evidence was observed for early binding of tactile basic features.

Disclosures: S. Kuroki: A. Employment/Salary (full or part-time):; NTT Communication Science Laboratories. **S. Nishida:** A. Employment/Salary (full or part-time):; NTT Communication Science Laboratories.

Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

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Program #/Poster #: P415.03

Topic: D.04. Somatosensation – Touch

Support: Fondation de France
Fondation Berthe Fouassier
ANR-19-CE37-0005

Title: The neural dynamics of tool-extended sensing

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Abstract: Tool use is one of the defining traits of humankind. Tools allow us to explore our environment and expand our sensorimotor abilities. For this reason, the topic of tool use has been extensively studied, though mostly from a motor control perspective. We recently demonstrated that humans can accurately localize tactile information (e.g. impacts) along the entire tool surface, raising questions about the neural mechanism underlying this ability. Previous EEG studies have found that the alpha (7-14 Hz) and beta (15-30 Hz) frequency bands are involved in the spatial processing of touch on the body. Activity in the alpha band contributes mainly to the mapping of touch in external spatial coordinate systems, whereas activity in the beta band seems to be modulated mainly when mapping touch in skin-centered coordinates. To date, whether these frequency bands also relate to spatial processing of touch on hand-held tools remains unknown. Our goal here was therefore to fill this gap. In a first study, participants had to judge the relative location of two successive contacts on a hand-held rod. Using analyses based on repetition effects, we found evidence that alpha oscillations may code for spatial aspects of touch on a tool (Fabio, et al., in prep). In a second study, we aimed at pinpointing the role of alpha oscillations during tool-

extended sensing. Participants performed a tactile detection task where contact was applied to either hands, or the tips of hand-held rods. The posture of the hands/tool-tips was uncrossed or crossed at participants' body midline. Notably, when tool-tips were crossed the hands remained uncrossed, thus allowing us to disentangle brain responses related to different coordinate systems. That is, whether brain response reflected the coding of contact on the tool in external or tool-centered spatial coordinates. Similar external-related signals in alpha were found for tools and hands, suggesting that the brain uses similar oscillatory mechanisms for mapping touch on a rod and on the body. Ongoing analyses are further exploring this effect.

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Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

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Program #/Poster #: P415.04

Topic: D.04. Somatosensation – Touch

Support: Defense Advanced Research Projects Agency's (DARPA; Arlington, VA)
Revolutionizing Prosthetics program (contract number N66001-10-C-4056)
Alfred E. Mann Foundation

Title: Single unit and population coding of bimanual interactions in human sensory cortex

Authors: J. VERGARA[1], R. W. NICKL[2], G. L. CANTARERO[3], M. S. FIFER[5], F. TENORE[6], P. A. CELNIK[4], *J. YAU[1];
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Abstract: Mundane tasks like fastening a button or tying shoelaces are possible because of specialized neural circuits for coordinating our use of two hands. Although bimanual movement control has received great attention, the coordination of sensory processing over the hands remains poorly understood. Tactile cues experienced on one hand exert systematic influences on the perception of cues experienced on the other hand revealing robust bimanual interactions. These interactions may be mediated by higher-order somatosensory cortical neurons which frequently have bilateral receptive fields that span both hands. Alternatively, bimanual touch may reflect integration in primary somatosensory cortex, where neural activity that is predominantly associated with touch on contralateral body sites can sometimes be modulated by ipsilateral cues.
Here, we recorded neural activity in microelectrode arrays implanted in the postcentral gyri of a patient with incomplete spinal cord injury (C5-C6 ASIA B). Exploiting his residual sensibilities, we required the participant to perform a simple oddball detection task that ensured attentional engagement with vibration cues delivered to his fingers. We characterized single unit responses to cues delivered only to the contralateral or ipsilateral hands, and compared these activity patterns to bimanual cue responses. We also determined how spiking activity related to variations in vibration frequency or amplitude. In addition to

single unit characterizations, we explored population coding of the unimanual cues and bimanual interactions using neural dimensionality reduction. These preliminary analyses establish how vibrotactile cues are signaled by individual neurons in human sensory cortex and how neural populations can dynamically represent cue interactions over the hands.

Disclosures: J. Vergara: None. **R.W. Nickl:** None. **G.L. Cantarero:** None. **M.S. Fifer:** None. **F. Tenore:** None. **P.A. Celnik:** None. **J. Yau:** None.

Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P415.05

Topic: D.04. Somatosensation – Touch

Title: Somatosensory and auditory systems support tactile frequency discrimination

Authors: *A. GRENIER, A. SHARP, P. ALBOUY;
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Abstract: Somatosensory and auditory systems support tactile frequency discriminationAuditory scene analysis is essential to many daily activities: understanding speech in noise, localization of sounds, musical perception, etc. Most of the time, several senses are involved in these activities. For example, when a violinist plays a note, sounds and vibrations are produced by the instrument. Hearing and tactile systems are activated. Understanding how the brain recruits each of these senses and how they interact with each other remains a matter of study. To better understand tactile perception, the study of neuroanatomical correlates is necessary via low-level perceptual tasks. Therefore, the main goal of this study was to investigate neural correlates of tactile perception during a simple frequency (pitch) discrimination task via the tactile modality only (no auditory perception). We hypothesized that both somatosensory and auditory cortices will be recruited during the frequency (pitch) discrimination task even if no sounds were presented to the auditory system. During the EEG recordings, using an oddball paradigm, tactile stimulation was delivered to 20 healthy participants through a left hand vibrotactile stimulation glove. The paradigm includes five deviant stimuli (225Hz, 250Hz, 500Hz, 800Hz, 1000Hz) differing in frequencies and presented randomly between the standard stimuli (200Hz). To control for auditory perception, participants were asked to listen to a continuous white noise while wearing earplugs during the entire experiment. Source reconstruction of vibro-tactile event related potentials showed right lateralized evoked response in both somatosensory and auditory regions for the average of all standard stimuli. The somatosensory response was earlier than the auditory response. For the detection of deviant sounds (as compared to standard sounds) two ERPs were observed. The first component was an early negative wave with a peak around 300ms, with generators in the auditory and somatosensory cortices. This wave was observable only in response to the 500Hz and the 800Hz deviant stimuli but not for the 225Hz, 250Hz and 1000Hz stimuli. A second positive wave was observed at around 450ms with generators in the dorsal stream and was observable only for deviants 500Hz, 800Hz and 1000Hz. These findings suggest that pitch discrimination without auditory perception is performed by an interplay between tactile and auditory systems but are limited by the frequency discrimination capacities of the

tactile system. These results provide a better understanding of multisensory interaction during tactile uni-sensory perception.

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Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P415.06

Topic: D.04. Somatosensation – Touch

Support: NIH R01MH111629
NIH R01MH107513
NIH R01MH119430
NIH R37HD090153

Title: Neural Specialization for Social and Interactive Touch in rTPJ

Authors: *T. BUCK[1], C. DICOCCO[1], J. L. CUZZOCREO[1], J. A. NOAH[1], X. ZHANG[1], J. HIRSCH[1,2,3,4,5];
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Abstract: Physical touch is a natural form of social and interactive communication. Although the neural representations of the sensory systems are well understood, the social and communicative functions associated with sensorimotor touch remain understudied. In one model the social/affective function would be processed by sensory pathways. However, the nexus model of social processing proposes that the right temporal parietal junction (rTPJ) serves as a neural hub for social functions and predicts that social touch would also be represented in the rTPJ[1]. We test these alternative models with real vs. simulated hand clasps using the right and left hands. The design of this study takes advantage of the anatomically crossed sensory and motor pathways where expected responses for sensory touch include contralateral regions in sensorimotor hand areas (Figure 1A. & 1B.) and test the hypothesis that social responses (real vs simulated hand clasps) are expected in right parietal regions. 15 dyads (n=30) performed right and left-hand clasps with their partners' hand (social) or a simulated hand (non-social condition). Neuroimaging findings for right- and left-hand handclasps with real vs. simulated hands were consistent with social properties of rTPJ and extend the nexus model to social touch (Figure 1C., $p < .001$, $t = 3.19$).
[1]Carter & Huettel (2013) *Trends in Cog Sci*.

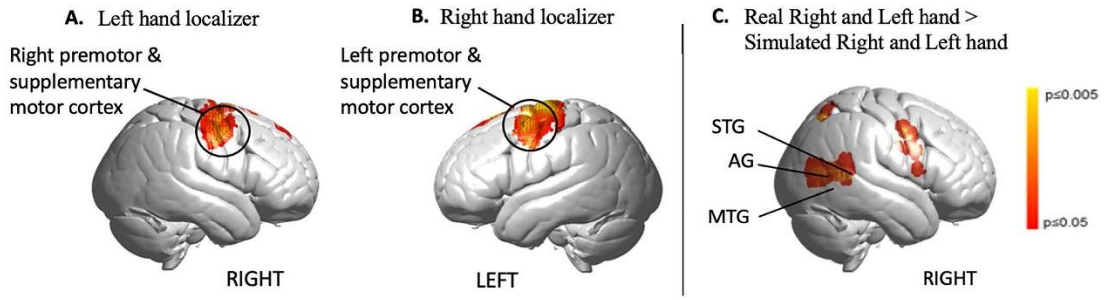


Figure 1. A. Left hand somatosensory localizer. **B.** Right hand somatosensory localizer. **C.** Contrast comparison of [Real Right & Real Left Hand > Simulated Right & Simulated Left Hand] activity, based on the combined OxyHb and deOxyHb signals (p≤0.05). Activity was observed in right hemisphere superior temporal gyrus (STG); middle temporal gyrus (MTG); and angular gyrus (AG), components of the right temporal parietal junction.

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Poster

P415. Stimulus Feature Neural Coding: Humans

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Program #/Poster #: P415.07

Topic: D.04. Somatosensation – Touch

Support: NWO Rubicon (Dutch Research Council, project 019.193SG.011)
NINDS UH3 NS107714

Title: Create your own sensations: from custom built intracortical microsimulation to tactile feedback for prosthetic control

Authors: *C. VERBAARSCHOT[1,4], V. KARAPETYAN[1,2], M. BONINGER[1,2,3], B. SORGER[4], R. A. GAUNT[1,2,3];
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Abstract: An ideal prosthetic arm should both act and feel like a healthy human arm to enable a user to interact naturally with individuals and objects around them. To do so, the prosthesis needs to convey physical object characteristics, such as how soft or rough something feels. Intracortical microstimulation (ICMS) may be a way to achieve such tactile feedback. To date, the effects of ICMS have been primarily explored using experimenter-driven parameter manipulations. In this study, we use a participant-driven

approach to test whether (1) specific ICMS settings can create distinguishable tactile sensations and (2) whether these artificially created sensations can convey object characteristics.
Two people with tetraplegia participated in this study and have microelectrode arrays implanted in their somatosensory cortex that can generate localized sensations in their right hand. The participants have limited arm control and used their left hand to interact with a tablet interface. The interface visually presented one of several objects to the participant and evoked ICMS stimulation when touched by the user. By moving a cursor around in two virtual rectangles with parameters randomly assigned to their axes, participants could manipulate four ICMS parameters: amplitude, frequency, transient shape and drag. Participants repeatedly defined specific ICMS parameter settings in the rectangles for each object, attempting to get their tactile perception as close to the pictured object as possible. To assess what the created sensations feel like and determine whether they are distinguishable, previously defined ICMS settings were replayed to the participants and they were asked to (1) describe the experienced tactile characteristics and (2) select the object that best matches this sensation.
Preliminary results indicate that participants can create distinct tactile experiences that represent object characteristics; participants verbally report experiences of compliance, temperature and texture. For example, ICMS-evoked sensations that were created for an 'apple' are repeatedly reported as feeling 'smooth' and 'cool'. Moreover, both participants report the ability to create intended object-specific sensations to a satisfactory degree.
In contrast to previous research, this study puts participants in control of their own brain stimulation. This increases experimental efficacy as participants can interactively review and update ICMS parameter settings according to their tactile experience. Moreover, the experimental design allows for the identification of ICMS parameters that significantly influence tactile sensation in an engaging way.

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Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P415.08

Topic: D.04. Somatosensation – Touch

Title: Somatosensory Duration Mismatch Negativity in Young Adults

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Abstract: Compared to other sensory domains, few studies exist that examine the neurophysiology of tactile perception. There are many disorders that involve dysregulated somatosensory processing, such as autism spectrum disorder and sensory processing disorder, yet little is known about the neurological underpinnings of atypical tactile sensitivity. In this experiment we aim to clarify the role of predictability in how the brain responds to tactile stimulation in neurotypical young adults. This study used a

somatosensory duration mismatch negativity (MMN) paradigm to assess vibrotactile novelty detection in 17 neurotypical young adults. The MMN is a specific event-related potential that occurs when a repeated sequence of identical, predictable 'standard' stimuli is interrupted by a novel, unpredictable 'deviant' stimulus that differs from the standard majority. By maintaining one stimulus as the majority of the input (80%), any perceived deviation from the anticipated stimulus results in a distinct, measurable electrophysiological response. In this study, vibrations of standard (100 ms) and deviant (115, 130, 145, and 160 ms) durations were presented while an electroencephalogram (EEG) measured cortical activity. Difference waves were calculated by subtracting the standard waveform from each respective deviant waveform. Peak amplitude of the difference wave was extracted from fronto-central electrodes between 150 and 210 ms after stimulus presentation to represent the MMN. The average peak difference wave amplitudes and standard deviations were as follows: 115 ms: -.54 (.60) μV, 130 ms: -1.15 (.66) μV, 145 ms: -.85 (.65) μV, 160 ms: -1.05 (.69) μV. A one-way ANOVA revealed a statistically significant difference in MMN amplitude between at least two groups ($F(3,64) = 2.88$, $p = .04$); this effect was driven by a significant difference between the 115ms and the 130ms amplitudes $t(16) = 3.58$, $p = .003$). This paradigm effectively captures cortical discrimination between predictable and unpredictable tactile stimulation. The differentiation of amplitudes in response to the deviant conditions indicates that this measure is sensitive not only to the presence of novelty, but also the degree of the novelty. We plan to expand this experiment to be used as a biomarker for tactile sensitivity in clinical populations.

Disclosures: E. Isenstein: None. **A. Xu:** None. **I. DeAndrea-Lazarus:** None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

P415. Stimulus Feature Neural Coding: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P415.09

Topic: D.04. Somatosensation – Touch

Title: Neural correlates of sensorimotor attenuation in a tetraplegic human

Authors: *T. GEORGE[1], M. SINGHALA[2], A. CASAMENTO-MORAN[3], R. NICKL[3], A. PAWAR[3], D. MCMULLEN[4], G. CANTARERO[3], J. BROWN[2];
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Abstract: Sensorimotor attenuation (SMA) is a phenomenon where a self-generated touch feels weaker than an externally generated touch of the same intensity. Because the brain can predict the sensory consequences of our own actions, it uses that prediction to attenuate afferent sensory feedback of our own movements, thereby increasing the saliency of external signals. Previous studies suggest that SMA is mediated by premotor cortical inputs to somatosensory cortex (Voss M et al., 2006). Although, some theories argue that SMA is based on efference copies of motor commands from primary motor cortex (M1) to other areas such as the cerebellum and primary somatosensory cortex (S1), our knowledge of the neural correlates of SMA in S1 and how it is related to the perception of SMA is lacking. To better understand the role of S1 in SMA, we performed, to our knowledge, the first study of SMA in the

sensorimotor domain in a human using intracortical recordings. The participant was a tetraplegic male with preserved cutaneous sensation (age 50 y.o., C5/C6 ASIA B), who was implanted with 3 microelectrode arrays in S1 (Blackrock Microsystems). We recorded the perceptual and multi-unit activity (MUA) and event-related potentials (ERPs) as the participant performed a bimanual, force comparison, self-touch paradigm with two taps per trial. The first tap of 2N, was either self-generated by the participant or externally generated by a motor. The second tap was externally generated by a motor and consisted of a range of force values. The participant was asked to identify whether the second tap was felt to be perceptual equal to the first tap. As a control, we repeated the paradigm on a sample of healthy adults without sensorimotor injuries (n=18, Average Age: 30.68+/- 12.42). We tested two hypotheses; (1) SMA would be retained given that sensation was preserved in the patient. (2) Neural activity in S1 would differ between the self and externally generated conditions; that is, MUA firing rates and ERPs would be lower in the self-generated condition than the externally generated condition, consistent with attenuation. Our healthy control results showed a perceptual attenuation of self-generated forces compared to externally generated forces. However, the patient showed no perceptual SMA of self-generated force compared to an externally generated force. Importantly, neural activity matched perception; there was no difference in S1 event-related activity and MUA between the two experimental conditions. Our results suggest that perceptual SMA is not observed in our tetraplegic participant and that the S1 MUA and ERP activity is closely related to the behavioral perception of force intensity.

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Poster

P415. Stimulus Feature Neural Coding: Humans

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Topic: D.04. Somatosensation – Touch

Support: EU Horizon 2020 grant agreement 813713 (NeuTouch)
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Title: Imaging dynamic sub-surface skin strain patterns during object interaction using Optical Coherence Tomography

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Abstract: The fingertip acts as an efficient tactile sensing organ with high acuity and sensibility. It is populated by thousands of mechanoreceptors responsible for translating the various aspects of the skin deformations into spike trains. However, receptors are located within the skin and separated from the surface, where object contact happens, by several layers of skin tissue. Little is known about the biomechanics of the skin below its immediate surface, even though sub-surface skin strains are ultimately

transduced by mechanoreceptors to form the first stage of sensory encoding in the tactile system.
In this study, we employ Optical Coherence Tomography (OCT), a non-invasive imaging technique appropriate for biological tissue, to capture the skin's internal morphology. The recorded data consists of images acquired with OCT at a rate of 20 frames per second and presents a sliced side view along the proximal-distal axis of the fingerpad with high spatial resolution (7.5 μm lateral and 5μm axial resolution). The images capture the finger pad while various surfaces slide against it along the imaging direction. The skin surface, the epidermal ridges, the stratum corneum, and the dermis-epidermis ridges can be identified in the acquired images.
To study the biomechanics of the captured tissues, we first tracked features of the movement of the skin in different layers. Then we reconstruct time-varying strain patterns to derive the local skin strain changes at different depths. In particular, a Delaunay triangulation was computed over the tracked features, and for each triangle, displacement field gradients were derived within adjacent frames and used to calculate Green-Lagrange strains. This technique allows us to reconstruct the skin mechanics at the location where mechanoreceptors are typically located.We found stereotypical spatiotemporal patterns of mechanical strain that depend on the mechanical, elastic, and geometrical features of both the sliding object and the skin. Interestingly, we observed differences in the strain propagation between and within different skin layers.
This study provides valuable insight into the mechanical transduction process at different skin layers. The data will help understand how surface strains propagate into deep layers of the skin tissues towards mechanoreceptor locations and shed light on the nature and function of skin morphology in encoding tactile stimuli.

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Poster

P415. Stimulus Feature Neural Coding: Humans

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Program #/Poster #: P415.11

Topic: D.04. Somatosensation – Touch

Title: Age-related changes of Merkel cell distribution in the human cheek and visualization of touch force propagation to activate Merkel cells

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Abstract: The face and fingers have high tactile sensitivity relative to other body parts and can be used for communication. As we get older, tactile sensation decreases in most body parts. One of the causes of tactile deterioration is thought to be a decrease of mechanoreceptors, such as Merkel cells (MCs), which transmit gentle touch sensations to nerve fibers. Surprisingly, recent studies have shown a new role for MC activation to reduce age-related itching.

Despite the importance of MC activation, the actual state of age-related changes in MCs in the face has not been investigated. Our aim was to clarify how the density and distribution of MCs—and connected nerve fibers in the cheek skin—change with age to propose a touch method that efficiently transmits tactile sensation even if there are fewer MCs.
Since only a few MCs were observable in vertical cross-sections of skin, we prepared epithelial sheets to acquire the distribution of MCs in horizontal sections of skin. Human cheek samples were obtained from 7 donors (60.9±23.0y). Those samples were stained by antibodies against K8 and K20 and observed using confocal laser scanning microscopy. PGP9.5 and NF200 immunostaining was also performed in the cross-sections from the same subjects and quantified. Cluster analysis was applied to evaluate the distribution of the MCs. Finally, a finite element method (FEM) was used to find an effective touch method when transmitting tactile sensation in consideration of the mechanical behavior of skin when pushing the cheek with a rigid object imitating a finger.
As a result, MCs were found around the hairs, glands, and ridged parts of the skin in accordance with previous reports. Surprisingly, MCs were basically scattered in cheek skin, but not clustered like a touch dome. MC density showed a dramatic reduction of roughly 75% when comparing a 27-year-old ($26.4 MCs/mm^2$) to a 91-year-old ($6.7 MCs/mm^2$). A comparison of A-fiber and MC densities in the same donor showed a positive correlation. Cluster analysis showed that MCs decreased in each small group, when the cutoff value was 50um in the complete linkage method. Taken together, these results suggest that they decrease as part of a MC-neurite complex rather than independently as single MCs.
In addition, we found that increasing the boundary of the contact surface between the finger and cheek is effective for transmitting strain energy to the surface layer of the skin where MCs are present.In conclusion, we observed a scattered distribution of MCs in the human cheek and a decrease in MC and A-fiber density due to aging. FEM analysis showed that the possibility of maintaining tactile sensation and alleviating itch regardless of fewer MCs.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

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Topic: D.06. Auditory & Vestibular Systems

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Title: Cortical projection neurons differentially contribute to the acquisition and expression of an auditory categorization task

Authors: *R. F. KRALL, M. P. ARNOLD, C. N. CHAMBERS, M. K. FRUM, R. S. WILLIAMSON; Otolaryngology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Sensory-guided behavior is ubiquitous in everyday life, whenever sensory information is used to guide the decisions we make and the actions we take. During sensory-guided behavior, distinct populations of neurons work to encode relevant sensory information and to transform it into an appropriate behavioral response. A fundamental open problem is identifying which neural circuits contribute to such behaviors. In the auditory system, information is first propagated through a feed-forward hierarchy that runs from the cochlea to the primary auditory cortex (ACtx). Corticofugal neurons in the ACtx send extensive projections to multiple nodes of this ascending auditory pathway as well as targeting distinct downstream regions associated with decision making, action, and reward. Through these diverse projections, corticofugal neurons are positioned to widely broadcast behaviorally-relevant information and shape auditory representations across brain-wide networks. We hypothesized that distinct classes of ACtx projection neurons critically and differentially mediate auditory-guided behaviors. To test this hypothesis, we developed a head-fixed behavioral task, where water-restricted mice are trained to categorize auditory stimuli into two groups to receive a water reward. Mice are tasked with categorizing amplitude-modulated noise bursts by licking one of two spouts yoked to the modulation frequency. To determine the role of ACtx in this behavior, we optogenetically silenced excitatory neurons during stimulus presentations using soma-targeted *Guillardia theta* anion-conducting channelrhodopsins (GtACRs). We found that sparse inactivation (20% of trials per session) of ACtx excitatory neurons did not disrupt task learning across days, allowing us to assess the contribution of ACtx neural populations longitudinally across task acquisition and expression. We found that inhibition of excitatory neurons in the ACtx altered task performance in a manner dependent on the extent of learning and task difficulty. Our ongoing research seeks to characterize the specific contributions of distinct ACtx projection neuron class using selective expression of GtACRs to inhibit activity across task acquisition and expression.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

Location: Virtual Only

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Topic: D.06. Auditory & Vestibular Systems

Support: Centre of Reconstructive Neuroscience, registration number CZ.02.1.01/0.0./0.0/15_003/0000419

Title: Noise exposure in postnatal critical period accelerates development of perineuronal nets in the rat auditory cortex

Authors: *J. SVOBODOVA BURIANOVA[1], J. W. FAWCETT[2], J. C. KWOK[3], J. SYKA[1]; [1]Inst. of Exptl. Med. CAS, Prague, Czech Republic; [2]John Van Geest Ctr. for Brain Repair, Univ. of

Cambridge, Cambridge, United Kingdom; [3]Sch. of Biomed. Sciences, Fac. of Biol. Sci., Univ. of Leeds, Leeds, United Kingdom

Abstract: In the rat auditory system, a period of increased vulnerability to external stimuli (known as the critical period, CP) starts with the onset of hearing (PD 12) and ends around three weeks later. It is expected that the closing of the critical period is paralleled with maturation of perineuronal nets (PNNs), lattice-like extracellular matrix structures that appear around the soma and proximal dendrites of mainly parvalbumin (PV) expressing inhibitory neurons. The exposure to loud sound during the CP can significantly affect morphology and electrophysiology of neurons in the rat auditory cortex. Whether the exposure can also change the pattern of PNN maturation remains unknown. Long-Evans rats were exposed at PD14 to a 125 dB SPL broad-band noise for 8 min. The content of PNNs was evaluated in auditory cortex sections stained for *Wisteria floribunda* agglutinin in exposed rats aging from PD14 to PD106, and compared with non-exposed controls. We did not observe visible PNNs at PD14, neither in the exposed animals nor in the controls. PNN appeared in both groups, however, in a significantly greater number in exposed than control animals. The number of PNNs further increased at PD28, but the difference between groups remained to be present. The development of PNNs of both groups had aligned since PD35. Interestingly, despite the different onset of PNNs development, no morphological differences in PNNs between the groups were found in PD106 when PNNs are considered mature. To summarize, the early development of PNNs appeared to be more accelerated in the noise-exposed animals than in the non-exposed controls. These results suggest that noise exposure may lead to a premature closing of the CP window, thus limiting the plasticity of early postnatal development in the auditory cortex. In ongoing part of the experiment, using fluorescence staining, we plan to determine to what extent the accelerated development of PNN occurs in PV neurons by evaluating colocalization PNN with PV and PNN with GAD (glutamate dehydrogenase) that labels all GABAergic inhibitory neurons.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

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Title: Distinct populations of cortical projection neurons are differentially modulated by arousal

Authors: *K. J. KAUFMAN[1], R. F. KRALL[2], M. P. ARNOLD[2], R. S. WILLIAMSON[2];
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Abstract: Fluctuations in behavioral state, such as attention and arousal, persist during wakefulness and influence both task performance and sensory information processing. Many studies have now reported

strong correlations between pupil diameter, a biomarker of arousal state, and evoked neural activity in multiple sensory cortices. Lin et al (2019) found that arousal modulates both the frequency tuning and response magnitude of L2/3 pyramidal neurons in the primary auditory cortex (ACtx). ACtx pyramidal neurons massively innervate a variety of downstream targets, both within and outside of the central auditory pathway. These corticofugal neurons comprise a diverse set of projection neurons with unique anatomy, morphology, and intrinsic and synaptic properties. Corticofugal neurons broadly fall into three classes: intratelencephalic (IT), extratelencephalic (ET), and corticothalamic (CT). The distinct anatomy and connectivity profiles of these cells lead us to hypothesize that arousal states may differentially modulate their sensory tuning properties. To investigate this, we recorded neural activity from ACtx with two-photon calcium imaging in awake mice while simultaneously capturing facial movements and pupil dilations using high-speed videography. We drove GCaMP expression in IT/ET/CT populations through Cre-dependent viral transfection of GCaMP8s. Similar to Lin et al. (2019), we found arousal-dependent changes in the tuning properties of L2/3 IT cells, evidenced by an increase in bandwidth and response magnitude coinciding with higher arousal states. Our preliminary data suggests that the effect of arousal differs in other projection classes, with response magnitudes peaking at intermediate levels of arousal, following the classic inverted-U dependence (Yerkes-Dodson curve). The characterization of these state-dependent effects on distinct excitatory populations offers a key-first step towards understanding how sensory information is shared brain-wide to guide perception and action.

Disclosures: K.J. Kaufman: None. **R.F. Krall:** None. **M.P. Arnold:** None. **R.S. Williamson:** None.

Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

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Support: GM122645
MH123260.

Title: Auditory Long-range Parvalbumin Cortico-Striatal Neurons

Authors: *A. BERTERO, H. ZURITA, M. NORMANDIN, A. J. APICELLA;
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Abstract: For over 30 years the assumption has been that cortical auditory input to the striatum is exclusively excitatory. Only recently our lab showed a direct inhibitory projection from the cortex to the striatum via somatostatin-expressing neurons. Here we have characterized the nature and physiological impact of a previously unknown long-range GABAergic projection from the auditory cortex to the striatum via parvalbumin-expressing neurons. Particularly, we tested the hypothesis that the auditory cortex, via cortico-striatal parvalbumin-expressing neurons (CS-Parv), has a direct inhibitory projection to the dorsal striatum. We addressed this fundamental question by taking advantage of in vitro viral and non-viral anatomical, and electrophysiology approaches, demonstrating that the dorsal striatum not only receives glutamatergic excitatory inputs from the cortex but also inhibitory inputs. Our results establish a

previously unknown cortico-striatal long-range inhibitory circuit (**CS-Parv inhibitory projections → striatum**). We also demonstrated that the CS-Parv neurons have higher concentrations in infragranular layer (layer 5 and 6 of the auditory cortex). This is not reflecting the overall Parv neurons distribution, which generally show higher abundancy in layer 4, paralleling the distribution of excitatory auditory cortico-striatal projections. Moreover, we analyzed their characteristic voltage-dependent membrane potential gamma oscillation, generated by intrinsic membrane mechanisms and able to trigger intermittent and irregular bursts (stuttering) of action potential in response to steps of depolarizing current pulses. In fact, the first action potential of layer 5 CS-Parv neurons burst is triggered by an oscillation, whose frequency is in the gamma range (30-100 Hz), while the second action potential was maintained by a different membrane mechanism. These findings are very important for understanding how the transformation of auditory signals to an appropriate behavioral output is achieved by the dynamic interaction of specific neuronal circuits that process information through different cell-types. A direct inhibitory input to the dorsal striatum may suggest that the timing and ratio of excitation and inhibition, two opposing forces in the mammalian cerebral cortex, can dynamically affect the output of the striatum, providing a general mechanism for reward-learning, and action-selection behavior driven by auditory stimuli.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

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Topic: D.06. Auditory & Vestibular Systems

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R00DC015014

Title: Spatiotemporal dynamics of auditory responses of cholinergic projections to the auditory cortex

Authors: *F. ZHU[1], S. E. ELNOZAHY[1], J. LAWLOR BLONDEL[1], K. KUCHIBHOTLA[1,2];
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Abstract: The cholinergic basal forebrain (CBF) projects extensively to the cortical mantle, including to the auditory cortex (ACx). Multiple studies have shown that pairing external phasic stimulation of the CBF with a sensory stimulus drives long-lasting sensory cortical plasticity. For this to be a plausible mechanism of cortical plasticity during learning (i.e. without external stimulation), we hypothesize that the CBF should also exhibit a stimulus-evoked response. This phasic, sensory signal from the CBF potentially allows neutrally-valenced sensory stimuli to drive cortical plasticity. To date, however, little is known about the intrinsic sensory-evoked dynamics of the CBF.
Here, we use simultaneous two-color, two-photon imaging of CBF axon projections and cortical neurons in the ACx to examine stimulus-evoked responses in head-fixed mice passively-listening to a suite of auditory stimuli. We observed a striking, non-habituating, phasic response of CBF axons to neutral

auditory stimuli that depends on the level of tonic cholinergic activity, a known neural correlate of brain state. We then tested whether CBF axons exhibit 'tuning' in the frequency-dimension and whether that tuning correlates with the surrounding cortical network at a mesoscopic (tonotopy) or microscopic (nearby neurons) level. We observed no evidence of tonotopy in CBF axons; there is a coarse population tuning to low-to-mid frequencies that was consistent across the ACx. Interestingly, individual axon segments exhibited heterogenous tuning within imaging sites, allowing the CBF to respond to all the frequencies presented. Despite this microscopic heterogeneity, the tuning of axon segments and nearby cortical neurons was un-coupled. Finally, we investigated the sources of auditory information to the CBF. Using chemogenetic inactivation of the ACx and auditory thalamus while imaging CBF axons in the ACx, we demonstrate that inactivation of the auditory thalamus, but not the ACx, abolishes the frequency tuning of CBF axons and significantly dampens their responsiveness.
Our work proposes a novel, non-canonical function for the CBF in which it receives auditory input from the auditory thalamus, modulates these signals based on brain state, and then projects the multiplexed signal to the ACx. These signals are temporally-synchronous with cortical responses but differ in their underlying tuning, providing a potential mechanism to influence cortical sensory representations during learning and task engagement.

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Poster

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National University of Singapore Young Investigator Award (NUSYIA_FY16_P22)

Title: Different excitation-inhibition correlations between tone-evoked and spontaneous activity in primary auditory cortex neurons

Authors: K. C. M. CHEW, V. KUMAR, ***A. Y. Y. TAN**;
Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Tone-evoked synaptic excitation and inhibition are highly correlated in many primary auditory cortex neurons of pentobarbital-anesthetized rats. In contrast, there is less correlation between spontaneous excitation and inhibition in visual cortex neurons under the same anesthetic conditions. The corresponding correlation between spontaneous excitation and inhibition in the primary auditory cortex has not been measured. Here we report whole-cell voltage-clamp measurements of excitation and inhibition in primary auditory cortex neurons of pentobarbital-anesthetized rats. Spontaneous excitatory and inhibitory currents each appeared to consist of distinct events. The event rate was lower for inhibition than for excitation in many neurons. The spontaneous inhibitory event rate was sufficiently lower than the spontaneous excitatory event rate to suggest a lower excitatory-inhibitory correlation for spontaneous

activity than for tone-evoked responses in a subset of neurons with highly correlated tone-evoked excitation and inhibition.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

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Title: Auditory cortical projection neurons exhibit distinct organizational motifs

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Abstract: The auditory pathway is a beautifully complex series of brain stations that are dedicated to the processing and interpretation of our sense of sound. Incoming sensory signals traverse an ascending hierarchy from the cochlea to the primary auditory cortex (ACtx), before being propagated brain-wide through networks of excitatory projection neurons to inform emotion, attention, decision-making, and action. These neurons fall into three broad classes: intratelencephalic (IT), extratelencephalic (ET), and corticothalamic (CT). Of these classes, ET cells are unique as they form the only direct connection between the ACtx and myriad sub-cortical targets. Their distinct morphology, with prominent apical dendrites and diverse axonal targets, has led to their portrayal as canonical “broadcast” neurons that pool inputs and transmit signals throughout the brain. ET cells typically exhibit “one-to-many” connectivity motifs, placing them in a privileged position to broadcast sensory signals to multiple downstream targets simultaneously. However, the extent of their axonal collateralization, the spatial organization of their projections in downstream brain regions, and whether or not these distinct organizational motifs receive differential synaptic input remains unknown. To address these questions, we characterized the input/output circuitry of ACtx ET cells and compared their anatomical organization to that of IT and CT populations. Using an intersectional strategy utilizing both Cre- and Flp-recombinase, we drove selective expression of adeno-associated viruses in distinct sub-populations of ET cells, allowing us to both quantify downstream projection densities with high spatial resolution and identify local and long-range synaptic input through monosynaptic rabies tracing. Our preliminary results indicate that the majority of ET neurons collateralize to the non-lemniscal regions of the inferior colliculus and thalamus, confirming previous reports (Chen et al, 2019). Monosynaptic rabies tracing demonstrated widespread synaptic inputs to both ET and CT cells from many cortical and subcortical areas, including the thalamus, contralateral ACtx, as well as ipsilateral visual, somatosensory, and retrosplenial cortices. Our ongoing experiments are focused on extending these findings to distinct ET organizational motifs. This work will provide a foundation for understanding how brain-wide interactions between distinct areas cooperate to orchestrate sensory perception and guide behavior.

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Poster

P437. Auditory Processing: Circuits, Synapses, and Neurotrasmission I

Location: Virtual Only

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Program #/Poster #: P437.08

Topic: D.06. Auditory & Vestibular Systems

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Beckman Institute for Advanced Science and Technology

Title: Layer-specific branching patterns of mouse auditory cortico-collicular neurons

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Abstract: Multiple studies have shown that the auditory cortex exerts a powerful, yet heterogeneous, effect on the inferior colliculus. Similar to the corticothalamic system, cortico-collicular projections emanate from two distinct bands in the auditory cortex: one from layer 5 and the other from layer 6. These projections have distinct physiological and anatomic properties and likely have different roles in modulating their subcortical targets. In addition, while several studies have suggested that corticofugal projections from layer 5 branch widely to subcortical structures, other studies have suggested that there are multiple, mostly independent sets of layer 5 corticofugal projections. Even less is known about layer 6; no studies have examined whether layer 6 corticothalamic and cortico-collicular projections are independent. Therefore, we examined this issue using an intersectional anatomical approach employing viral tracers. A flippase-inducing, Cre-dependent retrograde transported Canine adenovirus virus 2 (Cav-flx-flp) was injected into the inferior colliculus of RBP4 (Layer 5)-Cre or FOXP2 (Layer 6)-Cre mice, followed by a flippase-dependent AAV9-mCherry virus into the auditory cortex. We found that this approach strongly labels layer 5 or layer 6 cortico-collicular neurons, respectively, and their branches. As expected from previous work (Asokan et al. 2018), layer 5 cortico-collicular branches heavily innervated the auditory thalamus. Layer 5 cortico-collicular branches were also seen across a spectrum of other subcortical targets, including striatum and amygdala, but not in the contralateral auditory cortex. Layer 6 cortico-collicular neurons also showed unexpectedly wide branching, with terminals throughout the thalamus and other subcortical forebrain and midbrain targets. These data suggest that both layer 5 and layer 6 cortico-collicular widely branch to subcortical targets, supporting the notion that one mode of action of corticofugal pathways to broadcast signals widely throughout the subcortical auditory system.

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Poster

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Title: Synaptic zinc release at specific cortical synapses shapes intracortical synaptic transmission in mouse auditory cortex

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Abstract: The primary auditory cortex is crucial for the perception of sounds. It contains highly organized networks of neurons that form precise synaptic microcircuits and process auditory information. Despite the importance of synaptic microcircuit organization of the cortex and the different functional properties of these synapses for auditory function, synaptic mechanisms that support the diversity and specificity of these connections are less-well understood.
This cortical area is highly enriched in synaptically released zinc which acts as a potent modulator of cortical function and sound processing. Zinc (as Zn2+) is loaded into synaptic vesicles by the zinc transporter protein ZnT3 where it is coreleased with glutamate during synaptic transmission. Synaptically released zinc shapes multiple aspects of synaptic signaling and can inhibit AMPA and NMDA glutamate receptor function. Mounting evidence strongly suggests that synaptic zinc is only released from a subset of glutamatergic cortical neurons and in a cortical layer-specific manner. Since the principals governing cortical microcircuit organization relate to both cortical layer and neuronal type, this suggests that synaptic zinc may contribute to the specificity and diversity of intracortical synaptic microcircuits.
Here, to understand the role of synaptic zinc signaling at specific cortical synapses, we optogenetically stimulated different presynaptic neuronal populations and recorded the synaptic inputs they provide to the same class of postsynaptic cortical neuron. In acute brain slices of the auditory cortex, we performed whole-cell patch-clamp recordings from identified layer 5 corticocollicular neurons while optogenetically stimulating inputs from specific presynaptic neuronal populations of cortical Cre-expressing neurons in layer 2/3 and layer 5. Our results reveal that the effects of synaptic zinc release are cell-type specific and we also find a novel role for synaptic zinc in potentiating AMPA receptor function at specific intracortical synapses. Together, these results reveal a novel role of synaptic zinc within the cortex and suggest that synaptic zinc signaling contributes to the diversity and specificity of intracortical synaptic connections that support normal cortical function and auditory processing.

Disclosures: P.T.R. Bender: None. **C.T. Anderson:** None.

Poster

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Title: Differential Effects of Synaptic Zinc on Sound-Evoked Responses of Long-Range Cortical Projection Neurons in the Mouse Auditory Cortex

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Abstract: The primary auditory cortex is crucial for the perception of sound. This structure integrates ascending auditory information with a variety of corticocortical and thalamocortical input and sends descending long-range axonal projections to subcortical auditory processing areas such as the striatum, thalamus, inferior colliculus, and brainstem. As a monosynaptic connection from the auditory cortex, these long-range axonal projections allow cortical input to directly influence the activity of neurons in subcortical auditory structures. In layer 5 of the auditory cortex, there are two major classes of long-range projection neurons: pyramidal tract (PT)-type neurons and intratelencephalic (IT)-type neurons. Although it is known that these long-range projection neurons are important for dynamic tuning, auditory learning, and auditory plasticity, much less is understood about the intracortical synaptic mechanisms that shape their activity. The auditory cortex is highly enriched with synaptic zinc. Zinc (as Zn^{2+}) is loaded into presynaptic vesicles by the membrane zinc transporter protein ZnT3 and is coreleased with glutamate during synaptic transmission. Synaptic zinc is a potent modulator of synaptic signaling and refines the sound-encoding properties of layer 2/3 auditory cortical neurons in a cell-type specific manner. Since long-range projection neurons integrate information from a variety of local sources (including layer 2/3 neurons) and convey these computations to multiple targets, they are the key link between cortical processing and subcortical signaling. However, the effect of synaptic zinc signaling on the sound-evoked activity of these long-range projection neurons remains unknown.Here, we performed widefield and 2-photon calcium imaging from PT and IT-type neurons in layer 5 of the auditory cortex in awake mice. We find that synaptic zinc signaling differentially shapes the sound-evoked properties of these layer 5 long-range projection neurons. Synaptic zinc increases the sound frequency tuning bandwidth and suppresses the response gain of PT-type neurons while it has the opposite effects on layer 5 IT-type neurons. By differentially supporting the sound frequency tuning and the response gain of these neurons, synaptic zinc serves to support the diverse sound-evoked properties of these neuronal populations. Our experiments reveal a novel role for synaptic zinc in shaping the output of long-range projection neurons in the auditory cortex and suggest a novel intracortical mechanism capable of modulating auditory processing.

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Poster

P446. Auditory Processing: Brain Network

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Topic: D.06. Auditory & Vestibular Systems

Title: Decoding selective attention from EEG during simultaneous presentation of two melodies

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Abstract: Introduction: People can pay selective attention to music or speech from various sounds. It has been reported that while speeches are presented, the attentional task not only enhances neural entrainment [1] but also affects the spatial distribution of electroencephalogram (EEG) [2]. However, the attentional effect on EEG is still unclear when listening to multiple pieces of music at the same time. In this study, we hypothesized that attention under multiple music presentations would enhance neural entrainment to the attended music and that the spatial distribution of EEG is different depending on the attentional task. Methods: Fifteen healthy young adults (eight males, mean age 21.7 ± 1.16; range 20–23 years old) participated in the experiment. All participants had normal hearing. They gave their written informed consent, and the research ethics committee approved the study in the institution. In this experiment, we measured EEGs while two melodies with different tempos were presented simultaneously from spatially different directions. The participants were instructed to pay attention to one of the melodies. In the analysis, the cross-correlation function calculated between the filtered EEG (0.4–40 Hz) and the envelope of the melodies was used as a feature to classify the direction of attention using a support vector machine (SVM). Next, to search the effect of attention on the spatial distribution, we extracted features by the common spatial pattern (CSP) method from both EEG and cross-correlation function, respectively. For each feature, we estimated the direction of attention using the SVM. Results: As a result of task classification using the cross-correlation function as a feature, three participants achieved a classification accuracy of over 90%. Therefore, as well as speeches, attention affects neural entrainment when listening to melodies. Furthermore, in the classification results using CSP as a feature, nine participants achieved a classification accuracy of over 90%. Hence, we found that attention affected neural entrainment and the spatial distribution under the presentation of multiple pieces of music.References:[1] Horton et al., *J. Neurophysiol.*, 2013[2] Deng et al., *NeuroImage*, 2020

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Poster

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Topic: D.06. Auditory & Vestibular Systems

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Title: Auditory discomfort in migraine and the visually sensitive

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Abstract: Sensory sensitivity is commonly reported in a range of clinical conditions, including migraine. While stimuli that evoke visual discomfort are well-defined, little is known about auditory discomfort. Here, we manipulated pitch and the manner in which it was varied in three separate experiments to begin to map the parameters of auditory stimuli that make them uncomfortable to hear. We then compared the discomfort reported from individuals with migraine (total N=65) and headache-free controls (total N=60). In Experiments 2 and 3, we also measured number of illusions seen in the Pattern Glare (PG) Test to examine whether those individuals who experience visual sensitivity (>=2 illusions) exhibited greater discomfort to the sounds compared to those with low PG (<2 illusions). In Experiment 1 (N=58; 46F/12M/1 declined; age 18-32 years), we measured discomfort to amplitude-modulated (AM) tones that differed in their pitch (250-8000Hz) and modulation frequency (0-32Hz). Discomfort significantly increased with pitch (p<.001). Discomfort also increased with modulation frequency (p=.027) but higher modulation frequencies reduced the effect of pitch on discomfort (p<.001). Specifically, 3000Hz and 4000Hz tones were significantly more comfortable when modulated by a 32Hz carrier than a 2Hz or 0Hz carrier. To further examine the effects of temporal presentation frequency, in Experiment 2 (N=70; 51F/18M/1 declined; age 18-27 years), we manipulated the number of frequency-modulated (FM) sweeps presented per second (5-50Hz). As with the AM tones, the greater the number of sweeps, the greater the discomfort (p<.001). In Experiment 3 (N=63; 34F/28M/1 declined; age 18-23 years), we manipulated the central frequency (625-1875Hz) and the range of frequencies (250-1500Hz) contained within FM sweeps. There was no linear effect of range on discomfort. However, the higher the central frequency, the greater the discomfort (p<.001; similar to the pitch of the AM tones). For all experiments, we found that individuals with migraine experienced slightly but non-significantly greater discomfort compared to those who were headache-free (ps>.05; Cohen's d~0.33). However, those with high PG reported more auditory discomfort than those with low PG (ps<.05; Cohen's d>0.5). This suggests that sensitivity in one sensory modality might generalize to another, and that those with migraine do not necessarily experience greater auditory discomfort. In addition, while temporal presentation (AM modulation and FM sweep frequency) impacted discomfort, pitch had stronger effects on discomfort.

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Poster

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Title: The interplay between uncertainty and relevance in sound categorization

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Abstract: Everyday hearing and communication require that we categorize sounds encountered under different levels of uncertainty or relevance. For example, background noise can reduce both the certainty about the sound we hear, as well as introduce irrelevant sound components. However, little is understood about how sound uncertainty and relevance affect perception. Bayesian theory postulates that both relevance and uncertainty affect human auditory categorization, while accounting for multiple strategies for their interplay. In the first experiment, to understand which strategy humans use in categorizing sounds with varying uncertainty and relevance, we asked subjects to categorize sequences of three tones into a high or low frequency category. The three tones were drawn from a complex probability distribution, such that the tones were 70% likely to be drawn from a "signal" Gaussian distribution with the mean of 354.8 Hz (low) or 707.9 Hz (high), and a standard deviation of 0.5 Octaves; or 30% from a uniform distribution over the 90-3000 Hz range. Subjects incorporated relevance in decision making using three different strategies - 1. Categorization based on the average of all three tones, 2. Categorization by averaging over the "signal" tones only, 3. Categorization using a voting strategy wherein each tone is individually classified as "high" or "low" and then a cumulative decision is made. We modeled this variability in strategies using an optimal Bayesian model that is built on uncertainty, formalizes relevance and estimates priors. We also analyzed the subject data using a generalized linear model (GLM) which captured the weight assigned to each experimental tone for categorization. Using parameters obtained from the Bayesian model and the GLM fits, we characterize the diversity in subjects' decision making. We found that while some subjects can be clearly found to follow one of the three strategies, others will combine them. In the second experiment, we asked how long-term statistics of sounds affects categorization by imposing a bias on the prior category probabilities. A subset of subjects detected the prior, which affected their categorization, while others did not. Subjects exhibiting behavioral long-term bias performed less accurately than unbiased subjects. Those exhibiting long-term bias used a combination of the voting and categorization based on mean of all tones strategies, whereas the others recognized irrelevant tones and classified trials according to the mean of the signal tones. Combined, our results provide for an elegant quantification for the interplay between estimating stimulus uncertainty and relevance in auditory categorization.

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Poster

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Topic: D.06. Auditory & Vestibular Systems

Title: Relationships between transducer placements and peripheral propagation of the cartilage-conduction assessed by hearing threshold with water injection into the ear canal

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Abstract: In bone-conduction (BC), a sound transducer is attached to the mastoid process of the temporal bone and the sound is transmitted as 4 components: (1) the osseotympanic component, (2) the inertial BC component, (3) the compressional BC component, and (4) the air-conducted (AC) component. BC has been applied to devices such as hearing aids for the conductive hearing loss. However, BC also has some disadvantage in wearability of a sound transducer. Therefore, cartilage conduction (CC) has been proposed and applied to devices such as hearing aids and smartphones. In CC, a sound transducer is placed on the cartilage portion of the pinna, and AC and the osseotympanic components are said to be dominantly transmitted. On the other hand, even in CC, the transducer often contacts not only with the aural cartilage but also with the osseous parts of/around the pinna and generate change of sound sensation. In this study, relationships between the transducer placements and the hearing thresholds were investigated. Contributions of AC and the osseotympanic components to CC perception were evaluated by blocking each of them using water injection into the auditory canal.5 normal-hearing participants took part in the experiment. The transducer was placed on (1) the pinna, (2) the mastoid process, and (3) the ear-front point (middle of between the tragus and the mandibular condyle). The hearing thresholds measurements were conducted under condition that participants' auditory canal was filled water. The amount of the injected water was varied 0, 20, 40, 60, 80 and 100% of the volume of the auditory canal. Under the water injection conditions, the increase of hearing thresholds in the pinna and ear-front point was generally larger than that in the mastoid. Since the increase of the hearing thresholds arise from AC and the osseotympanic components blocked by the injected water, it is thought that the contribution of AC and the osseotympanic components are larger for the pinna and ear-front point. However, in the low frequency range (250 and 500 Hz) for the pinna and ear-front point, the hearing thresholds decreased as the amount of the injected water increased. It is thought that as the injected water increases, the osseotympanic component which is dominant in the low frequency range is transmitted through the water. On the other hand, the effect of the amount of the injected water was not observed at the mastoid, indicating that contribution of the osseotympanic component is less than other locations.These results suggest that the proportion of the inertial and compressional BC components within the entire perception increases when the transducer is presented to the osseous parts.

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Poster

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Title: Acute impact of anterior temporal lobe disconnection on fronto-temporal neural signals

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Abstract: Understanding the impact and compensatory mechanisms of surgical disconnection on neural responses in the human brain could advance models of normal neurophysiology and its disruption by pathology. We present rare data from two patients (one woman and one man; 63 and 32 years of age, respectively) who underwent surgical disconnection of the anterior temporal lobe (ATL) as part of their clinical procedure to treat intractable epilepsy. During the surgery, we obtained both pre- and post-resection intraoperative electrocorticographic (ECoG) recordings while the patients were lightly sedated, but awake and responsive during a speech-sound perceptual prediction task. We also obtained pre- and post-operative magnetic resonance imaging (MRI) including T1 and T2 structural and diffusion-weighted scans. Diffusion MRI tractography from ATL seed regions confirmed disconnection of the temporal pole from other cortical areas. Post-disconnection neurophysiological responses to the speech sounds showed a striking dissociation from the pre-disconnection signal in the form of, 1) magnified responses in auditory cortex (Heschl's gyrus) across oscillatory frequency bands (3-150 Hz); and, 2) disrupted oscillatory responses in prefrontal cortex (Inferior Frontal Gyrus, IFG). Moreover, after the disconnection auditory cortical mismatch responses and theta-gamma coupling to the speech sounds were disrupted, while neural responses to different speech sounds became less segregable (i.e., more similar). State-space conditional Granger Causality analyses revealed substantial change in neural information flow between auditory cortex and IFG post disconnection. The results with these rare datasets demonstrate an immediate and incomplete compensation by intact frontal and auditory cortical areas responding to speech sounds after the loss of ATL neural signals.

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Poster

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Title: Functional geometry of human auditory cortical resting state networks derived from intracranial electrophysiology

Authors: *M. I. BANKS[1], B. M. KRAUSE[1], D. G. BERGER[1], D. I. CAMPBELL[1], H. KAWASAKI[2], M. STEINSCHNEIDER[3], K. V. NOURSKI[2];
[1]Anesthesiol., Univ. of Wisconsin Sch. of Med. and Publ. Hlth., Madison, WI; [2]Neurosurg., The Univ. of Iowa, Iowa City, IA; [3]Neurol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Introduction: Critical organizational features of human auditory cortex (AC) remain unclear, including the definition of information streams (e.g., dorsal, ventral) and the relationship of AC to non-auditory regions of interest (ROI). We investigated these features using diffusion map embedding (DME) applied to functional connectivity derived from intracranial electroencephalographic (iEEG) recordings in neurosurgical patients. DME maps data into a space in which distance represents similarity in connectivity to the rest of the sampled network, and has been applied previously to resting state functional connectivity data to elucidate the hierarchical structure of neocortex and structural changes across treatments, disorders, and aging. **Methods:** Resting state iEEG data were obtained from 41 adult neurosurgical patients (18 female). Data were analyzed from 5836 recording sites, including AC, temporo-parietal auditory, prefrontal (PFC), sensorimotor and limbic/paralimbic cortex. Data were denoised and segmented into 1-minute epochs, and functional connectivity was measured via gamma band power envelope correlations. Connectivity was averaged within ROI, then across subjects, thresholded (top 33%) and normalized to yield the transition probability matrix **P**, which was analyzed using DME. **Results:** The eigenvalue spectrum $|\lambda_i|$ of **P** showed a clear inflection for $i>3$, indicating that a 3-D representation is a reasonable approximation. The data in embedding space roughly formed a tetrahedron, with clusters of functionally-related ROIs at each of four corners: (1) AC; (2) temporal and parietal auditory-related; (3) limbic and paralimbic cortex; and (4) PFC. Some regions scattered along the edges (e.g. lower bank of the superior temporal sulcus [STS], planum polare [PP], insula, sensorimotor and anterior cingulate cortex) and in the interior of the data cloud (e.g., anterior portions of superior and middle temporal gyrus, and cingulate gyrus). Clustering in embedding space segregated data into hierarchically-related functional groups, including portions of dorsal and ventral auditory streams. **Conclusions:** Distances between the two banks of the STS, and between PP and the rest of AC, are consistent with previously reported functional segregation of these regions. ROIs in the interior of the data cloud may correspond to global hubs. The relative positions of (a) AC, (b) posterior vs anterior insula, PP, and anterior superior temporal gyrus, and (c) limbic ROIs suggest a distinct auditory limbic stream that may carry memory- and emotion-related auditory information.

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Poster

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Title: Comparison of functional geometry of cortical networks derived from functional magnetic resonance imaging (fMRI) versus intracranial electroencephalography (iEEG)

Authors: *D. G. BERGER[1], B. M. KRAUSE[2], D. I. CAMPBELL[3], A. D. BOES[4], J. E. BRUSS[5], H. KAWASAKI[6], K. V. NOURSKI[7], M. I. BANKS[8];
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Abstract: Introduction: Resting state networks (RSNs) are typically derived from fMRI, but iEEG offers superior spatiotemporal resolution. However, iEEG samples from only a subset of brain regions of interest (ROIs), with non-uniform electrode coverage of each ROI. Sparse, non-uniform sampling may distort RSNs derived from iEEG. We studied this issue by comparing cortical networks derived from iEEG vs fMRI data using diffusion map embedding (DME), which maps data into a space where distance represents similarity in connectivity to the rest of the network.
Methods: Resting state functional connectivity was obtained in 10 neurosurgical patients via iEEG [θ 3-8 Hz;α 8-12 Hz;β 12-30 Hz;γ 30-80 Hz; γH80-150 Hz power envelope correlations, n = 84 -220 recording sites/patient in temporal, parietal, and frontal cortex] and pre-surgical fMRI(BOLD time series Pearson correlations). MRI voxels corresponding only to electrode locations (er-fMRI) or to the full scan (f-fMRI) were used. DME analysis was applied to thresholded, normalized connectivity matrices for iEEG and fMRI data, which was compared via correlations between inter-node distances in DME space. Nodes are averaged across electrodes in an ROI (avgEl; iEEG, er-fMRI), or averaged across entire ROIs (avgROI; er-fMRI, f-fMRI). Three sets of comparisons are made: (1) iEEG_avgEl vs er-fMRI_avgEl, to inform the relevance of fMRI for evaluating iEEG; (2) er-fMRI_avgEl vs er-fMRI_avgROI, to evaluate non-uniform within-ROI sampling; (3) er-fMRI_avgROI vs f-fMRI_avgROI, to evaluate limited brain sampling.
Results: iEEG vs fMRI correlations (r =0.41 -0.64) were RSN and frequency band-dependent(Ctrl: α>β>θ>γH>γ, DMN: α>β>θ>γH>γ, dAttn: θ>β>α>γ>γH, Limbic: γ>β>α>γH>θ, Sal/vAttn: α>γ>θ>β>γH, SomMot: θ>α>γ>β>γH, Vis: θ>γ>γH>α>β). Correlations restricted to auditory cortex were 0.68 -0.87 (γH>γ>β>α>θ). Correlation across all sampled ROIs were 0.24 -0.54 (γ>γH>β>α>θ). Correlations for er-fMRI_avgEl vs er-fMRI_avgROI and f-fMRI_avgROI vs er-fMRI_avgROI were 0.49±0.13 and 0.88±0.031 (mn±SD across subject), respectively.
Conclusions: Correlations between iEEG and fMRI data are consistent with previous results, which motivates using fMRI data to evaluate the effects of limited, non-random sampling. Within RSNs, frequency dependence is variable, while in auditory cortex and across all ROIs fMRI matches iEEG best at higher frequencies. Correlations between f-fMRI_avgROI vs er-fMRI_avgROI show that network structure is retained when using a non-random sub-sample of ROIs. However, weaker er-fMRI_avgElec vs er-fMRI_avgROI correlations suggest that sparse sampling within a given ROI is more consequential.

Disclosures: D.G. Berger: None. **B.M. Krause:** None. **D.I. Campbell:** None. **A.D. Boes:** None. **J.E. Bruss:** None. **H. Kawasaki:** None. **K.V. Nourski:** None. **M.I. Banks:** None.

Poster

P446. Auditory Processing: Brain Network

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P446.08

Topic: D.06. Auditory & Vestibular Systems

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NHRI Taiwan: NHRI-EX109-10905NI

Title: Listening to music modulates the theta-gamma cross-frequency coupling of human cortical and subcortical neurons

Authors: H.-J. LEE[1,2], *W.-J. KUO[3,4], H.-Y. YU[5,4], C.-C. CHOU[5], C.-C. LEE[6,4], *F.-H. LIN[1,2]; [1]Physical Sci., Sunnybrook Res. Inst., Toronto, ON, Canada; [2]Dept. of Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [3]Inst. of Neurosci., [4]Brain Res. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [5]Neurol. Dept., [6]Dept. of Neurosurg., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Neuronal oscillations interact at different frequencies. Such cross-frequency coupling at the hippocampus is particularly active between the theta (5-10 Hz) and gamma (30-100 Hz) bands. In particular, the amplitude of gamma-band oscillation correlates with the phases of the theta-band oscillation. Phase-amplitude coupling (PAC) has also been reported for cortical neuronal oscillations in humans.

Here, we used stereo-electroencephalography (SEEG) data collected from epilepsy patients (n = 4) to study the PAC at both cortical and subcortical regions. Specifically, we examined the PAC at the hippocampus and the temporal lobe in both the resting state and during music listening. SEEG was recorded with 2,048 Hz. Electrode contacts were localized by magnetic resonance imaging.

Significant neuronal oscillation coupling was found between phases at theta-alpha (4-16 Hz) bands and amplitudes at beta-gamma (20-60 Hz) bands during the resting state at the hippocampus. This PAC was significant and reproducible during music listening. Strong PAC was found at the resting state at the auditory cortex between phases at theta-alpha (4-16 Hz) bands and amplitudes at beta-gamma (20-200 Hz) bands. PAC was strongly suppressed during music listening, showing significant PAC only between phases for 10-Hz oscillations and amplitudes around 40-Hz oscillations.

In summary, SEEG provided a spatiotemporally accurate recording of neuronal oscillations. The revealed task-dependent PAC in humans in both cortical and subcortical regions suggests the neural mechanism supporting the information processing and integration under naturalistic stimuli.

Disclosures: H. Lee: None. **W. Kuo:** None. **H. Yu:** None. **C. Chou:** None. **C. Lee:** None. **F. Lin:** None.

Poster

P446. Auditory Processing: Brain Network

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Program #/Poster #: P446.09

Topic: H.10. Human Learning and Cognition

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BBSRC (BB/J009849/1)
European Research Council (ERC CoG-MECHIDENT)
NIH (R01-DC04290, UL1-RR024979)

Title: Neurocomputational transformations of sequences into mental structures: Relational codes and fronto-temporal information flow

Authors: *R. M. CALMUS[1], B. WILSON[1,2,3], Y. KIKUCHI[1], Z. KOCSIS[4,1], H. KAWASAKI[4], T. D. GRIFFITHS[1], M. A. HOWARD, III[4], C. I. PETKOV[1];
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Abstract: Understanding how the brain represents and binds complex information distributed over time is a challenging problem, requiring computationally and neurobiologically informed approaches to solve. The combinatorial binding problem is highly relevant to language, where human syntactic knowledge facilitates 'movement' and hierarchical restructuring of words/phrases for perception and cognition. Yet the problem is also broadly relevant for cognitive neuroscience. For instance, structured-sequence-learning tasks engage fronto-temporal regions including inferior frontal areas 44/45 ("Broca's area") and the frontal operculum. However, how neural representations emerge as these and other areas interact - and by which binding mechanisms - remains unknown. We recently proposed a vector-symbolic computational model, VS-BIND, which triangulates reported findings across a broad fronto-temporal network, specifying mechanistic roles for regions including areas 44/45 and motor/premotor cortex during interactions with temporal cortex (Calmus et al., 2019). We test this model here using human behavioural and intracranial recordings obtained under an Artificial Grammar Learning (AGL) task in neurosurgery patients being monitored for epilepsy treatment. Under the AGL task, 12 patients listened to auditory speech sequences containing adjacent and non-adjacent dependencies, and were then tested on their ability to distinguish novel "grammatical" and "ungrammatical" sequences. We analysed intracranial data using traditional methods, demonstrating engagement of the fronto-temporal network, and additionally undertook a battery of established and novel multivariate analyses to reveal: 1) the representational geometry of regional speech encodings; 2) time-resolved representational patterns; and 3) causal representational information flow between fronto-temporal regions. The results reveal that certain prefrontal areas integrate relational information, including the ordinal position of items in a sequence, in concordance with site-specific predictions of the VS-BIND model. Furthermore, we observed net causal information flow consistent with feed-forward and feedback predictive signalling, suggesting that expectation-driven predictions are fed back to primary auditory cortex from areas including 44/45. These results indicate a critical role for fronto-temporal areas in transforming the sensory world into mental structures and, more specifically, provide evidence for the integration of key stimulus features using relational codes.

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Poster

P495. Context Modulation in Visual Pathways

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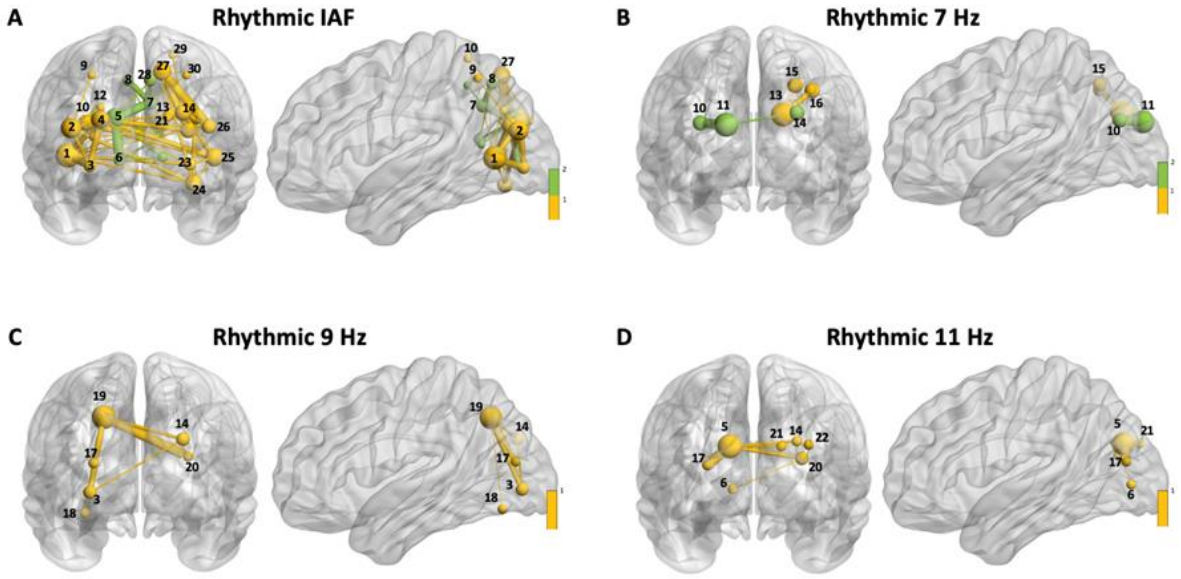
Program #/Poster #: P495.01

Topic: D.07. Vision

Title: Rhythmic visual stimulation at the subject specific intrinsic alpha frequencies causes increased connectivity within the occipito-parietal cortex

Authors: C. JAEGER, R. NUTALL, C. SORG, ***A. WOHLSCHLAEGER**;
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Abstract: The “communication through coherence” hypothesis poses that processing of the bottom-up information flow in the visual cortex is controlled by top-down processes in the alpha-beta band (Fries 2015 Neuron) which are inhibitory in nature. Posterior alpha range processes are a prominent feature in electrophysiological measurements. Individual subject exhibit different peak frequencies. Spontaneous power increases within the alpha frequency band during rest are associated with reduced fMRI functional connectivity (FC) within the occipital cortex (Scheeringa 2012 brain conn). Active stimulation via visual flicker leads to a reduced fMRI response (Parkes 2004 Neuroimage) conforming with the notion of inhibition. However, it remains unclear how decidedly targeting the subjects’ specific individual alpha frequencies (IAF) by a bottom-up process affects the intrinsic communication within the occipito-parietal cortex. We addressed this question by contrasting FC during sustained rhythmic flicker stimulation at the IAF to arhythmic stimulation as well as to stimulations at other frequencies of the alpha range. The preprocessed fMRI time series from the occipito-parietal cortex were parcellated into regions of the Glasser atlas (Glasser 2016 Nature) and cross-correlated for each flicker condition separately. The resulting FC measures were tested for connectivity differences between conditions (Zalesky 2010 Neuroimage). Rhythmic stimulation at the IAF induced significantly more connected networks that ranged across occipital and parietal regions and across hemispheres as compared to rhythmic stimulation at all other frequencies. This suggests that rhythmic stimulation at the IAF frequency results in entrainment and a higher degree of synchronization across occipital and parietal regions. Our results show that modulatory changes to the intrinsic alpha rhythm influences the degree of synchronicity of neural activity across the visual cortex and may thus help regulate visual information processing and communication during visual processing.



1 – L MST, 2 – L PGp, 3 – L V4, 4 – L V7, 5 – L V6, 6 – L V1, 7 – R 7m, 8 – R 7Pm, 9 – L LIPv, 10 - L IP0, 11 – V3A, 12 – L IPS1, 13 – R V6, 14 – R V7, 15 – R MIP, 16 – R IP1, 17 – L V3B, 18 – L V8, 19 – L MIP, 20 – R V3B, 21 – R V3A, 22 – R IP0, 23 – R V4, 24 – R V8, 25 – R MST, 26 – R PGp, 27 – R 7PL, 28 – R 7P, 29 – R 7AL, 30 – R LIPv

Disclosures: C. Jaeger: None. **A. Wohlschlaeger:** None.

Poster

P495. Context Modulation in Visual Pathways

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Topic: D.07. Vision

Support: NIH Grant R35NS097287
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Title: Visual Thalamocortical Mechanisms of Movement/Arousal-Related Activity and Alpha Oscillations

Authors: *D. NESTVOGEL, D. MCCORMICK;
Univ. of Oregon, Eugene, OR

Abstract: The brain exhibits highly variable patterns of spontaneous, ongoing activity that are commonly referred to as brain states. Brain states are strongly related to animal behaviors, such as the levels of motor movements and arousal, and are known to profoundly shape sensory responses and behavioral performance. The neural mechanisms underlying the generation and modulation of brain states are incompletely understood, but results from several studies suggest that the thalamus plays a central role in this process. Here, we studied the role of thalamocortical interactions in regulating two prominent brain

states in the primary visual cortex (V1) of awake mice - 1) a state-dependent 3-5 Hz oscillation that is thought to be an evolutionary precursor of the primate alpha oscillation and 2) rapid membrane potential depolarizations that occur during movement / high arousal. To this end, we employed intra- and extracellular electrophysiology techniques in awake behaving mice together with pharmacological and optogenetic manipulations. Our results indicate that the alpha-like oscillation in mice reflects a thalamocortical rhythm that involves low threshold Ca^{2+} spike (LTS) mediated action potential bursting in thalamic neurons, depends upon thalamocortical interactions and predominantly occurs following a reduction in movement and/or arousal. We further found that visual thalamic activity correlates strongly with the rapid arousal/movement-related membrane potential depolarizations in V1 and strongly shapes these signals in V1. Taken together, our results indicate that thalamocortical interactions together with cell-intrinsic properties of thalamocortical cells play an essential role in regulating the 3-5 Hz alpha-like oscillation and rapid membrane potential depolarizations of V1 cells during movements / high arousal. These two prominent brain states, in turn, are known to shape sensory responses and to impact behavioral performance.

Disclosures: D. Nestvogel: None. **D. McCormick:** None.

Poster

P495. Context Modulation in Visual Pathways

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Program #/Poster #: P495.03

Topic: D.07. Vision

Support: NIH Grant 1R01MH112583-01A1

Title: Joseph Emerson

Authors: *J. H. EMERSON[1], C. A. OLMAN[2];
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Abstract: Perception of visual features is influenced by context. The influence of context on low-level visual perception is observed in the orientation tilt illusion in which the perceived orientation of a grating stimulus is influenced by the orientation of a surrounding grating stimulus. This phenomenon can be explained by interactions between the classical receptive field (CRF) and the extra-classical receptive field (eCRF). Recent theoretical work suggests that a specific recurrent circuit motif implemented in primary visual cortex (V1) can account for the tilt illusion. This circuit motif posits that two subpopulations within the eCRF, an excitatory near surround and an inhibitory far surround, exert complementary influence on the CRF. While this work has shown that the steady-state activation of neural populations observed during the orientation tilt illusion can be recapitulated using this circuit motif, it has not yet been shown whether neural dynamics are similarly accounted for, which would provide important insights into the function of the underlying circuits. We hypothesized that by incorporating this circuit motif into a model based on recurrent amplification, the tilt illusion could be recapitulated, while providing more biologically plausible dynamics. We found that the model was

capable of reliably reproducing steady-state behavior expected in the tilt illusion, while also generating gamma oscillations (30-100 Hz), a proposed biomarker for normalization. This model provides testable predictions for future studies examining neural dynamics with EEG and MEG and identifies a plausible neural circuit mechanism for context integration in primary visual cortex.

Disclosures: J.H. Emerson: None. **C.A. Olman:** None.

Poster

P495. Context Modulation in Visual Pathways

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Program #/Poster #: P495.04

Topic: D.07. Vision

Support: F31 EY031975
R01 EY029250

Title: The influence of expectation on neural population activity during natural scene discrimination

Authors: *P. L. STAN[1], M. A. SMITH[2];
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Abstract: Expectation heavily influences our visual perception, allowing us to identify relevant information from the vast amount of visual input found in the natural world. Behaviorally, expectation biases visual perception and improves stimulus detection. However, most studies showing a clear behavioral effect of expectation do not assess the neural underpinnings of these effects. Studies that do assess the effects of expectation on brain activity have primarily used fMRI, with few looking at the neuronal level. Although a handful of studies have focused on single neuron activity, little work has sought to understand how populations of sensory cortical neurons change their responses with expectation. Additionally, the majority of studies manipulate expectation in a way that is dissociated from behavioral performance (i.e. subjects passively view expected or unexpected images). The lack of neuronal level data paired with a task where expectation is decision-relevant greatly limits our ability to understand how expectation influences neural activity and shapes our perceptual abilities. To probe the effects of expectation on visual perception and neural activity, we recorded from populations of V4 neurons using implanted 100-electrode arrays in alert macaques engaged in a natural scene change detection task. We modulated the expectation of which image the subject will need to detect a change in on the following trial. During high expectation blocks, the same image (e.g. image A) was used on every trial. During low expectation blocks, a random image (from 10 possible images, including image A) was chosen for each trial, thereby reducing the expectation that image A would be selected for the following trial. We then compared both neural activity and behavior for image A during high expectation blocks with image A during low expectation blocks. Data from 3 monkeys showed a robust improvement in the ability to detect a change in an image when the image was expected. Our recordings from 2 monkeys showed that, in contrast to the typical enhancement seen for attention, expectation decreased neural activity. For the same image, firing rates were lessened when the image was expected. Additionally, we saw changes in the magnitude and distribution of pairwise correlations as well as in population-level

metrics such as shared variability and dimensionality. Our data offers a novel view into the neural changes in sensory areas that underpin expectation, and our results suggest that shifts in individual neuron activity and interactions between neurons underlie perceptual improvements due to expectation.

Disclosures: P.L. Stan: None. **M.A. Smith:** None.

Poster

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Topic: D.07. Vision

Support: Whitehall
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Title: Representation of Uncertainty by Macaque V1 Populations

Authors: *Z. M. BOUNDY-SINGER, C. M. ZIEMBA, R. L. T. GORIS;
Univ. of Texas At Austin, Austin, TX

Abstract: Perception is fundamentally uncertain. As a consequence, probabilistic inference as formalized by Bayesian theory is the "right" way to solve perceptual tasks. This in turn implies that the neural circuits which process sensory information must also survey the uncertainty of this information and put this estimate to use for perceptual inference. How this works is unknown. A prominent general hypothesis is that the same sensory neurons that encode a given stimulus feature also encode the uncertainty about this feature. Here, we investigate this notion in macaque V1, where neural populations encode local image orientation. We recorded V1 population activity from awake, fixating macaques using linear electrode arrays while presenting stimuli with varying orientation and uncertainty. We manipulated uncertainty in two distinct ways. First, by lowering stimulus contrast, thereby exposing noise internal to the system. And second, by increasing spread in the orientation domain, thereby adding noise external to the system. To investigate how V1 populations encode stimulus orientation and orientation uncertainty, we first fit each neuron's responses with a stimulus-response model built from operations of linear filtering, nonlinear transduction, gain control, and a doubly stochastic noise process. This model captured the effects of orientation, contrast, and spread on the neurons' response mean and variance. We then used this model to derive the maximum likelihood estimator of stimulus orientation on the basis of V1 population activity. Stimulus orientation estimates were on average unbiased, even in the presence of nuisance variation (contrast and spread). On individual trials, orientation estimation error tended to be small for high contrast, small spread stimuli, but could be substantial when contrast was low or spread was high. Thus, as expected, stimulus orientation estimates decoded from V1 population activity are less precise when either internal or external noise corrupts neural activity. We then asked which aspect of neural activity distinguishes uncertain from certain trials. We identified two candidate representations of uncertainty. First, the overall level of activity (the higher the population firing rate, the better the quality of the

orientation estimate). And second, a model-based estimate of cross-neural variability in response gain (the higher this variability, the lower the quality of the orientation estimate). These findings clarify how sensory circuits jointly encode stimulus features and their uncertainty.

Disclosures: Z.M. Boundy-Singer: None. **C.M. Ziemba:** None. **R.L.T. Goris:** None.

Poster

P495. Context Modulation in Visual Pathways

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JSPS KAKENHI 19J12634
JSPS KAKENHI 16K18380
JSPS KAKENHI 19H05028
JSPS KAKENHI 19K06948

Title: State representation of non-sensory neuron in the visual cortical area

Authors: *Y. OSAKO[1], T. OHNUKI[2], Y. TANISUMI[6], K. SHIOTANI[3], H. MANABE[7], Y. SAKURAI[4], J. HIROKAWA[5];
[1]Doshisha Univ., Kyotanabe/Kyoto, Japan; [2]Grad. Sch. of Brain Sci., Doshisha Univ., Kyotanabe, Japan; [3]Grad. Sch. of Brain Sci., Doshisha Univ., Kyoto, Japan; [4]Doshisha Univ., Kyotanabe-Shi, Japan; [5]Lab. of Neural Information, Doshisha Univ., Kyoto, Japan; [6]Lab. of Neural Information, Grad. Sch. of Brain Science, Doshisha Univers, Kawanishi-Shi / Hyogo, Japan; [7]Grad., Sch., of Brain Science, Doshisha Univ., Kyoto, Japan

Abstract: It is widely assumed that trial-by-trial variability in visual detection performance is explained by the fidelity of visual responses in visual cortical areas influenced by fluctuations of internal states, such as vigilance and behavioral history. However, it is not clear which neuronal ensembles represent such different internal states. Here, we utilized a visual detection task, which distinguishes internal states in response to identical stimuli, while recording neurons simultaneously from the primary visual cortex (V1) and the posterior parietal cortex (PPC). We found that rats sometimes withheld their responses to visual stimuli despite the robust presence of visual responses in V1. Our unsupervised analysis revealed distinct population dynamics segregating hit responses from misses, orthogonally embedded to visual response dynamics in both V1 and PPC. Heterogeneous non-sensory neurons in V1 and PPC significantly contributed to population-level encoding accompanied with the modulation of noise correlation only in V1. These results highlight the non-trivial contributions of non-sensory neurons in V1 and PPC for population-level computations that reflect the animals' internal states to drive behavioral responses to visual stimuli.

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Poster

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Topic: D.07. Vision

Support: Marie Sklodowska-Curie grant H2020-MSCA-IF-2017-795807 to G.L.-U.

Title: Interpreting sensory and cognitive signals in the cortical reading network

Authors: *G. LERMA-USABIAGA[1], R. LE[2], C. GAFNI[4], M. BEN-SHACHAR[5], B. A. WANDELL[3]; [1]BCBL. Basque Ctr. On Cognition, Brain and Langua, Donostia-San Sebastian, Spain; [3]Psychology, [2]Stanford Univ., Stanford, CA; [4]Univ. of Haifa, Haifa, Israel; [5]Bar Ilan Univ., Ramat Gan, Israel

Abstract: Many important tasks, such as reading, require the coordination of sensory and cognitive processing. Regions of ventral occipito-temporal (VOT) cortex, close to the visual field maps, are part of the neural circuitry that is engaged by reading: we refer to the regions of the VOT that are more responsive to words than to other stimulus categories as the VOT reading circuitry (VOTRC). In previous work, we used fMRI and the population receptive field (pRF) analysis to characterize the visual responses in the VOTRC. The FOV of a region of interest (ROI) defines the portion of the visual field that reliably evokes a response in any of the ROI voxels. We showed that the FOV of the VOTRC is largely confined to the central portion of the visual fields and that the position of the FOV is stimulus-dependent, differing when contrast patterns comprised words versus checkers. This finding can be explained by at least two types of neural models. The first model is that responses in the VOTRC voxels are dominated by sensory input: changing the stimulus from checkers to words shifts the sensory input so that the VOTRC receives signals from different regions of visual space. A second model is that the signals reaching the VOTRC include a large contribution from non-visual, cognitive regions. In this case, using the pRF model to analyze the VOTRC responses incorrectly assigns differences in the BOLD response to changes in receptive field center locations and sizes. To understand the origin of this stimulus dependency in the VOTRC, here we expand on the prior reports: we quantify the stimulus-dependency in the ventral visual field maps (V1, V2, V3, hV4, VO-1) whose signals are delivered to the VOTRC. A small stimulus-dependent effect is measured as early as V1 and becomes more pronounced in every subsequent map. The stimulus-dependent differences in pRF center location are systematic: the word stimuli generally produce estimates that are as much as 3-4 deg closer to the fovea and fall along radial visual field lines. We further observe stimulus-dependent differences in pRF center positions using false-fonts and Hebrew script stimuli. Specifically, VO-1 responds similarly to words and false fonts, whereas the VOTRC responses differ between false fonts and words. We suggest that VOTRC responses are a combination of sensory and cognitive terms: interpreting the VOTRC responses with purely sensory pRF model, and thus as shifts in visual field position and extent, may miss an important aspect of the signal. We propose an extension of the pRF model to account for this cognitive signal.

Disclosures: G. Lerma-Usabiaga: None. **R. Le:** None. **C. Gafni:** None. **M. Ben-Shachar:** None. **B.A. Wandell:** None.

Poster

P495. Context Modulation in Visual Pathways

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Program #/Poster #: P495.08

Topic: D.07. Vision

Support: ERC SPATEMP
BMF BINDA

Title: A mechanism for inter-areal coherence through communication based on connectivity and oscillatory power

Authors: M. SCHNEIDER[1], A. S. BROGGINI[2], B. DANN[3], A. TZANOU[1], C. URAN[1], S. SHESHADRI[3], H. SCHERBERGER[3], ***M. VINCK**[1];
[1]Ernst Struengmann Inst. for Neurosci. in Cooperation with Max Planck Society, Frankfurt Am Main, Germany; [2]Ernst Strüngmann Inst., Frankfurt am Main, Germany; [3]German Primate Ctr., Goettingen, Germany

Abstract: Inter-areal coherence between cortical field potentials is a widespread phenomenon and depends on numerous behavioral and cognitive factors. It has been hypothesized that inter-areal coherence reflects phase-synchronization between local oscillations and can flexibly gate communication. Here, we reveal an alternative mechanism, in which coherence is a consequence and not the cause of communication, and naturally emerges as a consequence of the fact that spiking activity in a sending area causes post-synaptic inputs both in the same area and in other target areas. Consequently, coherence depends in a lawful manner on the oscillatory power and phase-locking in a sending area and connectivity between a sender and receiver. We show that local changes in oscillatory power explain prominent changes in long-range beta-coherence during a visually guided reach task, and LGN-V1 gamma-coherence with arousal and visual stimulation. Optogenetic silencing of spiking in area V1 and simulations of E/I networks demonstrate that afferent synaptic inputs rather than spiking entrainment are the main determinant of inter-areal coherence. These findings suggest that the unique spectral profiles of different brain areas automatically give rise to large-scale inter-areal coherence and Granger-causality patterns that follow anatomical connectivity and continuously reconfigure as a function of behavior and cognition. In a second study, we show that feedforward gamma (LGN to V1, V1 to V2) results in phase-locked responses of fast-spiking interneurons in the granular layer of the receiving area, however with much weaker phase-locked responses of excitatory neurons in the receiver, compatible with the low-pass filtering properties of excitatory neurons. The latter findings suggest that gamma is not a mechanism to promote feedforward communication, but that gamma may recruit inhibition in downstream areas and thereby contribute to normalization mechanisms.

Disclosures: M. Schneider: None. **A.S. Broggini:** None. **B. Dann:** None. **A. Tzanou:** None. **C. Uran:** None. **S. Sheshadri:** None. **H. Scherberger:** None. **M. Vinck:** None.

Poster

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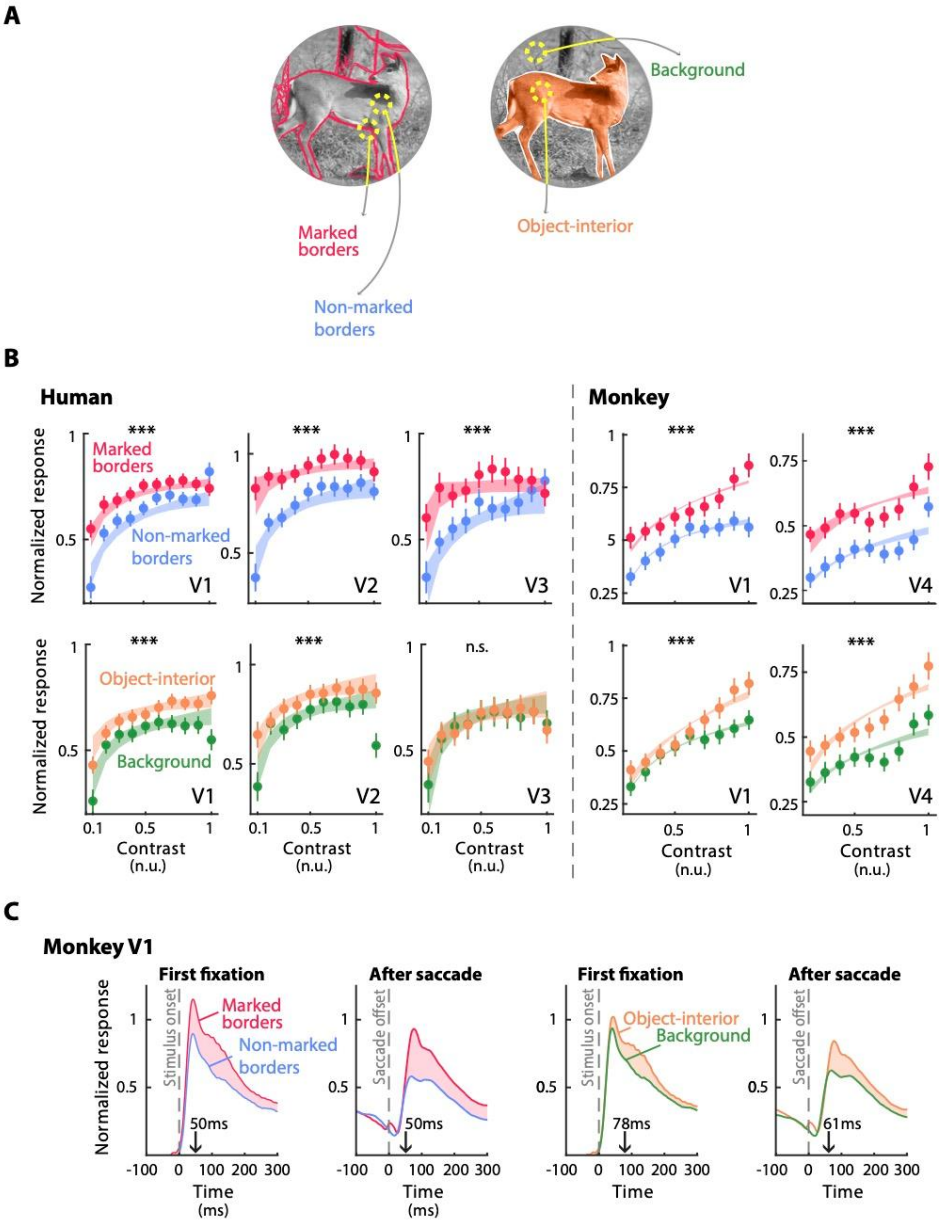
Topic: D.07. Vision

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NWO Vidi 452.08.008
NWO Vici 016.vici.185.050
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Title: Object perception shapes the representation of natural images in both human and monkey early visual cortex

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Abstract: Neurons in visual cortex are sensitive to the image elements in their receptive field (RF) but also to the context determining if the elements are part of an object or not. These contextual modulations of neural activity have been extensively studied with artificial stimuli but not in natural vision. Here we determined the effect of object perception (object boundaries and interiors) on neural activity in early visual cortex elicited by natural images. We recorded the response of several visual regions in humans using fMRI and the activity of neurons in V1 and in V4 using electrophysiology in macaques. We presented images from the BSD, a library of natural images in which human observers marked object boundaries (Fig. 1A). We report that the early visual cortex (V1, V2 and V3 in humans and V1 and V4 in monkeys: Fig. 1B) responded stronger to marked boundaries than to non-marked boundaries with similar contrast. We also observed that the interiors of objects elicited stronger responses than the background (in V1 and V2 in humans and V1 and V4 in monkeys: Fig. 1B). Our experiments revealed that boundary effects occur remarkably early in V1, ~50ms after stimulus onset. The latency of the response enhancement elicited by object interiors is later (~80ms) if the monkey sees the image for the first time, and earlier (~60ms) if a previous saccade shifted the object into the RF, indicating that the enhancement of object interiors builds up across eye movements (Fig. 1C). The boundary modulation in V1 is earlier than the latency of ~95ms observed in studies with synthetic images, suggesting that visual cortical neurons are tuned to features characterizing object boundaries in natural scenes. We tested this hypothesis in two further experiments in V1 in monkeys and observed that the boundary modulation is explained by RF tuning and is delayed (to ~80ms) by a change in context while keeping the content in the RF the same. Our results reveal how object perception shapes the representation of natural images in early visual cortex in both humans and monkeys, by enhancing the representation of object boundaries and interiors.



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Poster

P495. Context Modulation in Visual Pathways

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Program #/Poster #: P495.10

Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01 EY022951
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McKnight Scholar Award

Title: Pulses of gamma activity in mouse V1 predict visually guided behavior

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Abstract: Neocortical gamma band activity (30-80Hz) is a hallmark of active wakefulness and cognition in rodents and humans, and its disruption is associated with several neurodevelopmental disorders including schizophrenia and autism. Gamma activity is easily detectable in the frequency spectrum using Fourier analysis or its derivatives. However, the local network events underlying this broad gamma range activity are difficult to track in the temporal domain. Furthermore, cortical gamma oscillations largely occur in short bouts, rather than sustained oscillatory periods, presenting a challenge for precise detection. As a result, the mechanisms and function of gamma oscillations remain poorly understood. Here we studied gamma activity in the visual cortex (V1) of awake behaving mice using laminar probe and whole cell patch clamp recordings. Gamma activity typically increases in mouse V1 during running, providing a template for detection. Taking advantage of this, we developed an analytical method combining spectral analysis and unsupervised clustering called Clustering of Activity Motifs by State (CLAMS) for high-fidelity tracking of gamma bouts in the temporal domain. Using CLAMS, we find that gamma events in the cortical local field potential (LFP) correspond to transient pulses synchronizing the membrane potential dynamics of neurons in cortical layers 2 to 5. Gamma pulses coincide with a stereotypical propagation of activity from layer 4 into layer 2-3 and then into layer 5, suggesting that they may arise via feedforward thalamocortical processing. Though gamma pulses were more frequent during running, they occurred several times per second regardless of behavioral state. Using CLAMS, we examined state-dependent bouts of gamma activity in mouse V1 during learning and performance of a visual contrast detection task. We found that V1 gamma pulses increased in frequency preceding responses, but not miss, in mice trained to perform the task. The rate of gamma pulses was thus highly predictive of behavioral outcome on a trial-by-trial basis. This enhancement of gamma was not present in naïve mice prior to the formation of an association between the visual stimulus and reward but emerged following learning. In addition, increased gamma activity was modality-specific, as we observed no enhancement in gamma bouts in V1 during successful performance of an auditory task. Based on these findings, gamma in V1 may correspond to pulses of synchronized cortical activity that facilitate sensory integration during visually guided behavior.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

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Title: Sub-regions of the SCN receive a heterogeneous synaptic input from the retina

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Abstract: The suprachiasmatic nucleus (SCN) of the hypothalamus is the central pacemaker regulating the circadian rhythmicity of tissues throughout the body. The SCN is receiving photic information through melanopsin-expressing ganglion cells of the retina (mRGCs) to synchronize the body with the environmental light cycles. The SCN is a complex nucleus composed of several subtypes of neurons receiving information from the retina as well as other brain regions. Understanding how these different inputs affect the SCN network is crucial to understand the regulation by light of the circadian clock. This level of detail is not accessible using common light microscopy techniques, we thus used a Cre-dependant electron microscopy reporter, APEX2, to specifically label mitochondria of mRGCs axons, and serial blockface electron microscopy to access the fine structures of the SCN that cannot be done in light microscopy. We thus obtained the first in deep study of the connectome organization of SCN in two specific regions, the core and the shell, known to be composed of different neuronal subtypes, and their mRGCs inputs. Our results indicate that a network of neurons forming dendro-dendritic synapses is present in both sub-regions of the SCN and receives denser mRGCs synaptic input in the shell compared to the core. This challenges the idea that photic information coming directly from the retina is mainly integrated by the core region of the SCN.

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Poster

P495. Context Modulation in Visual Pathways

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Topic: D.08. Visual Sensory-motor Processing

Support: B.R.A.I.N. - MH111439

Title: Active vision modulates neural excitability in human auditory and speech processing systems

Authors: *M. LESZCZYNSKI[1], S. BICKEL[2], M. NENTWICH[3], B. E. RUSS[4], L. C. PARRA[3], A. D. MEHTA[5], C. E. SCHROEDER[6];
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Abstract: Sensing is an active process. Humans use saccadic eye movements to relocate the fovea and sample different bits of information multiple times per second. Saccades modulate neuronal oscillations across the visual system shifting neuron ensembles to a common momentary state just after fixation. Whether these effects extend outside of the visual system is unknown. Here, we combined intracranial electroencephalography (iEEG) with eye tracking during natural free viewing in lieu of auditory stimulation to evaluate the possibility that saccades modulate neural activity in classical auditory and speech processing cortical areas. Studying fixation-locked field potentials, we discovered two anatomically separate mechanisms operating in synchrony with the eye movements: one operating in low level auditory areas and another in higher order speech processing areas. We also found dynamical multiplexed connectivity between the auditory system and regions involved in generation of saccades. Our results support an active vision model in which saccades are tied to dynamic modulation of neural excitability across a network that extends into the auditory system.

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Poster

P521. Systems Behavior I

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Program #/Poster #: P521.01

Topic: E.03. Basal Ganglia

Support: DC017163

Title: Learning-induced changes in the dorsal regions of auditory and motor striatum support associative learning through sensorimotor integration.

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Abstract: Background: Prior to behavioral output, information from the sensory and motor systems are integrated in a region of the basal ganglia, known as the striatum. There, sensory information about the environment (e.g., stimuli) is utilized to shape a motor output (e.g., behavior). For naïve animals, a sensory input will not reliably evoke a specific behavioral response (absence of stimulus response association). In contrast, in animals that have mastered an associative learning task, a particular sensory input will reliably produce a desired behavioral response. In this study, we asked how neuronal response properties in the motor and auditory regions of the dorsal striatum change as a function of associative learning of a Go-Nogo task.
Methods: Adult Mongolian gerbils (n=5) were implanted with wireless 64-channel electrode array that spanned the dorsal striatum from the anterior motor regions to the posterior auditory/visual regions. Each animal was trained on an amplitude-modulation (AM) rate discrimination task using an appetitive reinforcement operant conditioning procedure. The freely-moving animals were trained to initiate each trial by a nose poke, and a 12-Hz AM stimulus indicated the availability of a food pellet (Go stimulus), versus a 4-Hz AM stimulus which signaled the absence of a reward (Nogo stimulus). A sensitivity measure, dprime (d' = z(hit rate) - z(false alarm rate), was computed for each animal across training days.
Results: Single-unit recordings (N=815; Motor MSNs (418), Aud MSNs (397)) were carried out for each day of training and compared as a function of task trial type response (Go-hit, Nogo-false alarm, Nogo-correct reject), learning state (naïve, acquisition, mastery), and striatal region (motor, auditory). Response latency was also calculated and compared within animals across learning states. As animals learned the task (d' improve), the neuronal responses to the Go and Nogo stimuli were significantly altered. The changes seen in neuronal responses accurately predicted task trial type response, learning states and response latencies. In addition, significant differences to stimulus evoked motor and auditory responses emerged as animals moved from the naïve learning state to the mastery phase (e.g., response magnitude, latency to peak, temporal coding precision).
Conclusions: Together, these results demonstrate how neuronal response properties in striatal circuits are altered by associative auditory learning. Those changes in striatal circuitry may be pivotal for additional learning of more complex associations.

Disclosures: J. Gay: None. **N. Paraouty:** None. **T. Mowery:** None.

Poster

P521. Systems Behavior I

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Title: Investigating the entopeduncular nucleus contribution to ipsi/contralateral movements and decisions

Authors: *A. VERMA RODRIGUEZ, J. O. RAMIREZ-JARQUIN, F. TECUAPETLA;
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Abstract: The entopeduncular nucleus (EPN, rodent analog of the Globus Pallidus internal segment, GPi) is one of the main outputs of the basal ganglia. It has been implicated in action evaluation via reward-related signals. As well, movement correlated activity under certain memory-dependent contexts has been suggested. Furthermore, the basal ganglia have been shown to differentially contribute to ipsilateral and contralateral decisions and movement-related variables (such as speed) in freely moving rodents. Given that studies focusing on the GPi have mostly been done in head-fixed tasks, this study intends to analyze the contribution of this nucleus to movement and decision in a freely behaving animal. Preliminary results:

- We trained mice in an auditory two-alternative forced-choice task that involved turning right or left and moving towards the reward port.
- The auditory stimuli were graded in difficulty such that a psychophysical curve could be obtained. The increased uncertainty in the decision increased the reaction time and decreased the speed of their movement.
- Preliminary analyses of recordings from the entopeduncular nucleus show activity correlated with the decision. Some units show anticipatory activity that distinguishes whether the turn will be ipsi- or contralateral.
- Reward-related signals are modulated according to the difficulty of the auditory stimulus.
- However, movement-related activity, especially involving speed, has not been conclusively established. Further analysis is needed to ascertain how the activity is related to movement parameters.

Disclosures: A. Verma Rodriguez: None. **J.O. Ramirez-Jarquin:** None. **F. Tecuapetla:** None.

Poster

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Program #/Poster #: P521.03

Topic: E.03. Basal Ganglia

Support: NIH R01NS094450
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Title: Longitudinal in vivo calcium imaging of striatal neurons during associative learning and chronic haloperidol administration

Authors: *S. S. BASKAR, T. J. VAJTAY, D. J. MARGOLIS;
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Abstract: The integration of sensory and motor signals is a key role of the dorsal subdivision of the dorsal striatum (DStr), the main input nucleus of the basal ganglia. This process is mediated by diverse microcircuitry that includes two spiny projection neuron (SPNs) and multiple interneuron populations. The interplay between these populations is critical for the coordination of sensory-guided behavior and sensorimotor learning. Our goal was to measure the activity dynamics of D1- and D2-SPNs (the major populations of dopamine receptor-expressing projection neurons) during learning of a cue-reward behavioral task, and how activity changed after chronic haloperidol administration, a D2-SPN antagonist that is used clinically as an antipsychotic. We injected double transgenic adult D1-tdTomato mice (100-150d; n=2) with a viral vector expressing the genetically encoded calcium indicator GCaMP6m, and implanted a gradient index (GRIN) lens above the DStr. Post-recovery (4-6wks), mice were water restricted and trained in a simple sensory paired conditioning task that paired air-puff whisker stimulation with water reward, and in vivo calcium signals of DStr neurons were recorded using a two-photon microscope. One week of baseline recordings was followed by 2 weeks of chronic intraperitoneal injections of Haloperidol (Hal; 1mg/kg; once daily). Analysis of the baseline week showed overall trends of cue-driven calcium signals in the majority of DStr neurons, suggesting that DStr neurons encode responses to sensory cues rather than general movement or reward. Interestingly, by the end of the week the same highly responsive cells had reduced their overall responding significantly, potentially suggesting a role in cue-associated sensory learning. Preliminary analysis of average cell activity of the Hal trials showed both an increase in overall spontaneous activity from the previous baseline day and distinct time-locked activation around the sensory cue on the first Hal session, which became less temporally stereotyped by the end of the week. These data suggest that chronic haloperidol administration may disrupt previously encoded learning cues, however it remains to be determined to what extent changes in behavioral state (e.g., catatonia) also contribute. Further analysis will elucidate the specific roles of D1 and D2-SPNs in the maintenance and recuperation of sensorimotor learning in the DStr.

Disclosures: S.S. Baskar: None. **T.J. Vajtay:** None. **D.J. Margolis:** None.

Poster

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Title: Motor skill learning and execution in a distributed brain network

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Abstract: The remarkable capacity of the brain to acquire and execute motor skills depends on a distributed motor network. While many components have been identified, less is known about their specific roles and how they interact during skill learning and execution. Here we probe this network through the lens of complex, spatiotemporally precise motor sequences we train in rats. We focus on the basal ganglia and the contributions made by their main inputs, from motor cortex and thalamus, respectively. Using electrophysiological recordings, we find that the dorsolateral striatum (DLS), the main motor-related input nucleus of the basal ganglia, encodes the detailed kinematic structure of the learned motor sequences. We further show that the DLS is necessary for their execution and that animals revert to simple innate behaviors after loss of the DLS. Moreover, we find that not only the DLS, but also the inputs it receives from motor cortex are necessary for learning the skills we train. This very same pathway, however, becomes dispensable after the behaviors are acquired. In contrast, thalamic inputs to the DLS remain crucial for the generation of the learned skills and loss of these inputs disrupts performance akin to DLS lesions. Taken together, our results identify the DLS as a central hub in the motor network and suggest that motor cortex 'tutors' sub-cortical motor circuits during learning, potentially by guiding plasticity at thalamostriatal synapses. Such adaptive reprogramming of lower-level motor circuits may broaden their flexibility and allow them to store and generate complex learned motor skills.

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Poster

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Topic: E.03. Basal Ganglia

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Title: Action learning process mediated by dopaminergic reinforcement

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Abstract: Animals have the remarkable ability to explore a novel environment in a self-paced manner and hone in on actions and action sequences that promote rewarding consequences. Dopamine is a reward signal involved in reward-prediction and motivated behavior. Emerging evidence suggests that dopamine acts at striatal synapses to mediate behavioral reinforcement, but it is unclear how dopamine

reinforcement transforms freely moving behavior such that animals can hone in on reward-causing actions. It remains even more elusive how dopamine mediates the learning of temporally distal actions that trigger rewards with variable delays. Here, we applied a novel closed-loop system to show that VTA dopaminergic self-stimulation not only reinforces the reward-causing target action, but also similar actions in naïve and experienced animals. Actions of the repertoire undergo differential dynamics as animals hone in on single targets, and specific dynamics can be predicted by an action's similarity and natural, temporal proximity to target. Notably, behavior performed within a 1-1.2 second window leading up to and during self-stimulation was reinforced. This critical window mediates learning of two-action sequences, which for target action pairs that are naturally performed with long time gaps, is characterized by preferential refinement for the proximal target early on in learning, and subsequently refinement of the distal target upon truncation of the proximal-to-distal action time interval below a critical level. These findings reveal the behavioral process by which the dopamine backpropagating critical window promotes learning and honing in on specific reward-causing action and action sequences in a spatiotemporal manner in freely moving animals.

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Poster

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Program #/Poster #: P521.06

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Title: Basal ganglia-spinal cord pathway that mediates locomotor asymmetries

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Abstract: The basal ganglia are critical for voluntary motor control, and dysregulation of basal ganglia circuitry contributes to locomotor impairments in Parkinson's disease. The basal ganglia are thought to initiate motor actions via disinhibitory control over a number of brainstem nuclei, whose detailed function and connectivity are under active investigation. One hallmark feature of hemi-Parkinsonism in mice and humans is the manifestation of locomotor asymmetries, e.g. turning, where locomotion exhibits a dominant directional tendency. The brainstem motor program which mediates hemi-Parkinsonian asymmetries is not known. Based on our recent finding that excitatory *Chx10* gigantocellular (Gi) neurons are required for locomotor asymmetries in mammals (Cregg et al. 2020), we hypothesized that basal

ganglia asymmetries act via this spinal projection pathway. Using deep brainstem calcium imaging in mice, we examined *Chx10* Gi Ca^{2+} responses to optogenetic stimulation of striatal D1 medium spiny neurons. D1 stimulation evoked contralateral turning accompanied by a time-locked increase in Ca^{2+} activity of *Chx10* Gi neurons on the contralateral side, suggesting a discrete pathway from basal ganglia output (i.e. substantia nigra pars reticulata, SNr) to *Chx10* Gi neurons. We used a viral screening strategy to identify brain regions that interface between SNr and Gi. This screen uncovered only one brainstem nucleus which links SNr to Gi. Excitatory neurons of this brainstem nucleus receive inhibitory input from the ipsilateral SNr and project to contralateral *Chx10* Gi neurons. Optical stimulation of this small cluster of brainstem neurons evoked contralateral turning, whereas photoinhibition evoked ipsilateral turning. Our results identify a dominant crossed pathway for locomotor asymmetries, from action selection in the basal ganglia to spinal motor output: D1 medium spiny neurons -> SNr -> brainstem nucleus -> contralateral *Chx10* Gi neurons -> spinal locomotor networks. These data indicate that selection of locomotor direction by basal ganglia circuits works via disinhibitory control over a small brainstem target that directs *Chx10* reticulospinal neurons to execute the movement.

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Poster

P521. Systems Behavior I

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Program #/Poster #: P521.07

Topic: E.03. Basal Ganglia

Title: Cell type/class specific inputs to the caudoputamen from visual cortical areas in the mouse

Authors: *Q. WANG, L. NG, M. NAEEMI, S. YAO, S. SORENSEN, H. ZENG;
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Abstract: The caudoputamen (CP, or dorsal striatum) is a major input component of the basal ganglia that is associated with motor control, cognition, emotion and learning. As in primate and cat, the CP in mouse receives topographic inputs from various cortical areas. In the previous studies, we have shown that mouse visual areas are organized in a hierarchical fashion and form ventral and dorsal streams (Harris et al., 2019; Wang et al., 2012). Cortical areas from both streams show differential projections to subcortical structures such as amygdala and superior colliculus. However, it remains unclear whether the dorsal and ventral stream areas project to the same territory in the CP or not. Furthermore, cell type/class specific inputs from visual cortical areas to CP have not been systemically investigated. Our recent study delineated ten visual cortical areas in a 3D mouse brain atlas - the Allen Mouse Brain Common Coordinate Framework version 3 (CCFv3) (Wang et al., 2020). Pan-neuronal and Cre-dependent anterograde AAV tracing data in the Allen Mouse Brain Connectivity Atlas, including these visual cortical areas (Harris et al., 2019; Oh et al., 2014), were remapped to the CCFv3. In this new 3D framework, we systemically studied pan-neuronal and layer/subclass-specific visual cortical inputs to CP. We found that the dorsal and ventral visual areas project to the visual zone of the CP but are partially overlapping. Specifically, the dorsal stream areas (VISal, VISrl, VISam, VISpm and VISa) send widely spread projections in the dorsal CP and shift the projections gradually away from the primary visual

cortex (VISp) zone toward the dorsolateral somatomotor zone. The ventral stream areas (VISl, VISpl, VISli and VISpor) send denser projections to posterior CP than to anterior CP. The higher visual areas send stronger projections to CP than the VISp. Projections of VISp were labeled from the dorsoposterior to anterior dorsomedial CP in a restricted longitudinal strip lining the lateral ventricle. We found that different cell types in each layer of visual areas send projections to the CP with different strengths. In general, across visual areas, layer (L) 2/3 IT neurons send sparse projections to the ipsilateral visual zone of CP. L4 IT and L6b IT neurons send extremely sparse projections to the ipsilateral visual zone of CP. L5 IT and a mixture type of L5 IT and PT neurons send strong projections to the visual zone of bilateral CP with an ipsilateral dominance. A subset of L5 PT and L6 CT neurons project sparsely to the ipsilateral visual zone of CP. Our results reveal cell type specific inputs to the CP from mouse visual cortical areas.

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Poster

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Topic: E.03. Basal Ganglia

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Title: Rhythm parameters were encoded by striatal neurons of mice running in complex stepping.

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Abstract: Our behavior encompasses many continuous movements such as running and playing musical instruments. Such behaviors consist of many individual actions of multiple body parts. When we play the piano, multiple fingers move simultaneously, or alternately, sequentially. The movement of fingers is often repetitive and rhythmic. In addition, each rhythm of the fingers is coordinated temporally as if all of the finger rhythms were connected each other. However, it is not clear how such coordination of movements is shaped in the brain. In our previous study, we developed a complex stepping task for mice, the step-wheel. The step-wheel is a motor-driven wheel in which mice run for water reward and can control the speed and their step-patterns. But the step-patterns can be experimenter-controlled by the arrangements of the of pegs that serve as footholds for the mice. The steps of mice can be detected by voltage sensors attached to each peg. Here, we recorded spike activity from the dorsal striatum as mice performed step-wheel tasks. We found neurons responding to events including the start or stop of drinking, licking of the spout, and touches of forelimb paws to pegs. Among them, we focused on neurons with phasic responses to touches. Even with complex peg-patterns, in which the arrangements of pegs

were irregular, the touch- responding neurons showed phasic responses correlated with the touches of forelimb paws to pegs. However, the responses were not uniform to every touch; responses were high for some touches but low for others. By aligning the spikes to right or left touches, we found that the responses to touch-to-touch intervals and/or left-right timing of limbs were different neuron by neuron. To confirm such responsiveness of the neurons, we used two peg-patterns: the peg-pattern I for Interval and peg-pattern P for left-right difference. In peg-pattern I, the space between two consecutive pegs were gradually changed from narrow to wide . In peg-pattern P, the relative positions of left and right pegs (phase) were gradually changed. We found that considerable number of touch-responsive neurons showed the modulation of firing rate by the interval and/or phase. In addition, we analyzed the relationship between stepping and spiking over several continuous steps to see whether the touch-responsive neuron activities were associated with repetition, another parameter of rhythm. We found that the firing rates of those neurons were increased in response to repeated touches with a particular touch interval. These findings indicate that the striatal neurons may coordinate body parts in repetitive movements using the parameters of rhythm, the phase, interval and repetition.

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Poster

P594. Parental Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P594.01

Topic: F.02. Behavioral Neuroendocrinology

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NIH DC12557
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NIH MH112232
NIH MH019524
AMED 16K15698

Title: Oxytocin neurons enable social transmission of maternal behavior

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Abstract: Maternal care is profoundly important for mammalian survival, and non-biological parents can also express maternal behavior after experience with infants. One critical maternal molecular signal is oxytocin, a hormone centrally released by hypothalamic paraventricular nucleus (PVN). In mice, oxytocin enables neuroplasticity in the auditory cortex, and these neural changes are required for maternal behavior in biological and non-biological mothers. However, it is unclear when hypothalamic signaling promotes cortical plasticity and onset of maternal care during initial parental experience. Here we determined what episodes activate PVN in non-biological parents, by continuously monitoring homecage behavior of female virgin mice co-housed with an experienced mother and litter. This documentary approach was synchronized with neural recordings from virgin PVN, including from oxytocin neurons. These cells were activated as virgins were enlisted in maternal care by experienced mothers, who shepherded virgins into the nest and demonstrated retrieval of isolated pups. Shepherding activated 19% of oxytocin and 9.2% of PVN neurons in virgins, nest entry activated 28.5% of oxytocin and 26.1% of PVN neurons, and maternal retrieval activated 29.4% of oxytocin and 14.4% of PVN neurons in virgins. Virgins visually observed maternal pup retrieval, which promoted their own retrieval behavior. When the observation was unhindered, 11/15 virgins learned to retrieve. When virgins observed mothers across a transparent barrier, 12/19 learned to retrieve. However, only 2/18 virgins retrieved after exposure to maternal pup retrievals across an opaque barrier. We find that monosynaptic projections from visual layers of the superior colliculus could engage oxytocin neurons during observation of maternal retrievals. Optogenetic stimulation of these projections induced retrieval in 4/5 virgins undergoing opaque barrier exposure. Thus rodents can acquire maternal behavior by social transmission, providing a mechanism for adapting brains of adult caregivers to infant needs via endogenous oxytocin.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.02

Topic: F.02. Behavioral Neuroendocrinology

Support: UMass FRG
Provost Undergraduate Research Fellowship

Title: Medial preoptic area projections to the infralimbic cortex and ventral tegmental area modulate caregiving behaviors attuned to the needs of offspring

Authors: *K. COPELAS, N. CELESTIN, M. PEREIRA;
Univ. of Massachusetts, Amherst, Amherst, MA

Abstract: The medial preoptic area (mPOA) is critical to the facilitation of maternal caregiving behavior, where hormonal signals and offspring-related sensory information converge. Prior research in the lab suggests that the mPOA orchestrates flexible caregiving behaviors to resolve the constantly changing needs of the young. The objective of this study was to determine whether varying need signals from the offspring are represented in maternal mPOA neurons projecting to two critical downstream areas: the infralimbic cortex (IL) and ventral tegmental area (VTA). To this aim, we used red and green Retrobeads retrograde tracers and cFos immunohistochemistry to identify the subregional origins of cFos-expressing mPOA->IL and mPOA->VTA neurons in the maternal mPOA during interactions with offspring of varying needs (normal needs (NDEM) versus increased needs (DEM)). Consistent with our prior work, Sprague-Dawley (SD) mother rats interacting with DEM pups adjusted their caregiving, resulting in significant behavioral differences between groups. Ongoing cFos analysis, using a supervised automated counting protocol, thus far indicates that the observed behavioral change in mothers interacting with DEM pups was accompanied by a significant upregulation of cFos expression in the mPOA, including neurons projecting to the IL and VTA. In addition, Retrobeads labeling analysis suggests that no mPOA neurons extend axons to both the IL and the VTA. Together, results further support our hypothesis that the mPOA participates in aspects of maternal sensitivity. Follow-up studies are being conducted to understand the specific role of the mPOA in this crucial maternal ability.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.03

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH RO1
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HHMI Gilliam Fellowship

Title: Social Transmission of Maternal BehaviorsthroughObservation

Authors: *N. LOPEZ-CARABALLO[1], K. QUINONES-LARACUENTE[2], A. SEIDENBERG[3], O. MAVRIDIS[3], R. C. FROEMKE[4], R. C. FROEMKE[4];
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Abstract: Oxytocin is a neuropeptide important for maternal physiology and social behaviors (Jurek & Neumann Physiol Rev 2018). One behavior influenced by central oxytocin signaling in rodents is pup retrieval (Marlin et al. Nature 2015; Scott et al. Nature 2015; Schiavo et al. Nature 2020). When pups are out of the nest, they emit vocalizations that prompt dams to fetch the pup back to the nest. Virgin females do not initially retrieve pups, but can learn to retrieve after several days of co-housing with an experienced mother and pups. In our lab we have filmed days-long videos of co-housing, allowing us to identify interactions that may serve as training for naïve virgins to learn maternal behaviors. We noticed mothers often spontaneously dragged pups out of the nest, generating retrieval episodes that co-housed virgins could potentially observe (Carcea et al. Nature 2021). To examine how maternal behavior might be socially transmitted through the visual system, we had non-co-housed virgins observe the mother retrieve through a transparent wall. We found that virgins learned to retrieve after four days of exposure and failed to acquire retrieval behavior when the barrier is opaque, impeding visual input. A population of neurons in the mouse superior colliculus seemed to provide this visual signal to hypothalamic oxytocin neurons (Carcea et al. Nature 2021). To explore what aspects of maternal behavior are socially transmitted, we showed audio-visual movies to head-fixed awake virgin female mice that initially did not retrieve pups. We found that head-fixed virgins exposed to audio-visual movies of maternal retrievals (N=18) expressed alloparenting earlier than virgins presented with dark backgrounds (N=21; p=0.0349) and more reliably by day two (p=0.0360). Conversely, virgins presented with videos of maternal mistakes (out of the nest retrievals; N=4) rarely expressed alloparenting behavior. Surprisingly, videos of other sole adult mice without pups (conspecifics, N=15; dam without pups, N=11) also accelerated pup retrieval learning. To further assess the role of oxytocin in this type of learning, we optogenetically suppressed oxytocin neuron activity during exposure to movies of dams retrieving pups, which prevented the enhancement of alloparenting by maternal video playback (N=4). These results demonstrate that maternal behavior in mice can be socially transmitted through a virtual experience and that the mouse visual system provides input to the oxytocin neurons for enhancement of alloparenting.

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Poster

P594. Parental Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: KAKENHI 15H05724
KAKENHI 19H03270

Title: Effect of ERα polymorphisms in maternal behavior of mouse

Authors: *L. DEVI[1,2], A. TANAVE[3], Y. IMAI[1], K. TAKANAMI[1,2], T. KOIDE[1,2];
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Abstract: Induction of maternal behavior in mammals relies on changes at the level of the genome. However, the ability to characterize a specific behavioral phenotype to a naturally occurring genetic change i.e. polymorphism is considered to be a rare phenomenon. Maternal responsiveness is thought to be mediated by several hormonal and neuronal changes, yet the effect of underlying polymorphisms on the extent of bonding cannot be foreseen. One of the well-studied protein for its role in determining maternal- infant bonding is Estrogen receptor α (ERα), encoded by gene estrogen receptor 1 (*Esr1*). The expression of ERα in hypothalamic medial preoptic area (MPOA) and the adjacent ventral bed nucleus of stria terminalis (vBNST) plays an essential role in controlling maternal behavior. Mice are extensively used model animals to study regulation and function of ERα *in-vivo*. In our study we identified that mice from different genetic background, laboratory strain C57BL/6J (B6) and wild derived mouse strain MSM/Ms (MSM) differs in *Esr1* gene structure. We found an insertion polymorphism, (insertion "A") in exonic region of B6 genome when compared to MSM. To analyse the role of the insertion "A", we developed an $Esr1^{\Delta A}$ mice in which the "A" sequence was deleted in B6 mice through CRISPR/Cas9-mediated genome editing. We report here that (i); $Esr1^{\Delta A}$ heterozygous mice showed reduced pup survival in the breeding. (ii); Maternal behavior analysis showed that $Esr1^{\Delta A}$ heterozygous mice were reluctant to retrieve pups (took more time) when compared to the wild type control. (iii); $Esr1^{\Delta A}$ heterozygous mice showed higher mRNA and lower protein expression, indicating the effect of polymorphism on regulation of translation. (iv); Reduced ERα and cFOS (immediate early gene) expression in the MPOA of $Esr1^{\Delta A}$ heterozygous mice after maternal behavior. Altogether, our study provides a glance of how a *Esr1* genetic polymorphism has affected the brain and maternal behavior within mice species. In future studies, we would like to understand how the abnormal maternal behavior was occurred in the $Esr1^{\Delta A}$ heterozygous mice using molecular and neural approaches.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.05

Topic: F.02. Behavioral Neuroendocrinology

Support: R01MH105447-01

Title: Disrupting serotonin system development via early life antidepressant exposure leads to impaired maternal care and increased serotonin receptor expression in adult female offspring

Authors: *K. A. UNROE[1], J. MALTMAN[1], E. A. SHUPE[2], S. CLINTON[2];
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Abstract: Experiments in rodents show that manipulating serotonin (5-HT) levels in the developing brain (via early-life SSRI treatment or genetic manipulation of 5-HT levels) has lifelong negative impact on emotional behavior. Neonatal SSRI exposure produces a variety of behavioral disturbances in adulthood. Neonatal SSRI treatment also triggers several neurobiological changes in the adult brain, including diminished expression of tryptophan hydroxylase and the serotonin transporter in the raphe and altered

monoamine levels in several brain regions. The role of 5-HT in maternal behavior has not well characterized up to this point, as most of the work has looked at more stereotypical neuropeptides (e.g., oxytocin). The current study has extended this work to determine whether early life SSRI exposure alters female offspring behavior once they become mothers themselves. To test this idea, we treated adult female Sprague Dawley rats with the SSRI citalopram in drinking water throughout pregnancy and the postpartum period. Female perinatal SSRI-exposed and control offspring were raised to adulthood and subsequently mated with male rats with no history of SSRI exposure. After the females gave birth, we observed maternal care in the SSRI-exposed and control mothers during both the light and dark phase of the day. Our results indicate that maternal care is impacted due to early-life exposure to SSRIs. Specifically, we found that perinatally SSRI-exposed mothers spend less time in contact with their pups, show less arched-back nursing, and decreased maternal behavior consistency in the light phase. In the dark phase, we found that SSRI-exposed mothers lick and groom their pups less, spend more time on non-care behaviors, and show decreased maternal behavior consistency. Next, since previous work demonstrated that early life exposure to SSRI exposure perturbs expression of 5HT-related molecules in the developing as well as adult brain, we sought to determine whether this included alterations within brain structures that play important roles in regulating maternal behavior. Thus, we used qRT-PCR to measure expression of multiple 5-HT receptor subtypes (e.g., 5-HTR1A, 1B, 2A, and 2C) in the basolateral amygdala, bed nucleus of the stria terminalis, medial preoptic area (mPOA), and the prefrontal cortex (PFC) of adult perinatal SSRI-exposed and control females. In the mPOA, we found increased expression of 5-HTR1A in perinatally SSRI-exposed mothers. In the PFC, we found increased expression of 5-HT1B, 5-HT2A, and 5-HT2C in perinatally SSRI-exposed mothers. Taken together, these results show the importance to 5-HT in the regulation of maternal care in rodents.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.06

Topic: F.02. Behavioral Neuroendocrinology

Support: GE100658U1024

Title: Individual variation in human infant microbiomes has minimal or no effect on rodent maternal behaviors in a small, pilot study

Authors: *A. WHITE[1], S. LIU[1], H. DUBEY, SR[2], J. S. LONSTEIN[3], R. KNICKMEYER[2];
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Abstract: Background: Maternal behaviors such as feeding, thermoregulation, and protection are essential to offspring survival. In both rodents and humans, reduced quality of maternal care is associated with reduced cognitive performance, impaired social affiliation, and increased anxiety in offspring**.** Given the lifelong impact of quality of maternal care on offspring neurodevelopment and mental health, it is essential to understand the factors that produce variations in the quality of maternal care. Multiple rodent

studies show that manipulating gut microbiota influences non-maternal social behaviors and alter cellular and molecular features in brain regions that also play a role in maternal behavior. Furthermore, a particular E. coli strain was recently shown to disrupt the maturation of maternal behavior in mice. However, no study has examined how normal variation in human gut microbiomes might influence maternal behavior.**Method**: Human infant gut microbiota dominated by Bacteroides (BAC), human infant gut microbiota dominated by Bifidobacterium (BIF), and murine specific pathogen-free gut microbiota (SPF) were transplanted into pregnant germ-free Swiss Webster mice (BAC n=2, BIF n=3, SPF n=2). Maternal behaviors were observed in a minimal/stress-free environment three days a week, from day five until day nineteen postpartum. During observation, dam behaviors were marked at every minute for twenty-five minutes.**Results**: Initial results suggest that maternal behavior is not affected by transplant with these particular human microbiomes.**Implications/Future Directions**: We will be studying offspring behavior, neuroanatomy, and neurochemistry. Current results suggest that any differences observed in offspring are not mediated by differences in maternal behavior.

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Poster

P594. Parental Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: KAKENHI Grant Number 18K07584, 20J22665
Suzuken Memorial Foundation

Title: The amygdalohippocampal area neurons projecting to the hypothalamus and bed nucleus of the stria terminalis mediates infanticide, aggression, and mating

Authors: *K. SATO, M. MINAMI, T. AMANO;
Dept. of Pharmacol., Grad. Sch. of Pharmaceut. Sciences, Hokkaido University., Hokkaido, Japan

Abstract: In rodents, the medial preoptic area (MPOA) is thought to be the most important region for parental behavior. Although tracing studies reveal that the MPOA receives input from multiple regions, the functional input to the MPOA remains unclear. Here, we focused on the amygdalohippocampal area (AHi), which projects to the MPOA and expresses oxytocin receptor (OXTR). c-Fos immunostaining experiments revealed that MPOA-projecting AHi neurons were activated by both parenting and aggression toward pups. Pharmacogenetic activation disrupted the expression of parental behavior in both paternal mice and partially paternal mice (father in gestation experience; FGE mice) which showed either parental or aggressive behaviors. Interestingly, in paternal mice, but not FGE mice we observed a decrease in the proportion of individuals exhibiting aggressive behavior from day to day. Next, to assess how OXT affects these neurons, we recorded inhibitory response of MPOA-projecting AHi neurons using whole-cell patch-clamp recording. Bath application of oxytocin increased the frequency of spontaneous inhibitory postsynaptic currents in both virgin and paternal mice, which a greater increase in paternal

mice, suggesting plasticity in sensitivity to oxytocin. Recent studies report that the AHi mediate other social behaviors such as aggression and mating via projecting to several brain regions. However, it is still unclear whether subpopulation in the AHi innervate downstream brain regions singly or collaterally. We found that MPOA-projecting AHi neurons send axons to multiple targets collaterally. Among them, the ventromedial nucleus of the hypothalamus (VMH) and bed nucleus of the stria terminalis (BNST) which were thought to be important regions for aggression and mating connected to MPOA-projecting AHi neurons via excitatory synapse. Retrograde tracing using cholera toxin subunit B (CTB) revealed that approximately half of projector in the AHi innervated two or three regions. Immunostaining against c-Fos, a marker of neuronal activity, combined with retrograde tracers showed that several subpopulations of the AHi were activated by specific social behaviors based on their projection patterns. In conclusion, our study suggested the presence of distinct inputs from the AHi to the MPOA, VMH, and BNST that biases male's behavior choice. The AHi is a neural locus that can expand the neural circuits underlying social behavior in response to the counterpart through direct excitatory control of MPOA, VMH, and BNST.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.08

Topic: F.02. Behavioral Neuroendocrinology

Support: R01MH119250

Title: A circuit from the locus coeruleus to the anterior cingulate cortex displays sex-dependent activity in offspring-directed behavior

Authors: *A. CORONA, P. OSTEN, S. D. SHEA;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: How sexually divergent behaviors arise from sex differences in the underlying neural networks for social behavior remains elusive. Interestingly, mice display pronounced sex differences in offspring directed behaviors. Parental behaviors are fundamental for survival of offspring, and while the maternal brain has been studied extensively in rodents, the neural networks underlying paternal care are less well understood. In order to compare the networks that underlie parenting behavior in males and females, we used *c-fos* as a marker for neuronal activation after pup interactions, and an automated pipeline to map whole-brain activity at cellular resolution. We identified candidate brain regions that responded to pup-directed behaviors including the anterior cingulate area (ACA). We chose to focus on ACA because it has been implicated in sensitivity to social distress and it is interconnected with the noradrenergic locus coeruleus (LC), an important regulator of maternal behavior. We used fiber photometry to observe activity in ACA and LC during free interactions with pups. We found that excitatory neurons in the ACA are differentially activated in males and females during pup retrieval behavior and that inhibitory neurons show reciprocal activity patterns. We also observed that pup retrieval behavior evokes strong sex-

dependent neuronal responses in LC. Moreover, using neuroanatomical tracing, we confirmed that ACA receives robust inputs from LC, and using a noradrenaline sensor, we observe that pup retrieval behavior evokes noradrenaline release in ACA. Finally, we showed that chemogenetic inactivation of excitatory neurons in ACA disrupts pup retrieval behavior in early postnatal days and decreases motivation to interact with pups in distress. Based on these findings, we hypothesize that the ACA signals social distress from the pups and guides decision making in parenting behavior. Moreover, sexually divergent activation of this circuit may contribute to behavioral differences between males and females.

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Poster

P594. Parental Behavior

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Program #/Poster #: P594.09

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH FHD102163A

Title: The role of the amygdalohippocampal transition area in cognition and parenting

Authors: *V. M. SEDWICK[1], K. OLUYEMI[1], *M. DAYE[3], A. E. AUTRY[1,2];
[1]Dominick P. Purpura Dept. of Neurosci., [2]Dept. of Psychiatry and Behavioral Sci., Albert Einstein Col. of Med., Bronx, NY; [3]Mercy Col., Bronx, NY

Abstract: Postpartum depression has a prevalence of 15-20% in new mothers and 10% in new fathers. While the condition is predominantly characterized by impairments in parental care and mood, diagnosed individuals also display cognitive impairments and metabolic disruptions such as memory loss and weight gain. In many species, particularly mammals, parenting behavior is highly conserved. The full spectrum of parental expression can be seen in laboratory mice. We have identified a nucleus in the amygdala, the amygdalohippocampal transition area (AHi), to be a key brain area in the parental behavior circuit. Several groups have shown that activation of AHi subpopulations promotes infant-directed aggression in virgin males and fathers as well as intermale aggression. We believe that the AHi plays a role in both sociosexual behaviors as well as cognitive functions such as memory. To test this hypothesis, we lesioned the AHi using NMDA in males and female (n=5/group), and saline for the controls. Through lesion studies, we find that total loss of function of the AHi results in increased infant-directed aggression and social dominance in females suggesting that the nucleus can promote both negative and positive parental expression. Additionally, we observed sexually dimorphic metabolic disruptions such as increase weight gain in females, and hyperphagia in males compared to non-lesioned controls. We also aim to identify whether AHi related deficits in parenting are also correlated with memory impairments. The goal for this study is to improve our understanding of the AHi's role in sociosexual behaviors such as parenting. We believe this study may offer better insights to the amygdala's role in pathologies related to parental behavior such as postpartum depression.

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Poster

P594. Parental Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: PNW Undergraduate Research Grant
PNW College of Engineering and Sciences Grant

Title: Observation of foster and biological mother offspring relationships and the development of orphaned Sumatran orangutans in captivity

Authors: A. KOCOSKI[1], E. E. ALPERS[1], V. S. QUINN[1], *C. M. RAGAN[2];
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Abstract: Sumatran orangutans (*Pongo abelii*) are a critically endangered subspecies of Great Apes found in Sumatra, Indonesia. Due to deforestation perpetrated through multiple sources, the Sumatran orangutan population is projected to further decrease throughout the next decade. Deforestation displaces offspring from their mothers which is devastating due to their heavy reliance on their mothers to learn essential survival skills. While studies have gauged the extent of deforestation and its impact on species survival, little research or public awareness efforts have been undertaken that explore effective primate conservation programs that can immediately help affected species or alert the public of this dire situation. Our study attempts to fill this gap by examining video observations among foster and biological Sumatran orangutan mother-offspring interactions from existing online footage and video recordings we collected at Zoo Atlanta. These observations allow us to explore comparisons between foster and biological family group interactions while highlighting current conservation efforts. We hypothesized that successful foster mother-offspring relationships should imitate biological mother-offspring relationships as foster conservation programs intend to simulate biological mother-offspring bonds while providing offspring with the same nurturing opportunities throughout development. Although publicly-available foster pair video observations are limited, we have begun to accumulate live footage throughout our study. Subjects include Sumatran orangutans at Zoo Atlanta and fourteen biological mother-offspring pairs obtained from online video resources. Preliminary findings from previously-recorded videos suggest both biological and foster mother-offspring pairs engage in similar levels of trademark behaviors. Both mother groups engaged in similar levels of movement-oriented behaviors like climbing and traveling. In addition, offspring groups engaged in similar levels of carried behavior, where offspring cling to their mothers' fur, which is an indicator of healthy orangutan development. These data, alongside existing foster studies in other primates, suggest foster programs are a feasible form of primate conservation. Upon completion of coding behavior from orangutans at Zoo Atlanta, we will analyze foster and biological mother-offspring interactions, such as: being carried, traveling, climbing, etc. Our foster pair analyses compared with biological mother-offspring interactions allow us to understand the benefits primate foster programs provide.

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Poster

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Program #/Poster #: P594.11

Topic: F.02. Behavioral Neuroendocrinology

Title: Association between quality of life and burden of care among informal caregivers of individuals with spinal cord injury: A mixed method study

Authors: R. A. OMOSEHIN, N. ODUNAIYA, J. O. OJO, O. ERINLE;
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Abstract:

Disclosures: R.A. Omosehin: None. **N. Odunaiya:** None. **J.O. Ojo:** None. **O. Erinle:** None.

Poster

P744. Molecular and Neural Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P744.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NRF Korea Grant (2019R1A2C1011262)

Title: Inactivation of basolateral amygdala by hM4D(Gi) inhibits the expression of amphetamine-induced conditioned place preference

Authors: H. RIM[1], J. HAN[1], W. CAI[2], W. KIM[2], *J.-H. KIM[1];
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Abstract: The environment repeatedly paired with drugs of abuse can be preferably chosen by animals. Such phenomenon called conditioned place preference (CPP) basically consists of 2 phases; acquisition and expression. Although basolateral amygdala (BLA) has been shown to be important in emotional and reward processing, it is not clearly determined yet what role it has in each phase of CPP. In this study, we examined whether amphetamine (AMPH)-induced CPP is influenced by activation of designer receptors exclusively activated by designer drugs (DREADDs) in the BLA. Male Sprague-Dawley rats received AAV encoding an inhibitory hM4D(Gi) bilaterally into the BLA. In experiment 1, rats received systemic injections of deschloroclozapine (DCZ) (0.02 or 0.1mg/kg, IP), a selective muscarinic DREADD actuator, or saline 15 minutes before the start of each AMPH (2.5 mg/kg) conditioning (acquisition phase) and they were tested for conditioning with no drugs. In experiment 2, rats received repeated AMPH with no DCZ but they were tested for conditioning with injection of DCZ (0.02 or 0.1mg/kg, IP) (expression phase).

Interestingly, we found that chemo-genetic inactivation of BLA neurons inhibited the expression of AMPH-induced CPP, while it has no effect on the acquisition. These results indicate that activation of the BLA is critical for the expression of cue-induced drug-associated memory and implicate its role in reward-seeking behavior.

Disclosures: H. Rim: None. **J. Han:** None. **W. Cai:** None. **W. Kim:** None. **J. Kim:** None.

Poster

P744. Molecular and Neural Mechanisms II

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Program #/Poster #: P744.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA02812

Title: Effects of methamphetamine on within and between network connectivity in healthy adults

Authors: M. MALINA[1], *S. KEEDY[1], J. WEAFER[2], K. VAN HEDGER[3], H. DEWIT[1];
[1]Univ. of Chicago, Chicago, IL; [2]Univ. of Kentucky, Lexington, KY; [3]Univ. of Western Onatario, London, ON, Canada

Abstract: Methamphetamine (MA) abuse remains an urgent public health problem. Understanding how the drug affects brain function will help to identify how it leads to abuse and dependence. Previous studies indicate that MA and other stimulants have complex effects on resting state functional connectivity. Here, we used a hypothesis-free approach to examine the acute effects of MA (20mg oral) vs placebo on neural connectivity in healthy adults aged 18 to 35 (n=22, 12 women). Using networks identified by an independent component analysis (ICA) using placebo data, we examined the effects of MA on within and between resting state networks, expanding the search for drug effects beyond conventional drug-reward circuitry. The placebo ICA scan yielded 28 networks, and MA reduced connectivity in 9 of these, including in the visual and sensorimotor cortex, and subcortical structures. MA had mixed effects on connectivity between networks. It increased connectivity between frontal, fronto-parietal and temporal networks, and between subcortical and cortical networks, but decreased connectivity across other networks, including basal ganglia and thalamus. MA produced its expected subjective effects, but these were not significantly related to connectivity. The findings extend our knowledge of how MA affects connectivity by delineating its effects both within and between networks. Future studies with other behavioral measures may reveal relationships between the neural and behavioral actions of the drug.

Disclosures: M. Malina: None. **S. Keedy:** None. **J. Weafer:** None. **K. Van Hedger:** None. **H. DeWit:** None.

Poster

P744. Molecular and Neural Mechanisms II

Location: Virtual Only

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Program #/Poster #: P744.03

Topic: G.09. Drugs of Abuse and Addiction

Support: DA038058

Title: The Role of Syntaxin 1 Phosphorylation in the Reverse Transport of Dopamine

Authors: *S. MABRY[1], A. SHEKAR[2], M. H. CHENG[3], D. ZANELLA[1], J. I. AGUILAR[2], S. M. PATEL[1], A. M. CARTER[1], I. BAHAR[3], H. MATTHIES[1], A. GALLI[1];
[1]Surgery, Univ. of Alabama Birmingham, Birmingham, AL; [2]Pharmacol., Vanderbilt Univ., Nashville, TN; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The dopamine (DA) transporter (DAT) is an *SLC6* family presynaptic membrane protein that maintains DA homeostasis in the brain via active reuptake of DA. Although the conventional role of this transporter, DA reuptake, is well-characterized, less is known about its less prevalent and unconventional role, reverse transport of DA (DA efflux). In this study, we defined the context and mechanisms underlying DA efflux *via* the DAT and its regulation by the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein syntaxin 1 (Stx1). We uncovered that N-terminal phosphorylation of DAT is required to promote both amphetamine (AMPH)-induced and constitutive DA efflux. We also determined that Stx1 interacts with the DAT N-terminus and this interaction enhances DA efflux. Furthermore, blocking of AMPH-induced Stx1 phosphorylation *via* pharmacological inhibition of casein kinase 2 (CK2) or by genetic manipulation prevents DA efflux. Insights from molecular dynamic simulations demonstrated that AMPH-induced phosphorylation of DAT and Stx1 leads to the breaking of multiple salt bridges in DAT, most notably between K66 and D345. The disruption of these salt bridges alters the dynamics of the intracellular gate in favor of an inward open conformation of DAT that binds DA on the intracellular face, a conformation we hypothesize promotes DA efflux. We translated these findings to *Drosophila melanogaster* where we found that AMPH-induced DA efflux and its behavioral consequences (increased locomotion, courtship behaviors, and preference) are inhibited by the pharmacological blockade of Stx1 phosphorylation. In conclusion, these studies have uncovered new mechanisms underlying DA efflux and identified key proteins in the reverse transport pathway. These proteins are potential therapeutic targets for patients that harbor DAT disease variants that exhibit constitutive DA efflux as well as patients that suffer from substance use disorders involving psychostimulant drugs like AMPH.

Disclosures: S. Mabry: None. **A. Shekar:** None. **M.H. Cheng:** None. **D. Zanella:** None. **J.I. Aguilar:** None. **S.M. Patel:** None. **A.M. Carter:** None. **I. Bahar:** None. **H. Matthies:** None. **A. Galli:** None.

Poster

P744. Molecular and Neural Mechanisms II

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Program #/Poster #: P744.04

Topic: G.09. Drugs of Abuse and Addiction

Support: Wayne State University Bridge Grant
NIH/NIDA DA034738
Yale/NIDA Neuroproteomics Center Pilot Research Project Grant

Title: Parkin Regulates Drug-Taking Behavior In Rat Model of Methamphetamine Use Disorder

Authors: A. SHARMA[1], B. L. SCHNEIDER[2], R. GARCIA-MILIAN[3], T. LAM[3], ***A. MOSZCZYNSKA**[1];
[1]Wayne State Univ., Detroit, MI; [2]Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland; [3]Yale Univ., New Haven, CT

Abstract: There is no FDA-approved medication for methamphetamine (METH) use disorder. New therapeutic approaches are needed, especially for people who use METH heavily and are at high risk for overdose. This study used genetically engineered rats to evaluate PARKIN as a potential target for METH use disorder. PARKIN knockout, PARKIN-overexpressing and wild type young adult male Long Evans rats were trained to self-administer high doses of METH using an extended-access METH self-administration paradigm. Reinforcing/rewarding properties of METH were assessed by quantifying drug-taking behavior and time spent in a METH-paired environment. PARKIN knockout rats self-administered more METH and spent more time in the METH-paired environment than wild type rats. Wild type rats overexpressing PARKIN self-administered less METH and spent less time in the METH-paired environment. PARKIN knockout rats overexpressing PARKIN self-administered less METH during the first half of drug self-administration days than PARKIN-deficient rats. Proteomic data suggests that different pathways mediate predisposition and resilience to METH addiction in these two genotypes. The results indicate that rats with PARKIN excess or PARKIN deficit are useful models for studying neural substrates underlying “resilience” or vulnerability to METH use disorder, and identify PARKIN as a novel potential drug target to treat heavy use of METH.

Disclosures: A. Sharma: None. **B.L. Schneider:** None. **R. Garcia-Milian:** None. **T. Lam:** None. **A. Moszczynska:** None.

Poster

P744. Molecular and Neural Mechanisms II

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Program #/Poster #: P744.05

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R03MH104851

Title: Prenatal methamphetamine exposure affects gene expression and cognitive development in a mouse model

Authors: ***T. T. ADEYELU**[1], P. A. ADENIYI[2,1], A. SHRESTHA[2,1], C. C. LEE[1];
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Abstract: Methamphetamine is a highly addictive drug, an adrenergic agonist, that activates reward circuitry. Prenatal exposure to methamphetamine is implicated in cardiac defects, neurological disorders, and cognitive decline, but these have not been well characterized. In this study, we employed behavioral approaches, biochemical assays, as well as RNA-based differential gene expression analysis, to assess the impact of prenatal exposure to methamphetamine on cognitive development. RNA samples from mice prenatally exposed to methamphetamine and saline control were analyzed by Novogene lab in which RNA-FASTQ transcripts were mapped to the reference genes. The gene expression levels were measured and the differentially expressed genes were obtained by comparing between groups. Bioinformatic analysis using GO annotations, KEGG pathways, and protein interaction networks revealed differentially expressed genes such as ADCY1, Camk2α, and Akt3 that are implicated in methamphetamine neurotoxicity. Furthermore, the behavioral analysis revealed a statistically significant ($p<0.05$) decline in cognitive behaviors of the methamphetamine exposed animals compared to controls. These data reveal links between methamphetamine neurotoxicity and alteration of several genes which might be implicated in altering pathways that are also implicated in memory formation and reward-seeking behaviors.

Disclosures: T.T. Adeyelu: None. **P.A. Adeniyi:** None. **A. Shrestha:** None. **C.C. Lee:** None.

Poster

P744. Molecular and Neural Mechanisms II

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Program #/Poster #: P744.06

Topic: G.09. Drugs of Abuse and Addiction

Support: extraordinary support VIEP-BUAP-2020

Title: Evaluation of the chronic oral administration of clobenzorex or amphetamine on motor behaviors, the glia, and the dopaminergic system.

Authors: *A. PATRICIO-MARTÍNEZ[1,2], G. D. APÓSTOL DEL ROSAL[1], I. MARTÍNEZ[3], I. D. LIMÓN[1];
[1]Lab. de Neurofarmacología-FCQ-Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [2]Facultad de Ciencias Biológicas-Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [3]Lab. de Neuroquímica-FCQ-Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Clobenzorex hydrochlorate, trade name Asenlix, is an N-substituted compound of S (+) - amphetamine. In Mexico, it is one of the five main anorectic drugs used to treat obesity. A controlled drug sold only by prescription, clobenzorex is available on the illicit market, where it is sold as a recreational drug. Some studies have shown that the consumption of clobenzorex produces hepatotoxicity and cardiovascular side effects such as heart failure, arterial hypertension, and pulmonary artery hypertension. However, its toxic effects on the central nervous system are unknown. Various studies have shown that amphetamines induce dopaminergic neurotoxicity and neuroinflammation in the striatum, symptoms which are associated with motor damage. For this reason, the aim of this study was to evaluate the effect of chronic clobenzorex administration on motor behaviors, TH immunoreactivity, gliosis, and the neurodegenerative process in the striatum and substantia nigra pars compacta (SNpc). The present

research was conducted on three experimental groups of male Wistar rats: the vehicle group; the amphetamine group (2 mg / kg); and, the clobenzorex group (30 mg / kg). All groups were subject to oral administration every 24 hours for 31 days. Motor activity and motor coordination were evaluated every 10 days in the open field test and the beam walking test, respectively. Thirty-two days post-administration the animals were euthanized to enable the extraction of their brains for the evaluation of tyrosine hydroxylase (TH) levels, the immunoreactivity of the glial cells (GFAP and Iba-1), and the neurodegeneration of both the striatum and SNpc. The results obtained show that amphetamine and clobenzorex administration decrease motor activity (distance traveled, average speed and number of rearings) and motor coordination (number of errors) in the beam walking test and cause increased gliosis in the striatum, while no significant changes were observed in terms of immunoreactivity to TH and neurodegeneration in both the striatum and SNpc. These results suggest that the chronic administration of clobenzorex may decrease motor function in a manner similar to amphetamine, via the neuroadaptive and non-neurotoxic changes caused to the striatum under this administration scheme.

Disclosures: A. Patricio-Martínez: None. **G.D. Apóstol del Rosal:** None. **I. Martínez:** None. **I.D. Limón:** None.

Poster

P744. Molecular and Neural Mechanisms II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P744.07

Topic: G.09. Drugs of Abuse and Addiction

Support: FONDECYT grant N° 1191274

Title: Reactive oxygen species modulate amphetamine induced effects

Authors: *C. BLANLOT, J. ZEGERS, J. NOVOA, F. CALDERON, H. YARUR, C. BASTIAS, K. GYSLING;
Dept. of Cell. and Mol. Biol., Pontificia Univ. Catolica De Chile, Santiago, Chile

Abstract: The increase of dopamine (DA) in the reward system is related to the reinforcing effects of drugs of abuse and hyper locomotion induced by psychostimulants. The increase of DA induced by drugs of abuse generates oxidative stress, a cellular condition produced by high amount of reactive oxygen species (ROS). Interestingly, it has been showed that ROS could modulate psychomotor response and reinforcing effects induced by drugs of abuse such as cocaine and methamphetamine (METH). Nevertheless, the relation of ROS and amphetamine (AMPH) has not been evaluated. Here, we show that administration of the ROS scavenger 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL) results in the attenuation of AMPH enhancement of locomotor activity in rats. Furthermore, TEMPOL also attenuates the oxidative stress and the increase of DA induced by AMPH in nucleus accumbens (Nac). Finally, TEMPOL reduce DAT phosphorylation when is co-infused with AMPH in Nac synaptosomes. Taking together, our results suggest that ROS modulate locomotor and reward effects induced by AMPH in rats. Funded by FONDECYT grant N° 1191274.

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Poster

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Program #/Poster #: P744.08

Topic: G.09. Drugs of Abuse and Addiction

Support: FONDECYT grant N° 1191274

Title: Amphetamine induced toxicity in PC12 cells is due to the production of oxidative stress

Authors: *C. BASTIAS[1], J. A. ZEGERS[2], K. GYSLING[1];
[1]Dept. of Cell. and Mol. Biol., [2]Fac. of Biol. Sci. Dept of Cell. and Mol. Biol., Pontificia Univ. Catolica De Chile, Santiago, Chile

Abstract: Amphetamine has been reported to cause toxicity in PC12 cells but the mechanism by which it occurs is unknown. Treatment with 2.5 mM amphetamine reduces cell number up to 4 times while treatment with 3mM amphetamine entirely eliminates PC12 cells. We used the oxidative stress marker 8-hydroxy-2′-deoxyguanosine (8-OHdG) to further study the effects of incubation of PC12 cells with amphetamine. A significant increase in the fluorescence of 8-OhdG in the cells was observed when PC12 cells were incubated with 1.5 and 2.5mM amphetamine, in addition to a morphological loss of cells. We propose that the effect of amphetamine may be generated by changes in the dopamine transporter (DAT). Thus, we are analyzing the levels of DAT and P-DAT in PC12 extracts. We expect that the effect of amphetamine will be attenuated or rescued with the co-incubation of amphetamine with antioxidants such as alpha-lipoic acid and Tempol.Funded by FONDECYT grant N° 1191274

Disclosures: C. Bastias: None. **J.A. Zegers:** None. **K. Gysling:** None.

Poster

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Program #/Poster #: P744.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA035263

Title: Mechanistic Insight into Microbial Regulation of Psychostimulant Abuse

Authors: S. J. MABRY[1], X. CAO[3], S. M. PATEL[1], A. M. ELAM[2], Y. ZHU[1], D. P. SALEEBY[1,3], H. WU[3], *A. GALLI[1], **A. M. CARTER**[1];
[1]Surgery, [2]Psychiatry, Univ. of Alabama Birmingham, Birmingham, AL; [3]Dent., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Amphetamines (AMPHs) are highly effective psychostimulants commonly used for the treatment of neuropsychiatric disorders and are abused with devastating outcomes. The abuse potential and psychomotor stimulant properties of AMPHs have been associated with their ability to increase extracellular dopamine (DA) levels. This increase is mediated, at least in part, by the reversal of DA transporter (DAT) function, which causes non-vesicular DA release, here defined as DA efflux. Recent studies suggest that imbalances in the gut microbiome (dysbiosis) participate in the pathogenesis of substance use disorders. Microbial products such as short-chain fatty acids (SCFAs), are suspected to play a fundamental role in this process. Among SCFAs, butyrate is known to cross the blood-brain barrier and directly act on neurons and glial cells. *Fusobacterium nucleatum* (*F. nucleatum*) is a bacterial species that secretes butyrate and whose abundance is increased by AMPH abuse in both rodents and humans. It is important to note that butyrate is a potent inhibitor of histone deacetylases (HDACs) and that inhibition of HDACs robustly increases expression of both DAT mRNA and protein levels in cultured cells. Changes in DAT expression regulates both AMPH-induced DA efflux and psychomotor actions. Here, we report that colonization of the intestinal tract of gnotobiotic *Drosophila* with *F. nucleatum* significantly enhances AMPH-induced DA efflux and associated behaviors such as locomotion, courting, and preference. This potentiation of AMPH actions by *F. nucleatum* was paralleled by oral administration of butyrate. In contrast, acetate, another SCFA secreted by *F. nucleatum*, failed to enhance both AMPH-induced DA efflux and locomotion. Further, inhibition of HDACs using Trichostatin A, as well as genetic knockdown of HDAC1 in DA neurons *via* RNAi, both increased AMPH-induced DA efflux and locomotion. Importantly, both pharmacological inhibition, as well as genetic knockdown of HDAC1, also lead to a significant increase in DAT expression. These data demonstrate that *F. nucleatum* modulates AMPH-induced behaviors through secretion of butyrate, inhibition of HDACs, elevation of DAT expression, and increased DA efflux. These findings suggest modulation of the gut microbiome as a therapeutic approach for the treatment of substance use disorders.

Disclosures: S.J. Mabry: None. **X. Cao:** None. **S.M. Patel:** None. **A.M. Elam:** None. **Y. Zhu:** None. **D.P. Saleeby:** None. **H. Wu:** None. **A. Galli:** None. **A.M. Carter:** None.

Poster

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Program #/Poster #: P744.10

Topic: G.09. Drugs of Abuse and Addiction

Title: Sigma-1 ligands modulate methamphetamine sensitization and reward circuitry

Authors: *A. R. ALLEYNE[1], L. L. WILSON[1], S. W. HARDEN[1], C. R. MCCURDY[2], C. J. FRAZIER[1], J. P. MCLAUGHLIN[1];
[1]Pharmacodynamics, [2]Medicinal Chem., Univ. of Florida, Gainesville, FL

Abstract: Sigma-1 receptors (σ1Rs) are ubiquitously expressed chaperone proteins implicated in neuroplasticity, neuroprotection, and cardiovascular function. While basally located within the mitochondria-associated membrane, cellular stress promotes σ1R translocation to the plasma membrane where they modulate the function of other receptors and ion channels to alter cellular physiology. Evaluating this state-dependent localization of σ1R activation has proven challenging. As σ1R antagonism within pain and reward circuitry has demonstrated therapeutic relevance in both preclinical and clinical studies, a better understanding of mechanisms regulating σ1R translocation and interaction with other proteins is needed. Using both *in vivo* and *ex vivo* techniques, we examined the role of σ1Rs in methamphetamine (METH)-induced locomotor sensitization, hypothesizing that σ1Rs modulate sensitization by promoting excitation in reward/locomotor circuitry which is attenuated with σ1R antagonism. Using mice treated twice daily for 7d with saline (0.9%, i.p.), METH (2 mg/kg, i.p.), the σ1R antagonist, CM304 (30 mg/kg, i.p.), or both METH & CM304, we recorded locomotor behavior resulting from a 1 mg/kg, i.p. treatment of METH. Following a 1 week washout without treatment, mice that had been treated with both METH & CM304 demonstrated a significant reduction in METH-induced hyperlocomotion compared to METH-treated positive controls, suggesting σ1R antagonism may prevent psychostimulant sensitization. To characterize potential cellular mechanisms driving this behavior, we used electrophysiological tools to evaluate the effect of σ1R ligands on medium spiny neurons (MSNs) within the nucleus accumbens (NAc), a key region within the reward pathway. We found that while acute application (10 min) of the σ1R agonist SA4503 (cutamesine; 10 μM) excites NAc MSNs, prolonged exposure (30-90 min) significantly reduces their ability to fire action potentials continuously during a maintained depolarization, interestingly without altering instantaneous firing frequency. In contrast, prolonged exposure to the σ1R antagonist S1RA increased the ability of MSNs to fire continuously in response to moderate current injections, also without altering instantaneous firing frequency. Together these findings suggest that σ1Rs may modulate the psychostimulant effects of drugs of abuse such as METH by altering neuronal excitability in reward circuitry sensitive to σ1R antagonist treatment, providing a novel target for the treatment of substance abuse disorder.

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Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

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Program #/Poster #: P791.01

Topic: H.03. Decision Making

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ARO W911NF1710554
NIH R01 DA047869

Title: Neural substrates of sex-specific modulation of motivation by value

Authors: *J. COX, W. T. FLEMING, C. HAYES, S. ORNELAS, A. BANDI, C. A. ZIMMERMAN, N. F. PARKER, I. B. WITTEN;
Princeton Univ., Princeton, NJ

Abstract: While there is emerging evidence of sex differences in decision-making behavior, the neural substrates that underlie such differences are largely unknown. To examine the neural basis of sex differences in value-based decision making, we trained mice to perform a self-initiated, probabilistic reversal learning task in which they regulated both their trial-by-trial choices as well as their motivation to engage in the task, based on recent experiences. We found that while choices were similar between the sexes, motivation to engage in the task was modulated by chosen value in females more strongly than in males. Both the prefrontal cortex (PFC) and the dorsomedial striatum (DMS) are thought to be important for making value-based choices and regulating motivation. Therefore, we performed single-photon calcium imaging and optogenetic inhibition of neurons in the anterior cingulate cortex that project to the DMS (ACC-DMS neurons) to determine whether there were sex differences in the representation of task-specific information in these neurons. Consistent with the behavioral differences, in females, ACC-DMS neurons had stronger representations of negative outcomes, and more neurons were active when the value of the chosen option was low, compared to males. In contrast to these differences in the representation of outcomes and the value of the chosen option, the representation of each choice was similar between the sexes. Finally, optogenetic inhibition of activity in ACC-DMS neurons disrupted the relationship between chosen value and motivation specifically in females, without affecting motivation in males. Additionally, this inhibition did not affect choice in either sex. Thus, we show that the projection from ACC to DMS has a sex-specific role in the modulation of motivation by value.

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Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

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Topic: H.03. Decision Making

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National Science Foundation Grant DBI-1460880
New York University (NYU Research Challenge Fund; NYU Dean's Dissertation Fellowship)
Vulnerable Brain Project

Title: Gabaergic interneurons driven by dorsal raphe-projecting pyramidal neurons of medial prefrontal cortex regulate feeding of adolescent female mice undergoing activity-based anorexia

Authors: *M. DU[1,2], A. N. SANTIAGO[2], C. J. AOKI[2];
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Abstract: Anorexia Nervosa (AN) is a mental illness, characterized by voluntary food restriction and excessive exercise and with a mortality rate that surpasses that of major depression. An animal model, activity-based anorexia (ABA), captures the characteristics of AN and has been used to understand the neurobiological mechanisms underlying individual differences in vulnerability to AN. Previous studies have uncovered the role of dorsal raphe (DR) in regulating feeding behaviors of mice. Interestingly, DR does not receive any direct input from the primary sensory or motor cortices but does receive substantial input from layer 5 pyramidal cells of the medial prefrontal cortex (mPFC), suggestive of higher-order cognitive control. In this study, we used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to activate layer 5 pyramidal cells of mPFC projecting to DR (mPFC-DR) to explore the role of mPFC in an animal's decision to eat within the context of ABA. Contrary to expectations, although intraperitoneal Compound 21 (C21) could activate ~44% of the mPFC-DR cells, this did not reveal significant group mean difference in the amount of food intake of ABA mice undergoing food restriction (N=7, female), compared to the control ABA mice without mPFC-DR cell activation (N=11, female). However, further analysis through triple immunofluorescence (IF) of individual animals' responses to C21 during ABA revealed a significant and positive correlation between DREADD-expressing cells that co-express the immediate early gene, cFos, and the food intake ($r=0.78$, $p=0.0384$). Furthermore, triple IF used to label mCherry (for mPFC-DR pyramidal neurons), GABA cells and cFos within mPFC revealed that ~8.6% of GABA cells also expressed cFos, a level that was significantly greater than that in the control group ($p=0.043$), suggesting that mPFC-DR pyramidal cells recruit GABA cells. Besides, electron microscopic immunohistochemistry showed that GABAergic innervation is 60% stronger for the mPFC-DR cells than that of the non-DR-projecting pyramidal cells in layer 5 ($p=0.0312$) and correlates negatively with the food intake specifically on the day of C21 administration ($r=-0.9181$, $p=0.0035$). Thus, C21 is likely to have resulted in minimal change of food intake due to activation of two antagonistic pathways in the mPFC: (1) mPFC-DR pyramidal cells that promote food intake, and (2) GABA cells in mPFC that dampen food intake through feed-forward inhibition of mPFC-DR pyramidal cells. These results indicate that GABA cells driven by mPFC-DR cells may participate in regulating feeding of adolescent female mice undergoing ABA, and may be a potential target for treating AN.

Disclosures: M. Du: None. **A.N. Santiago:** None. **C.J. Aoki:** None.

Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

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Program #/Poster #: P791.03

Topic: H.03. Decision Making

Support: NYU Dean's Undergraduate Research Fund
Vulnerable Brain Project

Title: To eat or to run. A chemogenetic investigation of the role of PV/GABA cells in the prefrontal cortex of food restriction-stressed adolescent mice in an animal model for anorexia nervosa

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Abstract: Anorexia Nervosa (AN) is a mental illness characterized by severe self-imposed starvation and intense anxiety manifested as fear of gaining weight. With no accepted pharmacological treatments available and high mortality and relapse rates, better understanding of the neurobiological basis of AN is needed. Activity-based anorexia (ABA) is an animal model of AN that captures the core features of AN: voluntary food restriction (FR), excessive exercise heightened anxiety. The FR-evoked excessive running can become lethal if energy expenditure exceeds caloric availability. Chemogenetic modulation of the medial prefrontal cortex (mPFC) pyramidal cells can bi-directionally alter running during hours preceding limited food availability, but not during days with ad libitum food access in the ABA model (Santiago, Makowicz et al., 2020). The same study yielded a new hypothesis - that axo-somatic inhibition by parvalbumin-containing GABAergic interneurons (PV) of the mPFC is the site of plasticity, yielding individual differences in resilience to FR-evoked stress, such as ABA. We tested this hypothesis by chemogenetically modulating PV cells in the mPFC during the FR phase of ABA using excitatory and inhibitory DREADDs transfected by the cre-dependent AAV in PV-Cre knockin mice. The active cells in the mPFC were identified by cFos immunoreactivity (ir). cFos+/GAD+ ir was identified as activated GABA cells while cFos+/GAD- was identified as activated pyramidal cells. mCherry ir identified PV cells expressing Gq-DREADDs and driven by Compound 21 (C21). We report on three results supporting the hypothesis: (1) The calories an animal consumed on the FR days that PV cells were chemogenetically modulated correlated negatively with the percent of all cells encountered (immunolabeled for GAD and/or cFos and/or mCherry) that were activated GABA cells (r=-0.8; p=0.055, N=6, FR4) and were positively identified to be PV cells (r=-0.95, p=0.012, N=5, FR2) This result supports the idea that PV/GABAergic suppression of the excitatory outflow from mPFC suppresses food consumption. (2) The percentage of activated GABA cells and calories the animal consumed on FR4, relative to their average food consumption prior to FR correlated positively (r=0.94; p=0.04, N=6) as did the cells positively identified to be PV (r=0.98 , p=0.004, N=5, FR4). The reversal in the correlation direction is explained largely by (3) the positive correlation between the GABA cell firing and food consumption prior to FR (r=0.83; p=0.04, N=6). These results suggest that individual differences in ABA resilience is strongly dictated by the GABAergic inhibitory tone in mPFC that precedes the onset of FR stress.

Disclosures: C. Akiz: None. **A.N. Santiago:** None. **C.J. Aoki:** None.

Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P791.04

Topic: H.03. Decision Making

Support: ERC H2020: SEE-ACC

Title: A hierarchy of distributed representations in the anterior cingulate cortex

Authors: *T. R. COLIN, I. IKINK, C. B. HOLROYD;
Ghent university, Ghent, Belgium

Abstract: The function of the anterior cingulate cortex (ACC) remains mysterious. Univariate functional magnetic resonance imaging (fMRI) analyses fail to discriminate between dominant theories, which predict similar univariate responses: the ACC is sensitive to errors, conflict, difficulty, rewards and punishments, and shows activation during many sequential decision-making tasks. We used multivariate fMRI and computational modeling to investigate the hypothesis that ACC implements distributed representations of hierarchically-organized task sequences. First, we developed a family of artificial recurrent neural network (RNN) models of the ACC and trained those models on a hierarchical sequence task (i.e., making coffee or tea according to a pre-specified set of rules). Second, we conducted a representational similarity analysis using a searchlight procedure to compare the activity patterns of these RNN models to multivoxel patterns of fMRI activity of participants performing the same task. Comparisons were obtained using three successively more complex models: (1) an Elman RNN (2) an Elman RNN with "goal" units and (3) a goal model that incorporated an "abstraction gradient" in the hidden layer of the network. We find that all three models produce representations that match caudal areas of the ACC, but models (2) and (3) also match more rostral areas, confirming the hypothesis. Finally, we evaluate the goal model behaviourally by scaling up the task and stressing the model; consistent with previous observations, we find that the model degrades in a manner that resembles a distracted human's action slips.

Disclosures: T.R. Colin: None. **I. Ikink:** None. **C.B. Holroyd:** None.

Poster

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Topic: H.03. Decision Making

Support: NRF Grant 2020R1A2C2014830
NRF Grant 2017H1A2A1044665
NRF Grant 2021M3E5D2A01023887

Title: Temporal neural ensemble decoding of approach-avoidance behavior in prelimbic and infralimbic cortex in rats

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Abstract: The medial prefrontal cortex (mPFC) has been implicated in various cognitive processes including threat evaluation and defensive behaviors in both humans and animals. In the current study, food-deprived rats, approaching for sucrose solution, were faced with a robot predator. The robot was programmed to evoke a fast attack motion 3- or 6-s after the first lick which produces an immediate withdrawal response in rats. The rats have to decide when to stop consuming sucrose solution to avoid the attack. Several responses were identified: head entry to the lick port (ENT), avoidance before the attack

(AVO), and escape after the attack (ESC). In-vivo ensemble recordings using tetrodes revealed different encoding patterns in the prelimbic (PL) and infralimbic cortex (IL). Specifically, machine learning analysis using a support vector machine (SVM) showed that ensemble activity in PL was strongly correlated with ENT but could not distinguish between AVO and ESC. In contrast, an SVM trained from IL ensemble activity was able to discriminate all three responses. Furthermore, we performed classification accuracy analysis along the time axis to determine the critical time window for predicting the impending behavior. The IL ensemble data 3~5 seconds before the event were sufficient to reach accuracy asymptote, but PL showed linearly increasing performance peaked at the onset of the behavior. Taken together, these results suggest that two sub-regions in the mPFC encode distinctive aspects of approach-avoidance behavior, notably, IL may contribute to threat evaluation before the execution of the behavior in the conflict situation.

Disclosures: J. Jeong: None. **J. Choi:** None.

Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

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Program #/Poster #: P791.06

Topic: H.03. Decision Making

Title: A role for prefrontal cortex dopamine in regulating cognitive control

Authors: *Y. YANG, H. J. RICE, M. A. TRONOLONE, H. CHANG, I. T. ELLWOOD;
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Abstract: A critical role of the prefrontal cortex (PFC) in behavior is to allow for the context-dependent selection of appropriate actions, while inhibiting unwanted behaviors. The dopamine system in the PFC is believed to regulate this process by increasing or decreasing cognitive flexibility. Despite this, recent recordings of PFC dopamine in rodents have found release primarily following aversive stimuli. Using fluorescent dopamine sensors, we recorded dopamine concentrations in the PFC while mice performed two reward-seeking tasks that required behavioral inhibition. In our first task, mice had to cross over a metal grating where they had previously received a shock to obtain a reward. We found that dopamine levels increased prior to them crossing and decreased as they crossed. In our second task, mice had to decide whether to stay at a reward port for a chance at a reward or leave and reset the trial and we found that PFC dopamine increased when mice decided to leave. Together, our findings suggest that higher levels of PFC dopamine correlate with increased cognitive control, suppressing either aversive associations or reward associations that are not currently valid.

Disclosures: Y. Yang: None. **H.J. Rice:** None. **M.A. Tronolone:** None. **H. Chang:** None. **I.T. Ellwood:** None.

Poster

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Topic: H.03. Decision Making

Support: 1 F32 MH126505 (Malcolm Campbell) NIMH
3 U19NS113201 (Naoshige Uchida) NINDS

Title: Ramping activity in the medial prefrontal cortex integrates time and rewards in opposing directions during patch foraging

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Abstract: As animals forage for food and water, a key decision they need to make is when to abandon a depleting resource to search elsewhere in the environment. The Marginal Value Theorem (MVT) provides a normative framework for this behavior: Animals should leave a depleting 'patch' of resources once the instantaneous reward rate in the patch drops below the average value of the environment. Computing the exact patch leaving time in this manner requires comprehensive knowledge of one's environment — knowledge that animals do not have under naturalistic conditions. Despite this epistemic limitation, many species appear to well-approximate the MVT. How they do, however, remains largely unknown. To address this question, we designed a patch foraging task wherein head-fixed mice run along a 1-dimensional virtual track in search of patches containing water rewards. To mimic naturalistic conditions, rewards were delivered with varying probabilities, with probability decaying over time within patches to simulate a depleting resource. We confirmed a key prediction of the theory: Mice had greater patch residence times when rewards were larger or more frequent ($p<0.0001$ for both reward size and frequency, generalized linear mixed effects model, n = 18 mice). To investigate the neural basis of patch leave decisions, we recorded activity of neurons in the medial prefrontal cortex (mPFC) using high-density probes (Neuropixels) during the foraging task (3,683 neurons, 5 mice). We observed task-relevant dynamics throughout mPFC, most prominently in a neural population whose activity, in the absence of reward, ramped up over time as a patch leave decision became more imminent. When rewards were delivered, this same ramping population's activity dipped, suggesting an evidence accumulation process that approximates the normative strategy by integrating time and rewards in opposing directions relative to a leave decision. To quantify coding properties of the recorded neurons, we fit a generalized linear model (GLM) of spiking activity as a function of task-relevant variables carrying information about rewards and time, as well as motor activity such as running and licking. Of the 1,664 neurons that met a minimum firing rate criterion for inclusion in the GLM analysis, ~50% carried information about key foraging variables. Of these, ~40% were identified as ramping units based on unsupervised clustering using a Gaussian mixture model. Taken together, our results suggest an evidence accumulation process occurs during foraging decisions, and that it is widely represented as ramping activity throughout mPFC.

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Poster

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Program #/Poster #: P791.08

Topic: H.03. Decision Making

Title: Change and maintenance of neural representations across different behavioral context in primate medial frontal cortex

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Abstract: Flexible, context dependent behavior necessitates the selection of diverse protocols to convert sensory information into valid action (i.e. behavioral tactics).The central nervous system of higher mammals can perform diverse cognitive tasks but little is known about how such flexible switching of function is implemented at cellular level. Specifically, does a neuron encoding a particular aspect of behavior (e.g. action) preserve that representation across different tasks, or that neural representation of behavioral factors changes dynamically under different behavioral context? To answer this question we designed a behavioral task that required monkeys to remember the tactics cues (pro-reach or anti-reach) and the position cue(left or right) separately by presenting first tactics and then position cues (tactics-precued) and vice versa(position-precued). Then monkeys were required to integrate two pieces of information to determine appropriate action. Under the first condition (tactics-precued), a trial started as the monkeys pressed the home button attached to a primate chair. Then a color cue briefly appeared (0.5s) to instruct the tactics (cyan/green color instructed pro- and blue/red for anti-reach) but not action, then disappeared. After a variable length of delay period, a position cue (illuminated either the left or the right button) prompted the monkeys to perform an action to reach either left or right button based on tactics. Under the second condition (position-precued), the order of presentation of tactics cue and position cue was reversed. While the monkeys were performing this task, neuronal activity was recorded from the posterior medial prefrontal cortex (pmPFC), the presupplementary motor area (preSMA) and the supplementary motor area (SMA) and their relation to the cued tactics, cue position and the monkeys' action was done by epoch-based analysis.
We found that tactics, cue position, and action were represented in medial frontal areas. We compared neuronal activities under the tactics- and position-precued condition. Our results indicate that the three cortical areas play distinct roles in representing and integrating position and tactics information into action under two behavioral paradigms.

Disclosures: M. Awan: None. **H. Mushiake:** None. **Y. Matsuzaka:** None.

Poster

P791. Medial Prefrontal Cortex: Physiology and Circuitry

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Program #/Poster #: P791.09

Topic: H.03. Decision Making

Support: NIDA - 1R01DA043443

Title: Delineating the role of cortico-cortical circuits in adaptive decision making

Authors: *N. MOIN AFSHAR[1], N. Y. GUTIERREZ SACASA[2], P. VILLIAMMA[2], H. SANCHEZ[1], C. J. PITTENGER[3], S. M. GROMAN[3], J. TAYLOR[4];
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Abstract: Delineating the role of cortico-cortical circuits in adaptive decision making
Neema Moin Afshar[1], Nathalia Y. Gutiérrez Sacasa[2], Peroushini Villiamma[2], Hayde Sanchez[1], Christopher Pittenger[1,3], Stephanie M. Groman[1,2,4,*], and Jane R. Taylor[1,3,*]
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Adaptive decision making in dynamic environments requires the activation of multiple neural circuits including prefrontal networks that have not been extensively investigated. Our previous work has demonstrated that orbitofrontal-subcortical circuits control distinct reinforcement-learning computations, including updating of action values for positive and negative outcomes and maintaining value representations of unchosen options. The circuit responsible for maintaining value representations of the chosen option, however, is not known. Value representations may be stored in regions that are known to be involved in working memory, such as the medial prefrontal cortex (mPFC). We hypothesized that mPFC projections to the orbitofrontal cortex (OFC), but not OFC projections to the mPFC, would control the degree to which action values for chosen options would be maintained across subsequent trials. To test this, we trained and tested adult, male Long Evans rats (N=40) in a three-choice, probabilistic reversal-learning (PRL) task. Using a dual viral approach, we selectively expressed diphtheria toxin receptors in either mPFC projections to the OFC (N=20) or OFC projections to the mPFC (N=20). Rats were retrained on the PRL task and then received either saline (control; N=20) or diphtheria toxin (DT; N=20) to ablate individual circuits in a directionally selective manner. 72 h after the injections, the performance of rats on the PRL task was reassessed. Trial-by-trial choice data collected before and after saline/DT injections was fit with a differential forgetting reinforcement-learning algorithm and examined between circuit (mPFC◊OFC vs. OFC◊mPFC) and injection (saline vs. DT) groups. We found evidence suggesting dissociable roles of mPFC-OFC circuits in value representations that are consistent with our initial hypothesis and suggest a key role of working memory circuits in reinforcement learning. Our ongoing work is combining this circuit based viral approach with intravenous drug self-administration to determine how these reinforcement-learning circuits may be involved in addiction pathophysiology.

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Poster

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Program #/Poster #: P791.10

Topic: H.03. Decision Making

Support: NIH NIMH Grant R01MH119086

Title: The influence of cognitive fatigue on physical effort-based decision-making

Authors: *M. H. DRYZER, V. S. CHIB;
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Abstract: Fatigue is a lack of energy or motivation that can be caused by both physically and cognitively demanding tasks. It is often perceived that fatigue in one effort domain (e.g., cognition) can impact judgements of effort in another domain (e.g., physical). Despite these ubiquitous feelings of cross-talk between domains of fatigue, little is known about how fatigue in one domain influences decisions in another domain. In this experiment, we characterized individuals' subjective preferences for physical effort and examined how these preferences, and associated brain activity, changed when they were in a state of cognitive fatigue. To accomplish this, we scanned subjects with functional magnetic resonance imaging while they made decisions about exertion of physical effort (i.e., grip exertion), before and after they performed bouts of cognitively fatiguing exertion (i.e., working memory). Participants first learned an association between physical force produced and a numerical scale ranging from zero to one hundred relative to participants' maximum physical exertion. They then performed a series of risky binary gambles involving varying levels of physical exertion. During each choice, participants made a decision to risk equal probability of high physical exertion or rest, or forgo any risk and select a guaranteed lower level of exertion. After participants performed a baseline session of choices for physical effort, they performed a series of cognitively fatiguing n-back working memory trials. Following these cognitive fatigue bouts, they repeated the same physical exertion choices as in the baseline state. In a baseline state, we found that the majority of participants exhibited convex subjective effort value functions, indicating that the marginal subjective values of physical effort increased as more effort was required. When participants were in a cognitively fatigued state, the marginal subjective value of physical effort became more pronounced as indicated by an increased convexity in the subjective effort value function. Subsequent analyses of the neuroimaging data will examine brain regions with activity associated with participants' subjective preferences for physical effort, and shifts in physical effort value as a result of cognitive fatigue.

Disclosures: M.H. Dryzer: None. **V.S. Chib:** None.

Poster

P809. Human Behavior, Disorders, and Mechanisms II

Location: Virtual Only

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Program #/Poster #: P809.01

Topic: H.06. Social Cognition

Support: NRF-2019M3E5D2A01060299
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IBS-R015-D1

Title: The neural representation of people and relationships in social network

Authors: *D. KWON[1,3], W. SHIM[1,3,2];
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Abstract: Understanding the personal characteristics of individuals and their social relationships plays a crucial role in navigating the social world, such as knowing with whom to form a social group and how to interact with each individual. Previous studies have shown that the ventromedial prefrontal cortex (vmPFC) and hippocampus represent a cognitive map that contains relational information about non-spatial and even social knowledge, such as representations of social agents (Park et al., 2020). However, it remains unclear how social relationship structures that reflect a multidimensional bidirectional distance metric for individual relationships are represented. In this study, we investigated how neural representations of a small-sized social network that consists of node and edge information, which corresponds to each individual and their relationships respectively, are constructed using behavioral and fMRI data. During fMRI scanning, subjects watched a Web drama with rich and dynamically varying social interactions and rated the traits of each of six fictional characters (node) and pairwise directional social relationships between characters (edge) in multiple dimensions. From each subject's ratings, we constructed a behavioral representational dissimilarity matrix (RDM) for individual characters and a distance matrix (DM) for their pairwise relationships and calculated a rank correlation between behavioral RDMs and neural RDMs in 50 brain regions based on Neurosynth whole-brain parcellation. A neural RDM in vmPFC and hippocampus showed significant correlations with subjects' behavioral ratings for each character and the perceived distance of social relations among characters. These results suggest that the structured knowledge of a social network, which comprises multifaceted information on individuals and their directional relationships, is represented in the hippocampus and vmPFC.

Disclosures: D. Kwon: None. **W. Shim:** None.

Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Program #/Poster #: P809.02

Topic: H.06. Social Cognition

Support: Mission funding through the US DEVCOM Army Research Laboratory

Title: Elasticity in the brain: dynamic reconfigurations underlying cognition, vulnerabilities, and resilience

Authors: *J. O. GARCIA[1], I. L. D. PINTO[2], K. BANSAL[3];
[1]Human Res. and Engin. Directorate, US DEVCOM Army Res. Lab., San Francisco, CA; [2]Human Res. and Engin. Directorate, US DEVCOM Army Res. Lab., SAN FRANCISCO, CA; [3]Biomed. Engin., Columbia Univ., New York, NY

Abstract: The human brain is a complex dynamical network composed of a collection of heterogeneous modules that adaptively reorganize, much like an elastic system, for seamless interactions within a complex and dynamically changing environment. This particular architecture makes the brain sensitive to a wide range of stimuli and efficiently respond to situations with different cognitive demands. Advancements in network neuroscience approaches equipped us with ways to quantify the elasticity of the brain by computing how 'flexibly' the network modules of the brain reconfigure and have shown its importance in many cognitive phenomena, including learning and memory. Four of our recent and independent studies provide support for the hypothesis that the flexibility in the brain provides a necessary mechanism for behavioral resilience. First, we found that the flexibility of a group of brain regions increased following low sleep episodes during working memory task performance. Second, we found that the higher flexibility of the nodes within the frontal cortex relate negatively with the likelihood of opinion change (on various social issues, quantified through questionnaires before and after the interaction with a simulated social media platform with real and fake news). Third, we find significant differences in the flexibility of the awakening brain as compared to the fully awake brain during a psychomotor vigilance task. Typically, the brain experiences a decrease in cognitive performance during waking up from sleep, so-called sleep inertia. Across these studies, involving different cognitive experiments, flexibility of brain regions seems to be playing an important role in maintaining/ achieving optimal performance. Finally, with transcranial magnetic stimulation, we have shown that this flexibility may be triggered by non-invasive magnetic stimulation, further suggesting that elastic features may be not only cognitively relevant, but may be initiated to adapt and respond to in a rapidly changing environment, and perhaps even harnessed in future efforts in human-technology hybrid systems.

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Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Program #/Poster #: P809.03

Topic: H.06. Social Cognition

Title: Learning What Others Think of Us: Encoding and Consolidation of Social Feedback During Rest

Authors: *S. BRIETZKE[1], K. BARBAROSSA[2], *M. MEYER[3];
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Abstract: Learning what other people think about us is critical for social function, yet we know relatively little about how we encode and remember what people think about us. To help close this gap, we assessed two possibilities that come from the learning and memory literature: 1) that we consolidate what other

people think of us during rest periods that follow the feedback ('post-feedback rest') and 2) that the extent to which feedback violates our self-concept will impact memory. We ran an fMRI study (n=42) in which participants received feedback about which characters from the TV sitcom The Office they reminded a set of raters based on a video and photograph participants submitted prior to their scan session. Further, subjects viewed another person receiving feedback from other people. Interleaved between conditions were resting state scans to assess whether feedback is consolidated during post-feedback rest. Following the scan, subjects completed a surprise memory test. We found no difference in memory retention between self and other for consistent feedback. However, we found that for inconsistent feedback, memory for others' feedback degrades while the memory performance for self inconsistent feedback is preserved. We found that the interaction between consistency and target yielded significant activity in DMPFC and vMPFC. Larger degrees of discrepancy in self-inconsistent feedback were associated with greater activity in DMPFC, whereas larger degrees of discrepancy in self-consistent feedback were associated with greater activity in MPFC. Further, we will analyze resting state functional connectivity (rsFC) of default mode network (DMN) during rest. We predict there will be greater rsFC in core sub-system of DMN following feedback for the self and greater rsFC in the dorsomedial sub-system of DMN following feedback for the other. We hypothesize that greater DMN connectivity during post-feedback rest will correlate with better memory performance.

Disclosures: S. Brietzke: None. **K. Barbarossa:** None. **M. Meyer:** None.

Poster

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Topic: H.06. Social Cognition

Support: U01NS121616

Title: Cortical network properties of social personality traits and their disorder

Authors: *Y. KFIR, M. MUSTROPH, P. R. NG, M. JAMALI, Z. WILLIAMS;
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Abstract: Humans display an astonishingly wide array of social personality traits that powerfully influence our interactions with others. The cortical network properties that precisely underlie these traits or that underpin their dysfunction in conditions such as Autism spectrum disorder (ASD), however, remain largely unknown. Current research in humans is based mainly on non-invasive methods which have limited spatial and\or temporal resolution. Here, using a rare opportunity to perform intracranial recordings in large cohorts of participants and by employing a comprehensive battery of tests, we identify multidimensional social traits unique to each individual, their interrelation with other cognitive abilities, and overlap with ASD related psychopathology. By further examining local- and network-activities across individuals, we describe preliminary patterns that underlie specific traits. We also identify patterns that appear to be uniquely related to ASD. Together, these findings set the groundwork for building a

more comprehensive network-based understanding of social behavior and its disruption through disorders such as ASD.

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Poster

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PEDECIBA/Alícuota Estudiante T. Liberman
PEDECIBA/Alícuota Investigador M. Castelló

Title: Mindful Self-Compassion and Yoga training effects on neurobiological and psychological signs of empathy, emotional regulation, and stress in Uruguayan primary school teachers.

Authors: T. LIBERMAN[1], M. BIDEGAIN[1], F. LÓPEZ[3], R. SANZ[4], V. CONSONNI[5], F. ROMERO[5], P. LURASCHI[5], S. BLANCO[5], P. LLADO[6], S. LÓPEZ[7], C. PEREIRA[7], A. J. IBARRA[2], G. VARELA[8], *M. E. CASTELLÓ[9];
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Abstract: Teaching is a profession associated with high stress and burnout. The perceived effort due to cognitive and emotional workload reduces teachers well-being perception and increases disease prevalence. Teacher self-reported distress and burnout also affect students well-being, impacting on education. Uruguayan female pre-primary and primary public-school teachers exhibit the highest levels of stress and burnout in Latin America. Positive school environments and teacher well-being depend on their emotional regulation and stress-coping strategies, and the implementation of well-being-focused training programs as meditation in the education field is growing worldwide. Teachers training in Mindfulness or Self-Compassion skills reduce self-reported stress and improve social and emotional indexes, but the conjunction of both methodologies has not been assessed. We studied the effects of virtual training in Mindful Self-Compassion (MSC) on psychological and neurobiological signs of stress, empathy and emotional regulation in a sample of Uruguayan primary-school teachers. We used a quasi-experimental longitudinal pre-test post-test with an active control group (Kundalini yoga) experimental design. Teachers filled online questionnaires before and after MSC or Yoga training, to assess their global and work-related stress, empathy and emotion regulation. Teachers neural response to others perceived pain

was studied by EEC and ECG recordings during the visualization of a series of digital colour pictures showing right hands or feet of people in painful and non-painful situations involving nociceptive stimuli. ECG data are being analyzed in time and frequency domains to study several parameters of heart rate variability (HRV). EEG data are being analyzed in the frequency domain as well as the heart evoked potentials. Parametric and non-parametric statistical analysis of the psychological tests revealed a significant increase in the levels of mindfulness, self-kindness, common humanity, self-judgment, perspective taking and overall well-being, and a decrease in levels of personal distress, emotional exhaustion, global stress and emotional suppression in the MSC group. In the Yoga group, levels of mindfulness, self-kindness, self-judgment, over-identification and overall well-being significantly increased, and only the levels of global stress significantly decreased. Non-parametric statistical analysis of HRV evidenced a significant difference between MSC and Yoga in the change between post- and pre-training of the difference between pain and no pain situations, indicating greater parasympathetic tone after MSC than Yoga training.

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Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P809.06

Topic: H.06. Social Cognition

Support: NIH R01MH11629
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Title: Neural systems for gaze-cueing are modulated by visual dwell time

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Abstract: Eye gaze plays a salient role in social interactions by providing cues that assist in directing attention to another person or object. However, the underlying mechanisms for the relationship between visual sensing and face processing are not known. We compare a social robot with a simplified humanoid face and eye features, Maki[1], with a human partner to test the hypothesis that face processing mechanisms for real faces are modulated by visual sensing using functional near-infrared spectroscopy (fNIRS) and eye-tracking. Participants engaged in a gaze cueing task in which an initiator (robot or human) used eye gaze to direct the participant's eyes to one of two circular targets on a glass partition. During the gaze

cueing task, the initiator looked at the participant's eyes for 2-seconds and then averted gaze to a dot (left or right) for 2-seconds. The paradigm consisted of 3 gaze cueing events, followed by 15-seconds of rest, for a total of 3 minutes per run (two runs per condition). Eye following accuracy was 100% in both robot and human gaze cueing conditions. Visual dwell time during the first 2-seconds of the gaze cueing event decreased during human face viewing relative to robot face viewing [$t = 7.46$, $p < 0.0005$] for 21 neurotypical adult participants. To test whether dwell time modulated social processing of real faces, dwell time was used as a regressor for neural activity during face viewing and gaze cueing. The human gaze cueing condition showed greater activity in right supramarginal gyrus (56, -60, 42), right primary somatosensory cortex (20, -48, 74), right pre-motor and supplementary motor cortex, and right dorsolateral prefrontal cortex (46, 46, 14) than the robot gaze cueing. Additionally, activity in the visual cortices increased during the human gaze cueing condition relative to the robot gaze cueing condition. Regression with individual dwell time showed enhancement in the right inferior parietal lobule and dorsal lateral prefrontal cortex. These results are consistent with the hypothesis that visual sensing mechanisms as represented by dwell time play an important behavioral role in live face processing and visual attention.

[1]Kelley, M., Noah, J.A., Zhang, X., Scassellati, B., & Hirsch, J. (2021). Comparison of human social brain activity during eye-contact with another human and a humanoid robot. Frontiers in Robotic and AI, 7, 599581.

Disclosures: T. Parker: None. **X. Zhang:** None. **J.A. Noah:** None. **M. Kelley:** None. **J. Hirsch:** None.

Poster

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Program #/Poster #: P809.07

Topic: H.06. Social Cognition

Support: MOST 110-2634-F-002-040

Title: Real-time human-human and human-agent chitchats: An fMRI study

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Abstract: Recent advancements in artificial intelligence have led to a variety of impressive results and applications, such as human-like chatbots for companion or therapy purposes. While all of the deep-learning-based chatbots have been computationally evaluated and optimized during development based on some performance metrics, only some chatbots have been thoroughly tested with humans. The human-centered approach evaluates the quality of a chatbot by assessing the feelings of its users about the chatbot. Because of the loud scanning noises during scans of functional magnetic resonance imaging (fMRI), past fMRI studies on human-agent interaction often used simple games as their experimental paradigms, and human-centered evaluations of conversational agents primarily relied on surveys. By leveraging real-time denoising techniques, the present study explored the possibility of using fMRI to evaluate the quality of a conversational agent *during* rather than *after* human-agent conversations.

Compared to behavioral assessments, such neural assessments arguably surfer less from various response biases. Our results showed that 28 healthy participants engaged the right TemporoParietal Junction in the brains while conversing with a person or a chatbot (Mitsuku or XiaoIce), presumably exercising Theory of Mind. However, the participants showed greater brain activities in the Dorsal Attention Network during chitchats with chatbots than with a person, suggesting a higher cognitive load during human-agent than human-human conversations. Taken together, these results demonstrate the feasibility of using fMRI during real-time conversations, which helps to address the ecological validity issue in communication neuroscience.

Disclosures: J. Cheng: None. **T. Huang:** None.

Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Program #/Poster #: P809.08

Topic: H.06. Social Cognition

Title: Schizophrenia influences responses of the theory of mind network to socially awkward events

Authors: *E. PRZYSINDA[1], B. SHOVESTUL[2], A. SAXENA[2], E. DUDEK[3], J. LAMBERTI[4], E. LALOR[5], D. DODELL-FEDER[2];
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Abstract: Schizophrenia (SZ) is a debilitating and complex disorder. One often overlooked symptom is marked and persistent difficulties with social information processing. Increasing work has shown that these deficits can be attributed to abnormalities in the network of brain regions supporting mental state attribution, known as the theory of mind (ToM) network; namely, dorsal medial prefrontal cortex (dmPFC) and temporo-parietal junction (TPJ). The extant literature generally utilizes explicit tasks and non-naturalistic stimuli that only examine isolated aspects of social processing. However, social interactions are nuanced and context-dependent, so utilizing naturalistic stimuli more representative of daily social interactions could help us to better understand social difficulties in SZ. Here, we used an episode of the comedy TV show, *The Office*, as our stimulus because it contains a rich variety of social interactions, including some that may be violating social norms (i.e., awkward events). We modeled our analysis on a recent study (Pantelis et al. 2015) that examined the ToM network during awkward moments during the same episode of *The Office*. We focus on awkward moments because these scenes require complex social reasoning involving mentalizing about others' thoughts and feelings in addition to a thorough understanding of social norms. We aim to better understand the neural dynamics of the ToM network during scenes requiring mental state attribution, such as these socially awkward moments. We first replicated Pantelis et al's findings that across all participants, the ToM network was engaged during socially awkward moments. Preliminary comparison of 10 SZ patients with controls matched on age and sex showed group differences in the extent to which the ToM network is engaged during these awkward events; specifically the SZ group showed reduced recruitment of dorsal (d)mPFC compared to controls.

The dmPFC has been shown to be heavily involved in ToM assessment of others' evolving mental states, and these results indicate that these abilities might be impaired in patients with SZ. In summary, our preliminary results suggest that in those scenarios where mental state attribution is critical, patients with SZ failed to bring key regions of the ToM network online, possibly contributing to inappropriate social inferences and behaviors. Further analysis of behavioral data collected as part of this study will allow us to examine the behavioral consequences of functional abnormalities in the ToM network.

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Poster

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Topic: H.06. Social Cognition

Support: NIH/NIGMS 5U54GM104942

Title: Aberrant functional connectivity of brain networks for biological motion processing in Autism Spectrum Disorder

Authors: S. A. L. JARRELL[1], M. M. COLEMAN[1], S. Z. SALMASSI[1], P. J. WEBSTER[2], *J. W. LEWIS[1];
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Abstract: Autism spectrum disorder (ASD) often manifests with difficulties in social interactions, which are behaviors that have been variably associated with aberrant cortical network organizations. A recent fMRI study by our group (Webster et al., 2020) revealed a hypoactivated corticobasal network during a simple motor task while participants observed a person (below the head) bouncing a basketball. Together with eight other brain regions of interest (ROIs) associated with processing human biological motion, we identified a global brain network that could be more broadly tested for functional connectivity pattern differences across groups using resting state functional connectivity MRI (rsfMRI). Using the Autism Brain Imaging Data Exchange (ABIDE) database, we processed neuroimaging data from 97 individuals with ASD and 97 typically developed (TD) matched for age, gender, and IQ using structural vector auto-regression (SVAR) modeling. This connectivity analysis modeled both contemporaneous and lagged interactions. The main finding was that the ASD group showed significantly fewer path effects across multiple hubs of this network, which was a finding opposite from most traditional autocorrelation analyses. Complementing conventional instantaneous effects rsfMRI analyses of ASD groups, these findings are newly suggestive of physiological differences in information flow across specific brain regions involved in biological motion processing.

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Poster

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Topic: H.06. Social Cognition

Support: Synergy Grant 2018 - "Communication in Context"

Title: Investigating the neurocognitive processes of communicative language use in Autism Spectrum Disorder

Authors: *M. MANGNUS[1], S. KOCH[1], K. CAI[1], F. GOLTZ[1], P. HAGOORT[1], I. TONI[1], A. STOLK[2,1], J. BAŠNÁKOVÁ[1];
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Abstract: Everyday communication often requires us to rapidly search for relevant context. Autism Spectrum Disorder (ASD) is defined by persistent communicative challenges (Wadge et al., 2019). Yet, language and communication research in ASD to date has largely focused on the processing of words absent of any communicative context. Accordingly, it remains largely unknown whether the communicative challenges experienced by autistic individuals are due to core issues with processing linguistic material or communicative context. The present study combines fMRI with eye-tracking to examine how autistic individuals disambiguate the meanings of words employed in a communicative context. Specifically, our experiment will reveal what parts of context autistic interlocutors use to disambiguate the meaning of these words.In the task, participants read chat conversations in which the meaning of a target word in the first sentence, indicated with bold text, is either literal (e.g. “bears” stands for an animal) or slang (“bears” stands for the police). Moreover, in half of the dialogs, the word’s meaning is known to the participant beforehand (control condition). The participants are instructed to determine the meaning of the target word. Tracking the participants’ eye movements while reading reveals in real time which portions of the dialog they analyze to resolve the target word’s meaning. To analyze which features of the context the participants focus on, the amount of semantic exploration in the context is calculated by measuring the semantic similarity of the target word and the words fixated on by the participant. We expect that autistic participants fail to fully benefit from contextual information in the dialog, such as references to unusual objects or idiosyncratic inferences derived on the fly from previous lines. Instead, we expect them to focus more on strong semantic relations between words and thus engage in semantic exploration more than neurotypical participants. fMRI data is acquired to measure whether the participants use brain regions typically involved in language processing (using data from a language localizer) or Theory of Mind (via non-verbal ToM localizer) when searching for meaning of the target word in the communicative context. We will present preliminary results of approximately half of the intended sample size. Our findings will provide new insights into the underlying processes of the differences in communication in autistic and neurotypical individuals.
*References:*1. Wadge, H., Brewer, R., Bird, G., Toni, I., & Stolk, A. (2019). Communicative misalignment in autism spectrum disorder. *Cortex*, 115, 15-26.

Disclosures: M. Mangnus: None. **S. Koch:** None. **K. Cai:** None. **F. Goltz:** None. **P. Hagoort:** None. **I. Toni:** None. **A. Stolk:** None. **J. Bašnáková:** None.

Poster

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Program #/Poster #: P809.11

Topic: H.06. Social Cognition

Support: Synergy Grant 2018 - "Communication in Context

Title: Communication in Context: a dual-fMRI study on social interaction in autism spectrum disorder

Authors: *S. KOCH[1], K. CAI[1], M. MANGNUS[1], I. TONI[1], J. BASNAKOVA[1], A. STOLK[2];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized with deficits in social interaction and communication (APA 2013). When investigating communicative abilities during live social interactions, a recent behavioral study found that individuals diagnosed with ASD struggled to align their contextual knowledge of the interaction with that of others, despite having otherwise indistinguishable performance from neurotypicals (Wadge et al., 2019). However, the neural mechanisms of this contextual misalignment hampering contextually appropriate communication in ASD remain largely unknown.
In this dual-fMRI study, we investigate the neural mechanisms underlying contextual communication difficulties in ASD. Contextual communication is investigated in a dual-fMRI setting, in which 26 pairs of ASD individuals, 26 pairs of neurotypical controls, and 26 pairs of socially anxious participants solve novel communicative problems in a live interactive setting. Pairs are asked to reproduce a goal configuration of two geometrical tokens, shown to one of the participants only, the 'Communicator'. Given that the other player, the 'Addressee', cannot see this configuration, the Communicator has to move her token in a way on a digital gameboard that conveys the Addressee's target to the Addressee. The pairs face communicative problems they have previously established joint solutions for ('Known' trials), and problems that require them to reach a shared solution still ('Novel' trials) (94 trials in total). At the behavioural level, we investigate group differences in communicative success and communicative alignment (i.e. correspondence in communicative signals across successive interactions). At the neural level, we investigate activity during accessing (Known trials) and building of (Novel trials) shared meaning, which is compared between groups. Preliminary fMRI results replicate previous findings of increased activity in the motor cortex, left cuneus, right angular gyrus, medial frontal cortex and right superior temporal gyrus during Known compared to Novel problems (Stolk et al., 2014) ($n = 39$, all $p_{FWE} < .05$), thus when pairs have access to shared contextual knowledge. To investigate cerebral synchronization between communicators, we investigate (group differences in) neural alignment, defined as shared BOLD fluctuations in the right superior temporal gyrus (rSTG), as well as stimulus-independent interpersonal cerebral coherence in the rSTG when pairs align their contextual knowledge of the interaction (Stolk et al., 2014). Preliminary behavioural and fMRI results will be presented.

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Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Topic: H.06. Social Cognition

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NIMH R01MH121790
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Title: Engagement of the TPJ-pSTSRegion by Naturalistic Stimuli in Individuals at Clinical High Risk for Developing Schizophrenia

Authors: *J. K. LEE[1,2], N. CHOWDHURY[1,2], D. RUIZ-BETANCOURT[1], J. P. SANCHEZ-PEÑA[1,2], C. M. CORCORAN[3,4], D. C. JAVITT[1,2,5], G. H. PATEL[1,2];
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Abstract: Individuals with schizophrenia show deficits in inferring sarcasm based on prosody detection and have reduced activation in the temporoparietal junction and posterior superior temporal sulcus (TPJ-pSTS) during speech reception. Previous studies have found evidence that auditory processing impairments precede the onset of schizophrenia. However it is unclear whether these deficits affect naturalistic speech comprehension which is critical for social functioning. To this end, the present study evaluates the functionality of the TPJ-pSTS associated with naturalistic language processing in individuals at clinical high-risk for developing schizophrenia.
We collected functional MRI images in 14 healthy controls (HC), 15 individuals at clinical high-risk for developing schizophrenia (CHR) and 20 schizophrenia patients (SzP) while they listened to a spoken story “Pie Man”. The level of brain activity evoked in response to this narrated story was measured by inter-subject correlation (ISC) using HC as the reference. We then compared the ISC scores to the performance on the attitudinal prosody task, which evaluates one’s ability to detect prosodic features of sarcasm in naturalistic speech.
The three groups significantly differed in the extent of brain activation and performance on the attitudinal prosody task, with the highest ISC scores and sarcasm detection rate in CHR and the lowest in SzP. More specifically, in comparison to HC and SzP, CHR showed significantly increased activation in areas within the posterior TPJ (TPJp; $F2,46 = 4.96$, $p=0.012$), along with prefrontal cortex, auditory cortex and visual/face-processing areas. In addition, the CHRs performed better on the attitudinal prosody task, compared to the other two groups ($F2,46=4.32$, $p=0.019$). Interestingly, greater activation of the TPJp significantly correlated with better auditory sarcasm detection in the attitudinal prosody task only in CHR (β CHR $=0.54$, $p<0.01$)
Overall, the juxtaposition of results from CHR and SzP suggest that increased activity within the TPJp node of the mentalization network may compensate for an otherwise compromised system. The current

findings in the CHRs point to a potential target for rehabilitation and neuromodulation-based treatments for social functioning deficits in schizophrenia.

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Poster

P809. Human Behavior, Disorders, and Mechanisms II

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Topic: H.06. Social Cognition

Support: National Natural Science Foundation of China 32022031

Title: Redefining the posterior superior temporal sulcus: the functional organization of social interaction processing in the posterior superior temporal sulcus

Authors: *Q. LIANG, Y. LIANG, S.-G. KUAI;
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Abstract: Numerous studies recognized the posterior superior temporal sulcus (pSTS) as a key region for social information processing. However, looking into the details, some sharp incongruences come into view (e.g. whether the pSTS or extrastraite body area represents social interaction status). A major obstacle for understanding why these conflicts occurred is the lack of standard localizers for subregions in pSTS, mainly face area, biological motion area and social interaction area. A precise and well-controlled localizer is in urgent need. In this study, we conducted an fMRI study to examine the functional organization of social information processing in pSTS. We reviewed social perception and cognition studies in the past 10 years and adopted dynamic face perception task and biological motion perception task from the most cited studies. Since there was no standard task to locate social interaction area, we recruited four actors to perform dyadic social interactions and made videos and screenshots as stimuli. To make interactions varied, half of the stimuli were only with the face showed and the other half were face-masked full-body scenes. As for the comparative non-interacting conditions, we switched the positions of the two people and made them face away from each other. Then all the physical information was controlled and only the interaction status was altered. The social interaction area was defined by significantly higher activation in interacting conditions than non-interacting conditions. 20 healthy adults went through three fMRI sessions for functional localization. The results showed that the three areas were not overlapped with each other in individuals' brain. On the other hand, the areas that different kinds of social interaction activated were highly overlapped. Classifiers trained by neural activations in these areas succeeded in transfer decoding the interaction status (e.g., a classifier trained to decode whether a static

face-only scene was an interacting scene or not could also decode the interaction status in a dynamic body-only scene). These results showed that there was a region specialized for social interaction perception in pSTS and it represented abstract social interaction information. Moreover, our results suggested that these subregions should be defined individually since neither their coordinates were consistent among participants, nor the resting-state functional connectivity manifested these subareas. To sum up, our study indicates that there are functional subregions in pSTS specialized for different social information processing and they should be defined using well-controlled functional localizers individually.

Disclosures: Q. Liang: None. **Y. Liang:** None. **S. Kuai:** None.

Poster

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Topic: H.06. Social Cognition

Support: the National Natural Science Foundation of China (Grant No. 32071060)

Title: Transcultural differences of theory of mind among Chinese and Japanese cultures: an fMRI study

Authors: M. ZHANG[1], Z. LU[3,1], W. MA[2], *S. OTANI[4], Z. WANG[1];
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Abstract: Theory of mind (ToM) is an ability of explaining one's own and others' actions. Further studies revealed that the neural mechanisms of TOM can be shaped by culture differences and differential activations between Asains and Westerners have been reported. Furthermore, some studies that focused on transcultural differences of ToM indicate that the medial prefrontal cortex (mPFC) shows differential activations between Asians and Westerners. However, Whether the same neural mechanisms underlying ToM in similar Asian cultures, such as Chinese and Japanese, is unclear. Hence, using representational similarity analysis (RSA), we explored the neural representation of ToM in the brain to study representational differences between Chinese and Japanese participants. We recorded the brain activities of Chinese (N=12) and Japanese (N=12) participants (recruited in Shanghai), using functional magnetic resonance imaging (fMRI) during a ToM video task. Behavioral data showed no significant group differences in the subjects' post-scan subjective evaluation of the movies. However, fMRI results showed differences of ToM representational patterns between the two groups. We calculated the similarities between the fMRI searchlight RDMs (representational dissimilarity matrix) with two coding model RDMs, video-style RDM, and ToM RDM, respectively. We found that left middle occipital gyrus (MOG) showed a strong correlation with the video-style processing in the task. The middle frontal gyrus (MFG), the superior temporal gyrus (STG), and the precentral gyrus (PreCG) were found involved in encoding ToM processing. However, Chinese participants' right middle temporal gyrus(MTG)and right STG

showed a stronger representation of encoding ToM than Japanese participants. In contrast, Japanese participants' left PreCG showed a stronger ToM representation than Chinese. These results suggest that Chinese show a rightward lateralization of ToM representation while Japanese are non-lateralized. In summary, our study presents a novel finding of the neural mechanism of ToM in our brains using RSA. Furthermore, the difference of encoding ToM between Chinese and Japanese participants demonstrates that the diversity within Asian culture can affect the neural representation of ToM.

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Poster

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NIH ZIA MH002898
Brain Behavior Foundation NARSAD Young Investigator Award

Title: The road not taken: disconnection of a human-unique cortical pathway in schizophrenia and its effects on naturalistic social cognition

Authors: *G. H. PATEL[1], D. C. GRUSKIN[1], J. K. LEE[1], D. A. LEOPOLD[2], D. C. JAVITT[1];
[1]Columbia University/NYSPI, New York, NY; [2]NIMH, Bethesda, MD

Abstract: Background: Efficient processing of a complex dynamic social scene relies on intact connectivity of many underlying cortical areas and networks, but how structural deficits affect this functioning in social cognition remains unknown. Here we measure these relationships using functionally based localization of social cognition areas, resting-state functional connectivity, and movie-watching data.
Methods: In 42 schizophrenia participants (SzP) and 41 healthy controls (HC), we measured the functional connectivity of areas functionally localized by face-emotion processing, theory-of-mind, and attention tasks. We used weighted shortest path length between visual and medial prefrontal theory-of-mind areas in both populations to assess the impact of the functional connectivity deficits on the network structure. We then correlated connectivity along the shortest path in each group with movie-evoked activity in a key node of the theory-of-mind network (TPJp).
Results: SzP had pronounced connectivity deficits in temporoparietal junction/posterior superior temporal sulcus (TPJ-pSTS) areas involved in face-emotion processing ($t(81)=4.4$, $p=0.00002$). In HC the shortest path connecting visual and medial prefrontal theory-of-mind areas passed through TPJ-pSTS, whereas in SzP these deficits shifted the pathway to pass through prefrontal cortex (PFC). While movie-

evoked TPJp activity correlated with the connectivity along the TPJ-pSTS pathway in both groups ($r=0.43$, $p=0.002$), it additionally correlated with the connectivity along the PFC pathway only in SzP ($r_{SzP}=0.56$, $p=0.003$).
Conclusions: Connectivity along the human-unique TPJ-pSTS pathway affects both the structure and functioning of areas involved in processing complex dynamic social scenes. These results demonstrate how focal deficits can have widespread structural and functional impacts across cortex.

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Poster

P814. Human Long-Term Memory: Encoding and Retrieval

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P814.01

Topic: H.07. Long-Term Memory

Support: National Science Foundation of China Grant 31730038
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DFG Projektnummer 122679504 – SFB 874

Title: Transformative neural representations across memory encoding, maintenance and retrieval

Authors: *J. LIU[1], N. AXMACHER[2], G. XUE[1];
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Abstract: Emerging evidence has conceived memory as a dynamic process during which the mental representations are continuously transformed, yet the nature of this transformation and its functional significance have not been well understood. Combining intracranial EEG recordings, deep neural network models, representational similarity analysis, and a behavioral paradigm encompassing memory encoding, short-term maintenance, and long-term retrieval, we found that the cross-stage neural pattern similarity of the same item was significantly smaller than the within-stage pattern similarity. More importantly, neural representations during long-term memory retrieval were more similar to the representation during short-term maintenance than that during encoding. These results suggested that the memory representations went through continuous transformations from encoding, maintenance to retrieval. Critically, during encoding, items that experienced a greater neural transformation from visual processing to semantic processing were associated with better subsequent memory. These results provide novel insights regarding how human memory is formed and transformed.

Disclosures: J. Liu: None. **N. Axmacher:** None. **G. Xue:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P814.02

Topic: H.07. Long-Term Memory

Title: Insights into category learning through feature-level memory distortion

Authors: *M. C. TANDOC, C. V. DONG, A. C. SCHAPIRO;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Our semantic knowledge is rich and multi-faceted, encompassing both general patterns (most birds can fly) and unique details (herons have long legs). Our model of novel structured learning in the hippocampus (Schapiro et al., 2017, *Philos. Trans. R. Soc*) predicts that different forms of representation may best support these different kinds of knowledge, as shared structure benefits from pooling information across exemplars while idiosyncratic information benefits from keeping exemplars separate in memory. We leverage distortions in color memory (Chanales et al., 2021, *Psychol. Sci*) to behaviorally evaluate representational shifts in the learning of shared and unique features in a novel semantic domain. Participants learned two categories of novel "satellite" objects: Each satellite had parts that were shared with most members of the same category as well as a part that was unique to that exemplar. Each part had a specific color drawn from a 2D color space, with the parts for each category clustered in this space. As participants learned the features, we frequently tested their color memory to track representational change for each feature. Across learning, color memory resisted attraction to the category centre only for unique features. For shared features, attraction persisted throughout learning. Distortions in color memory across learning were thus systematically related to the category structure. This relative differentiation for unique relative to shared features should reduce interference in memory, and indeed, the unique features that most strongly resisted attraction were remembered best. Preliminary data in a separate sample appear to replicate these effects. These findings suggest that there are differences in the nature of the representations underlying shared and unique features in accordance with their different computational needs.

Disclosures: M.C. Tandoc: None. **C.V. Dong:** None. **A.C. Schapiro:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: P814.03

Topic: H.07. Long-Term Memory

Support: NIH Grant R01-NS112366

NIH Grant F32-AG054204

Title: Category representations after learning from both typical and atypical examples

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Abstract: Whether concepts are represented by individual category members as posited by exemplar models or an abstracted central tendency as posited by prototype models has been debated for decades. To date, neuroimaging findings have been conflicting, with one study finding only prototype correlates, one finding only exemplar correlates, and one finding a mix of prototype and exemplar correlates. What drives this difference across studies? One factor may be the structure of the training examples, which can bias individuals toward either abstraction or memorization of individual items. In particular, including atypical training items close to the category boundary can reduce reliance on prototype representations. In the present study, we tested whether including atypical items in a paradigm that had previously produced only prototype correlates in the brain would shift individuals toward exemplar-based representations. Participants completed a category-training task that included both typical items close to category prototypes and atypical items close to the category boundary. Participants then completed a surprise old/new recognition test on training items and new items varying in distance from category prototypes, followed by a category generalization test during fMRI. Behavioral results revealed better categorization accuracy for items close to prototypes but better recognition accuracy for items near the category boundary, suggesting that participants may have relied on memorization of the atypical boundary items. In fitting formal categorization models to generalization behavior, we found a relatively even split between subjects who relied on prototype vs. exemplar representations. Neuroimaging results mirrored these behavioral findings by showing a mix of prototype and exemplar representations, sometimes within a single brain region. These results support the hypothesis that individuals flexibly form different types of category representations in response to demands at the time of learning and that multiple representations can form in parallel in the brain.

Disclosures: C. Bowman: None. **T. Iwashita:** None. **D. Zeithamova:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P814.04

Topic: H.07. Long-Term Memory

Support: Cambridge International Trust
Mind Science Foundation BrainStorm Award 2018

Title: Mechanistic Models of Memory Control

Authors: *S. SANKARASUBRAMANIAN[1], D. APŠVALKA[1], Y. GUO[2], M. ANDERSON[1];
[1]MRC-CBU, Univ. of Cambridge, Cambridge, United Kingdom; [2]Siemens Advanta Consulting, Beijing, China

Abstract: Rationale and Aim(s) of the study: Mechanistic models of inhibitory motor control have identified cortical-sub cortical loops, involving the direct, indirect and hyper direct pathways. There are no such established pathways to explain how retrieval of episodic memories can be actively inhibited. Several previous studies have established that role of prefrontal regions in top-down memory control, but their functional interactions with sub-cortical and medial temporal lobe (MTL) structures, along with the mechanisms of action, are yet to be fully established.We sought to address this void, by looking at brain regions important for memory control, and mapping their mechanistic interactions. This project aims to investigate if the cortical and sub-cortical regions identified to be involved in motor control are also involved in memory control.**Materials and methods:** There are two studies in this project. Both studies sought to a) confirm if regions identified in motor inhibitory control are involved in memory control as well, b) explore the mechanisms of how memory retrieval is actively inhibited. Both studies used functional magnetic resonance imaging (fMRI) data, and dynamic causal modelling (DCM).***Study 1:*** 33 healthy young adults participated in the study. They performed two sessions inside the 3T scanner- an inhibitory Stop Signal motor task and a version of the Think No Think (TNT) memory inhibition task. ***Study 2:*** 10 previous TNT studies were pooled together, and key cortical and sub-cortical regions of interest (ROIs) taken from the motor inhibition literature, were investigated for engagement in the TNT memory control task. Preliminary functional connectivity analyses are currently underway to establish the mechanistic interactions between these structures. **Key results, and discussion:** For both the studies, we focussed on two key cortical areas: the right dorsolateral prefrontal cortex (rDLPFC), and the right ventrolateral prefrontal cortex (rVLPFC). The subcortical regions we focussed on includes the caudate nucleus, putamen, and sub-thalamic nucleus (STN). Both Study 1 and Study 2 revealed a novel discovery of the potential involvement of the STN in memory control. Both studies also revealed that akin to motor control, there are differential patterns of univariate activation seen for proactive versus reactive memory control. DCM efforts from Study 1 revealed that both the prefrontal regions, along with the basal ganglia, were causally involved in memory control. DCM analysis from Study 2 is expected to reveal the functional role of the STN in memory control, and also help us establish a mechanistic model of memory inhibition.

Disclosures: S. Sankarasubramanian: None. **D. Apšvalka:** None. **Y. Guo:** None. **M. Anderson:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: P814.05

Topic: H.07. Long-Term Memory

Support: Israel Science Foundation (ISF 526/17)
European Research Council (ERC-2019-COG 866093)

Title: Indirect downregulation of negative emotional memories

Authors: *S. KOZAK[1], N. HERZ[3], Y. BAR-HAIM[1,2], N. CENSOR[1,2];
[1]Sch. of Psychological Sci., [2]Sagol Sch. of Neurosci., Tel-Aviv Univ., Tel-Aviv, Israel; [3]Dept. of Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Dysfunctional negative emotional memories remain at the core of psychopathological conditions such as posttraumatic stress disorder (PTSD), depression and addiction. This has inspired research geared towards memory modulation, by direct targeting of the negative emotional memory. However, reliable downregulation of maladaptive episodic memory in humans remains elusive as emotional memories show high resistance to direct modulation. Given the existing challenges associated with direct emotional memory modulation, here we asked whether negative emotional visual memory may be modulated indirectly. To address this question, we leveraged a paradigm previously shown to indirectly modulate neutral visual memories, through direct instructions to forget or remember embedded verbal information (Kozak et al., 2021). Participants studied two lists of neutral words embedded within negative emotional pictorial context and as in previous directed forgetting experiments, received a cue to forget or remember the words of the first list (Anderson et al., 2014). While the instructions were given only for the words, both word and emotional picture memory were tested at the end of the study session. Preliminary results indicate that consistent with previous studies, the instructions directly modified word memory strength. The remember instruction enhanced word recall and the forget instruction reduced it. Importantly, these instructions modulated indirectly and inversely the memory for the emotional pictures. Specifically, instructions to remember the words reduced picture recognition memory, and vice versa for instructions to forget the words. Moreover, these effects on emotional picture recognition memory carried over to the second list in which no differential instructions were provided. These data suggest that upregulation of temporally adjacent memory may indirectly downregulate negative emotional memory, opening a new avenue for treatment of memory related pathologies.

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Poster

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Topic: H.07. Long-Term Memory

Support: NSF CRCNS Grant IIS-1822683 (to K. Kay)
NSF CRCNS Grant IIS-1822929 (to T. Naselaris)

Title: Multiple codes of memory signals in parietal cortex

Authors: *N. YOUNG[1], M. PRICE[1], E. J. ALLEN[2], Y. WU[2], T. NASELARIS[2], K. KAY[2], J. B. HUTCHINSON[1];
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Abstract: Memory recognition is a process that is strongly influenced by the passage of time—whether we recognize something from the past is thought to depend at least in part on a continuous signal that becomes weaker over time. This putative signal is a fundamental tenet of memory recognition, yet there remains substantial debate regarding where and how this signal is represented in the brain. Evidence from human neuroimaging suggests that parietal cortex possesses regions whose activity roughly tracks the degree to which someone believes they recognize a presented stimulus, as well as regions that represent

various continuous dimensions including egocentric space and the temporal distance of recalled memories. Building upon these studies, we conducted 7T fMRI during a continuous recognition memory task involving a very wide range of timescales spanning seconds to months. Specifically, eight participants viewed up to 10,000 unique images repeated 3 times each across 30 to 40 scanning sessions distributed over approximately 9 months. We examined how activity during correct recognition trials in each voxel varied as a function of the elapsed time from an item's prior presentation (i.e., lag). Preliminary results suggest that many regions in parietal cortex show response amplitudes that decline linearly as a function of the logarithm of the lag, consistent with a scalar signal that is used for recognition decisions. However, a significant proportion of voxels in medial parietal cortex exhibited maximal activity for windows of lag that were between relatively short and relatively long distances of time. There is also preliminary evidence that such voxels might be arranged in a topographic manner in which voxels tuned to longer lags are found more anterior and inferior relative to voxels tuned to intermediate and shorter lags. These results suggest that parietal cortex might support multiple codes of signals relevant to recognition memory in an organized, topographic fashion.

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Poster

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Program #/Poster #: P814.07

Topic: H.07. Long-Term Memory

Support: NIH R01: R01MH116914

Title: Executive and mnemonic functions of the human posterior cingulate cortex revealed by single-unit recordings

Authors: *L. APONIK-GREMILLION[1], Y. Y. CHEN[3], E. BARTOLI[2], B. Y. HAYDEN[4], S. A. SHETH[2], B. L. FOSTER[3];
[1]Neurosci., [2]Neurosurg., Baylor Col. of Med., Houston, TX; [3]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA; [4]Neurosci., Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Episodic memory supports the retrieval and construction of past events, facilitating experience-informed decision-making. In addition to the hippocampus, human neuroimaging has shown a consistent set of distributed neocortical regions are active during the retrieval of episodic memories, with the posterior cingulate cortex (PCC) serving as a core node of this retrieval network. In contrast to these findings, non-human primate single unit studies suggest a more executive role for the PCC, related to cognitive control and decision making. Consequentially, these divergent results have motivated radically different perspectives of PCC function across fields, leading to the question: *is the function of PCC mnemonic or executive in nature?* In order to reconcile these divergent perspectives and expand upon our understanding of PCC physiology, we utilized human intracranial stereo-electroencephalography (sEEG), including single-unit recordings, to allow for spatially and temporally precise investigation of PCC neural

activity during complex executive and mnemonic behavior. Additionally, hippocampal recordings were incorporated to provide a point of comparison for the selectivity and timing of task responses within PCC. Neurosurgical patients undergoing invasive monitoring performed an attention/memory switch task. On a given trial, subjects performed either an attention (search or arithmetic) or memory (past or future event) task, with a pre-trial cue indicating the trial type. Overall, PCC responses (unit and population measures) showed evidence for both attention and memory functions. A subset of PCC recordings exhibited sustained activation throughout the episodic memory conditions, similar to activity observed in the hippocampus, suggesting a role in the retrieval and construction of episodic memories. Other PCC recordings revealed activation of varying temporal profiles (i.e. transient and sustained) during the attention conditions. These results indicate that PCC populations are functionally heterogeneous and involved in both mnemonic and executive functions. These functionally divergent populations appear to be organized spatially across the dorsal-ventral axis of PCC, with more executive activity observed in the dorsal PCC, while mnemonic activity was predominately in the ventral PCC. Our findings help reconcile previously incongruous data across fields and suggest that PCC may serve as an important convergence zone of mnemonic and executive functions in order to support memory-based decision-making.

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Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: P814.08

Topic: H.07. Long-Term Memory

Title: Limited Evidence for a Triple Dissociation in the Medial Temporal Lobe: an fMRI Replication Study

Authors: *J. VAN[1], B. KIRWAN[2];
[2]Psychology, [1]Brigham Young Univ., Provo, UT

Abstract: What does the hippocampus do? A previous fMRI study demonstrated a triple dissociation within the medial temporal lobe, with different regions of the parahippocampal gyrus supporting subjective novelty and familiarity responses while the hippocampus supported subjective recollection regardless of the old/new status of stimuli (Daselaar SM, Fleck MS, Cabeza R [2006a] Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J Neurophysiol 96:1902–1911). However, a separate analysis of the same dataset demonstrated that the hippocampus responded to the objective old/new status of stimuli regardless of the subjective response as indicated by behavioral responses (Daselaar SM, Fleck MS, Prince SE, Cabeza R [2006b] The medial temporal lobe distinguishes old from new independently of consciousness. J Neurosci 26:5835–5839). To investigate this apparent conflict, we replicated the behavioral, fMRI scan acquisition, and data analysis procedures of the original studies as closely as possible. Fifty-three participants studied a list of words outside the MRI scanner and then were given a recognition memory test in the scanner in which they first indicated whether the word presented was repeated or novel and then indicated their confidence in their recognition memory decision.

Following the previous studies, two sets of analyses were conducted. In the first set of analyses, we contrasted objective old vs new stimuli (i.e., [hits + misses] > [correct rejections + false alarms]) and subjective old vs new responses (i.e., [hits + false alarms] > [misses + correct rejections]). We found evidence for objective old > new effects in the hippocampus (uncorrected $p < .01$, $k>40$ voxels) at coordinates similar to the original study (Daselaar et al., 2006b). In the second set of analyses, we modeled novelty, familiarity, and recollection. We found a robust recollection signal in the parahippocampal cortex but not in the hippocampus in contrast to the previous work (Daselaar et al., 2006a). Thus, the present work was able to partially replicate Daselaar et al. (2006a, 2006b) but found no evidence for a triple dissociation in the MTL. Keywords: fMRI, Memory, Hippocampus, Replication, Recollection, Familiarity, Novelty

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Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: P814.09

Topic: H.07. Long-Term Memory

Support: NIMH Division of Intramural Research Grant ZIA MH002920

Title: Graded hippocampal activity during naturalistic recall is observable after multi-echo, but not single-echo, fMRI processing

Authors: *A. W. GILMORE, A. M. AGRON, E. I. GONZÁLEZ-ARAYA, S. J. GOTTS, A. MARTIN; Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD

Abstract: Recent years have seen an increase in the use of multi-echo fMRI designs by cognitive neuroscientists. Acquiring multiple echoes allows one to reduce thermal noise, identify nuisance signal components, and improve the overall quality of BOLD data. At the same time, acquiring multiple echoes incurs a cost to the temporal and spatial resolution of the acquired BOLD data and increases the overall complexity of data analysis. Here, we re-examine a multi-echo dataset (Gilmore et al., 2021) analyzed using multi-echo ICA (ME-ICA) and compare the results to a “traditional” single-echo analysis of the same data. Both processing streams utilized the same initial preprocessing steps (despiking, slice-time correction, and rigid-body motion correction) and both were rescaled, detrended, and analyzed using the same modeling parameters. The task involved 40 human participants overtly recalling recent and remote autobiographical events for periods of ~2 minutes and was intended to test competing theories of hippocampal involvement in remote recall. The goal of the current analysis was to determine if ME-ICA’s theoretical benefits might lead to a practical difference in the overall results of the experiment. Three results are notable. First, the temporal signal to noise (tSNR) was significantly improved following ME-ICA denoising, especially in signal-poor regions such as orbitofrontal cortex. Second, as a result of this improved tSNR, ME-ICA denoising revealed temporally graded activity in right lateral parietal and left frontal regions that was not detected by the single-echo analysis. Third, region of interest analyses focusing on hippocampal subregions produced qualitatively different results patterns between the two

analysis approaches. Whereas no significant differences in hippocampal activity were observed as a function of event recency in the single-echo analysis, a temporally graded pattern (recent < remote) was observed in posterior hippocampal regions in the ME-ICA processed data. Compared to the ME-ICA data, single-echo results rarely differed from baseline activity in the hippocampus bilaterally. Thus, whereas the outcome of the single-echo analysis did not clearly support any specific model of hippocampal function, ME-ICA results supported predictions of the Standard Model of Consolidation and a time-limited hippocampal involvement (e.g., Zola-Morgan & Squire, 1990). These data provide a practical example of the benefits multi-echo acquisitions and ME-ICA might offer to naturalistic paradigms and emphasize that effects may emerge in ways that are subtle yet important for informing theoretical debate.

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Poster

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Program #/Poster #: P814.10

Topic: H.10. Human Learning and Cognition

Support: NSF Grant 1734735

Title: The neural basis for number processing and its relation to individual differences in adults' mathematical skills

Authors: *X. REN, M. N. COUTANCHE, J. A. FIEZ, M. E. LIBERTUS;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Number recognition is thought to be multi-constituent in nature. It relies on visual (e.g., written digits or number words), verbal (e.g., number names), semantic (e.g., dot arrays), and manual (e.g., fingers) formats to represent quantity. Here we will explore whether variations in brain activations associated with number processing of these different formats are predictive of adults' math achievements. To this end, we used functional magnetic resonance imaging (fMRI) to 1) broadly characterize visual, verbal, manual, and semantic neural constituents of adults' number processing that undergird number recognition and 2) investigate the relations between individual differences in the underlying brain activation and their math abilities. Specifically, we measured adult participants' brain activation while they completed a number comparison task (a semantic task) and a phonological comparison task (a verbal task) with two types of stimuli: Arabic numerals (visual code) and hand images (manual code). Participants' mathematical competence was measured using the math subtests of the Woodcock-Johnson Tests of Achievement in a separate behavioral session. Univariate contrasts of the fMRI tasks and stimuli revealed an extensive set of brain regions supporting each number format. We also applied a principal component analysis (PCA) to obtain two derived variables from the Woodcock-Johnson Tests. Correlational analyses revealed significant links between brain activation in regions such as left postcentral gyrus and left middle temporal gyrus, and participants' math abilities. In sum, our study

furthers our understanding of the neurocognitive architecture underlying number processing and its relation to individual differences in math achievement.

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Poster

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Program #/Poster #: P814.11

Topic: H.10. Human Learning and Cognition

Support: Israel Science Foundation (ISF 526/17)
European Research Council (ERC-2019-COG 866093)

Title: Reactivation-induced learning in the numeric domain

Authors: *G. SCHRIFT[1], D. DOTAN[2], N. CENSOR[1];
[1]Sch. of Psychological Sciences, Sagol Sch. of Neurosci., [2]Sch. of Education, Sagol Sch. of Neurosci., Tel-Aviv Univ., Tel Aviv, Israel

Abstract: Learning of arithmetic facts such as the multiplication table often requires repeated time-consuming execution to achieve gains in performance. Motivated by recent studies successfully extending memory reactivation frameworks from fear-conditioning in rodents to skill learning in humans, we asked whether learning numeric facts can be induced by brief memory reactivations. To investigate this question, we had adult participants perform a novel task modeling number-fact learning. 101 naive healthy participants (14 males, 87 females; mean age 23.8±2.1 standard deviation) were asked to learn 8 arithmetic-like numeric facts (e.g., 4 & 6 = 79). The initial session included encoding of the facts and was followed by a free recall baseline test. Reactivation training was done by brief visual-auditory reactivations of only 40 seconds each, conducted on 3 separate days. Learning was evaluated in a final retest session performed 8 days following initial encoding. The *Reactivation* group showed significant learning gains (mean score change = 7.7%±3.1% standard error, p= 0.02), indicating that passive reactivations can facilitate learning in the numeric domain. This is in contrast to the *Control* group subjects, who performed test-retest without reactivations, and showed deteriorated performance (mean score change = -22.0%±4.5%, p< 0.00003). A *Standard Training* group completed active problem-solving sessions also conducted on 3 separate days and showed significant learning gains (mean score change = 26.3%±3.1%, p<2E-10). Interestingly, while these gains were higher than those of the *Reactivation* group, subjects showing reactivation-induced learning were characterized by superior efficiency relative to standard training subjects, with higher rate of improvement per training time. Overall, the results demonstrate the possibility of learning numeric skills with brief reactivations. Time-efficient learning in the numeric domain carries potential enhancement of learning strategies in daily life settings, including in neurological conditions such as attention deficit disorders.

Disclosures: G. Schrift: None. **D. Dotan:** None. **N. Censor:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: P814.12

Topic: E.02. Cerebellum

Support: NIH/NEI ROIEY024056
NSF/SL-CN 1640914

Title: Rapid cognitive learning in the cerebellum

Authors: *L. LIKOVA, K. MINEFF;
Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Introduction: The main function of the cerebellum is generally understood to be in motor control and coordination, including a major role in motor learning; however recent neuroimaging studies have implicated it in many aspects of cognitive processing. Here we investigate the involvement of the cerebellum in two non-motor cognitive learning tasks - the memorization and mental visualization of visuo-spatial information. **Methods:** In a 3T Siemens Prisma scanner, participants performed a sequence of i) memorization of scientific or artistic visual images (30s) and ii) visualization-from-memory of these images (30s), interleaved with fixation periods (20s); this sequence was repeated three times for each image. Functional MRI, the SUIT cerebellar toolbox and Granger Causal connectivity analyses were used to establish and analyze the properties of the network structure and its rapid reorganization during these tasks. **Results:** Overall, the results revealed well-structured, task-specific bilateral activation at the lobule VI/Crus I border, and lobules VIIb, VIIIa/b and X, and suppression at the border of Crus I/Crus II, lobule IX, and at lobule VI of the vermis. At a cerebellar network level, both congruent and inverse Granger causal connectivity influences were identified for each task. The causal connectivity analysis also uncovered a characteristic dynamic of cross-coupling between key cerebellar regions of interest (ROIs) and large-scale brain networks such as the default mode network (DMN). In particular, DMN was shown to be the primary driver of the strong suppression in Crus I/Crus II during mental visualization. Remarkably rapid differentiation between the two tasks was observed in most cerebellar sites, in terms of different patterns of positive or negative changes of the BOLD responses over the repeats. Furthermore, the causal connectivity relationships between these local sites also underwent a rapid reorganization across the repeats. **Conclusions:** These multidimensional fMRI and connectivity findings provide a solid basis for a framework for the analysis of rapid cerebellar reorganization during non-motor cognitive tasks. To our knowledge, this is the first study to reveal this form of rapid non-motor/cognitive learning in the cerebellum - on the timescale of just a few minutes - as well as to do so at both the sub-lobular and the network causal connectivity levels. Collectively, the findings of this rapid cerebellar plasticity in the cognitive tasks of mental visualization and memorization offer novel insights into fundamental questions of cerebellar function.

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Poster

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Program #/Poster #: P814.13

Topic: H.10. Human Learning and Cognition

Support: JST CREST
JST PRESTO
JST SOUHATSU

Title: Defensive pessimists could promote the improvement of their ability and the brain structure in the competitive learning

Authors: *C. HOSODA[1,2], T. MATSUHASHI[2], K. OKANOYA[3];
[1]Univ. of Tokyo, Tokyo, Japan; [2]Advanced Comprehensive Res. Organization, Teikyo Univ., Tokyo, Japan; [3]Univ. od Tokyo, Tokyo, Japan

Abstract: The environment surrounding an individual has a significant impact on his/her behavior change. While people could improve their abilities by comparing with others, there was also a critical view of the competitive environment. This discrepancy might reflect individual differences in usage of the cognitive strategy in competitive environments. Some fMRI studies supported the comparison involved in the reward-related brain activity in estimating the advantages of yourself and others. Thus, the competitive-situation might evaluate in terms of reward processing, although an interaction between the competitive-situation and the behavior change (i.e. improvements of their ability) may occur independently of individual differences in the selection of their cognitive strategy. Here, we focus on the defensive pessimist (DP) that is the cognitive strategy making oneself think that a future performance will go poorly, so that one takes the necessary steps to make sure it does not go poorly. The purpose of this study is to elucidate the interaction between the degree of DP and the competitive-situation on the improvement of the ability.Fifty-one subjects were divided into two groups with no significant difference in DP score and English proficiency, gender, or age, and underwent a 12-week English listening (L2L) training. One group was in a competitive and the other was in a non-competitive-situations. Before and after training, we measured brain structure using magnetic resonance imaging scanning (3T-MRI, Siemens PRISMA,). To clarify the interaction between DP and the competitive-situations , we did a 2-by-2 ANOVA with a situations (competitive/non-competitive) and the degree of DP (high/low) as both of the between-subject variables. Consequently, we found two findings. Firstly, for the L2L improvement, the ANOVA revealed neither the main effect of the situations nor the degree of DP (ps >.50). An interaction of situations by the degree of DP was significant (p =.003). Post-hoc analysis revealed the improvement of L2L, in high DP, was greater in the competitive-situations than that in the non-competitive. (p =.009). Secondly, for gray matter volume of supramarginal gyrus involving in the phonology, neither circumstance effect nor trait (ps > .60) was obtained. Although an interaction was found (p = .047).We investigated the influence the individual difference in the cognitive strategy in the competition on the improvement of the ability. Suggesting that high DP strives to avoid the poor performance by making more pessimistic estimates of their future performance in a competition. Furthermore, it suggested that DP may also promote brain structural plasticity.

Disclosures: C. Hosoda: None. **T. Matsuhashi:** None. **K. Okanoya:** None.

Poster

P814. Human Long-Term Memory: Encoding and Retrieval

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P814.14

Topic: H.10. Human Learning and Cognition

Title: Neural bases of event memory encoding: cortical alignment of neural state boundaries is associated with boundary strength and hippocampal response

Authors: *Y. LEE, J. CHEN;
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Abstract: Sensory inputs from the world dynamically change from moment to moment, yet people spontaneously summarize information in meaningful units (events). Recent research shows that brain regions in the default mode network (DMN) chunk information at timescales which match those of human event perception during naturalistic movie-viewing. Shifts in stable DMN neural states, i.e., neural state boundaries, are associated with human-labeled event boundaries - the beginning of a new movie event perceived by humans (Baldassano et al., 2017). Studies have consistently reported two findings: 1) hippocampal activity increases at DMN neural state boundaries that match event boundaries (Baldassano et al., 2017; Ben-Yakov & Henson, 2018), 2) some neural state boundaries in the DMN overlap with those identified from lower level brain regions such as early visual cortex ("cortical alignment" of neural state boundaries; Baldassano et al., 2017; Geerligs et al., 2021). These findings led us to the question: are neural state boundaries with more widespread cortical alignment associated with stronger hippocampal activity, in turn facilitating event memory? By applying the GSBS event segmentation method (Geerligs et al., 2021) to a naturalistic movie-viewing dataset collected in a prior study (Lee & Chen, 2021; $N = 20$), we identified neural state boundaries in three regions along the cortical processing hierarchy: early visual cortex, posterior medial cortex, and medial prefrontal cortex (mPFC). To examine whether hippocampal activity is modulated by alignment of neural state boundaries across different cortical regions, mPFC boundaries were divided into 1) those that overlapped across all three regions (*Aligned*), and 2) those that were limited to mPFC (*mPFC-alone*). Preliminary results show that, 7-8 seconds after boundary onset, hippocampal activity for *Aligned* boundaries was significantly greater ($p < .05$) than for *mPFC-alone*. Furthermore, human judgments of boundary strength were numerically higher for *Aligned* than for *mPFC-alone*. These preliminary data suggest that hippocampal activity increases when meaningful changes in movie events simultaneously occur at multiple levels (e.g., changes in luminance, location, dialogue topics, etc.), consistent with the role of hippocampus in associative binding during episodic memory encoding (Ranganath, 2010; Staresina & Davachi, 2009). In next steps, we will examine a wider range of regions across the cortical hierarchy, and test whether neural state alignment predicts individuals' subsequent event memory.

Disclosures: Y. Lee: None. **J. Chen:** None.

Poster

P851. Dentate Gyrus

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P851.01

Topic: H.08. Learning and Memory

Support: NIH/NINDS R01NS115471
Posner Fellowship

Title: The role of young adult-born neurons in pattern separation

Authors: *C. CASTILLON, M. BARRAZA, J. ARMSTRONG, A. CONTRACTOR;
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Abstract: The birth and incorporation of new neurons into the dentate gyrus of the hippocampus of adult mice has been determined to be important for many forms of hippocampal dependent behaviors and memory. Postmitotic adult-born dentate granule cells (abDGCs) mature over several weeks forming synapses with other components of the hippocampal network and eventually having similar properties to developmentally born neurons. During the postmitotic maturation process young abDGCs have unique functional properties with both differential intrinsic excitability and distinct excitatory and inhibitory synaptic input compared to mature granule cells. Therefore, how effectively these neurons are engaged by sensory and contextual information, and themselves contribute to relevant behaviors, remains largely unknown. In particular a role has been described for abDGCs in pattern separation, a memory function that enables discrimination of similar but distinct representations into non-overlapping memories. Yet many questions remain about when and how these neurons facilitate an animal's ability to discriminate between similar situations. In this study we proposed to directly determine when and how adult-born neurons are activated when mice perform a pattern separation task, and moreover to determine their maturation stage and functional characteristics. To do this we developed a custom automated touch screen pattern separation paradigm and determined which neurons were active during different phases of the learning using a mouse that allows Targeted Recombination in Active Populations (TRAP2). Combining this with birth-dating of neurons we are determining which cohorts of young abDGCs are active and using ex-vivo single-cell patch-clamp recording of synaptic and intrinsic properties to assess if they possess distinct functional properties. These studies will ultimately refine our understanding of how abDGCs are functionally incorporated into the hippocampal network and how they contribute to the ability of an animal to discriminate between distinct representations.

Disclosures: C. Castillon: None. **M. Barraza:** None. **J. Armstrong:** None. **A. Contractor:** None.

Poster

P851. Dentate Gyrus

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Program #/Poster #: P851.02

Topic: H.08. Learning and Memory

Support: NIH K99MH12226

NIMH R01 MH68542
HDRF MPPN8883

Title: The effects of chronic and transient ablation of adult born granule cells on neural flexibility in the Dentate Gyrus

Authors: *S. N. TUNCDEMIR[1], V. LUNA[1], H. CHUNG[2], A. GROSMARK[3], C. LACEFIELD[1], R. HEN[1];
[1]RFMH Columbia Univ., New York, NY; [2]NYSPI/ Columbia Univ., NY, NY; [3]Neurosci., Columbia Univ., New York, NY

Abstract: The dentate gyrus (DG) exhibits a unique form of neural plasticity that results from continuous integration of newborn excitatory granule cells. Recent studies have proposed that adult neurogenesis promotes cognitive flexibility, the ability to encode new memories without interference from previously stored memories that share similar features. However, the manner in which adult neurogenesis contributes to DG network activity and computations is incompletely understood. Here, we employed focal X-ray-irradiation (IR) of the hippocampus to suppress neurogenesis and examined population neural activity using *in vivo* 2-photon Ca^{2+} imaging. To assess the degree of remapping of neural representations of space, we compared the similarity between single-cell spatial tuning profiles by subjecting the mice to two sequential exposures of either identical or different environments. While spatial rate maps in Sham mice were less stable across than within environments (i.e., display remapping), IR mice exhibited significantly lower levels of remapping compared to controls. In addition, we found perseverance during reversal learning behavior and more stable spatial maps across days in IR mice compared to controls. To address the role of adult born granule cells specifically during their critical period of maturation we chemogenetically inhibited immature granule cells using an inducible AsclCreER; hM4Di transgenic mouse line. We confirmed that transiently silencing immature granule cells disinhibits mature granule cells' activity both *in vivo* and *in vitro*, consistent with the prevailing model. Our preliminary results also indicate that the transient and selective silencing of adult born granule cells resulted in significantly higher levels of stability in spatial rate maps across different environments compared to control mice, in line with the effects of chronically suppressing adult neurogenesis. Our ongoing work is aimed at untangling the mechanisms linking neuronal sparsity and flexibility in the DG. Our results highlight the long-hypothesized role of adult born granule cells in providing flexibility for DG to rapidly generate a context specific, distributed representation of important sensory stimuli such as spatial cues, which ultimately promotes cognitive flexibility.

Disclosures: S.N. Tuncdemir: None. **V. Luna:** None. **H. Chung:** None. **A. Grosmark:** None. **C. Lacefield:** None. **R. Hen:** None.

Poster

P851. Dentate Gyrus

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Program #/Poster #: P851.03

Topic: H.08. Learning and Memory

Support: NIH RF1 AG017139
NIH R37 AG008796

Title: Changes in cellular activity of different dentate gyrus cell types during acquisition of trace eyeblink conditioning in mice

Authors: *L. N. MILLER, C. WEISS, J. F. DISTERHOFT;
Northwestern Univ., Chicago, IL

Abstract: The dentate gyrus (DG) serves as the first site for information processing in the classical hippocampal trisynaptic circuit. This position makes it an important structure for the formation of associative memories. The DG contains two types of excitatory neurons: granule cells and mossy cells. While prior research has demonstrated that granule cells are necessary for memory formation, the functional role of mossy cells in learning has not been thoroughly explored. Additionally, previous work from our laboratory had found populations of cells within DG of rabbits that may bridge the temporal gap between stimuli to support memory formation during an associative learning task, trace eyeblink conditioning. However, the identity of the cells showing this type of activity is still unknown. Therefore, we utilized *in vivo* single-neuron recording in conjunction with histological and physiological determination of cell types to investigate the functional role of mossy cells and granule cells during learning. To do this, male and female young-adult mice were implanted with Neuralynx Halo-10-Mini Microdrives prior to being trained on trace eyeblink conditioning, a hippocampal-dependent temporal associative memory task, for a total of ten days. The conditioned group received 50 trials per day of paired stimuli, while the pseudoconditioned group, serving as the control group, received 100 trials per day of randomly presented unpaired stimuli. Animals in the pseudoconditioned group never reached learning criterion, while conditioned mice were able to successfully learn the task (>60% adaptive CRs). Male mice learned at a significantly faster rate than female mice. In conditioned mice, granule cells tended to show an increase in firing rate during either the conditioned stimulus or the unconditioned stimulus. On the other hand, mossy cells from conditioned animals had a tendency to show a decrease in firing rate during the trace interval and the unconditioned stimulus. Given the connections between the two cell types, this decrease in mossy cell activity should act to enhance granule cell firing through disinhibition. These results indicate a novel role for mossy cells in bridging the temporal gap during an associative learning task, and indicates that the DG is involved in learning that does not involve pattern separation. This work builds and expands upon our knowledge of DG function, which then improves our ability to discern how aging and disease might disrupt this process.

Disclosures: L.N. Miller: None. **C. Weiss:** None. **J.F. Disterhoft:** None.

Poster

P851. Dentate Gyrus

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Topic: H.08. Learning and Memory

Support: NSF (DMS-1042134)

NIH (MH052090)

Title: Distinct Rhythmic Profiles of Neurons in the Dentate Gyrus During Associative Memory Processing

Authors: *C. R. HEYMAN, M. BORZELLO, P. D. RIVIERE, L. M. RANGEL;
Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: As a region important for associative memory, the hippocampus receives a variety of converging inputs. These inputs, which are thought to convey sensory and visuospatial information, target neurons along each hippocampal subregion, including the dentate gyrus (DG). This subregion is thus poised to play a crucial role in associative memory processing. To evaluate this hypothesis, we investigated the engagement of DG neurons in rhythmic circuit activity during an associative memory task. Specifically, we examined single neuron and local field potential activity from the DG as rats performed a task in which pairs of odors were associated with the contexts in which they were rewarded. We found that several DG rhythms exhibited abrupt shifts in amplitude during key intervals in which rats were presented with odor cues. For instance, theta (5-10Hz) and high gamma (75-115Hz) amplitude decreased significantly during odor cue intervals preceding correct trials only. Additionally, during odor cue intervals, cells became entrained to one or more local rhythms in a manner that was predictive of associative memory task performance. These results differed across putative principal cells (i.e. granule and/or mossy cells) and putative interneuron populations. Specifically, during correct performance, most putative principal cells exhibited rhythmic entrainment to only one rhythm, while most putative interneurons exhibited entrainment to multiple rhythms. Putative principal cell firing rates did not change across trial outcomes, suggesting that their engagement in specific rhythmic circuits was more predictive of successful associative memory processing than their gross activity levels. A subset of putative interneurons exhibited significant differences in firing rate across trial outcomes, with increases in firing rate preceding incorrect (unrewarded) trials. However, these cells exhibited higher rhythmic engagement during correct (rewarded) trials and *not* incorrect trials, suggesting that rhythmic engagement coincides with successful performance despite lower firing rates in these trials. Overall, these results suggest that DG neurons engage in exquisitely timed and rhythmically coordinated interactions during successful associative memory processing.

Disclosures: C.R. Heyman: None. **M. Borzello:** None. **P.D. Riviere:** None. **L.M. Rangel:** None.

Poster

P851. Dentate Gyrus

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Support: DFG SFB 1089, Project C04
DFG FOR2715
DFG Research Priority Program SPP Computational Connectomics
DFG EXC 2151

Volkswagen Foundation
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Title: Synchronous activity patterns in the dentate gyrus during immobility

Authors: *M. POFAHL[1], N. NIKBAKHT[1], A. N. HAUBRICH[1], T. NGUYEN[1], N. MASALA[1], F. DISTLER[1], O. BRAGANZA[1], J. H. MACKE[2], L. A. EWELL[1], K. GOLCUK[1], H. W. BECK[1];
[1]Inst. of Exptl. Epileptology and Cognition Res., Univ. of Bonn Med. Ctr., Bonn, Germany; [2]Dept. Empirical Inference, Max Planck Inst. for Intelligent Systems, Tübingen, Germany

Abstract: The hippocampal dentate gyrus is an important relay conveying sensory information from the entorhinal cortex to the hippocampus proper. During exploration, the dentate gyrus has been proposed to act as a pattern separator. However, the dentate gyrus also shows structured activity during immobility and sleep. The properties of these activity patterns at cellular resolution, and their role in hippocampal-dependent memory processes have remained unclear. Using dual-color in-vivo two-photon Ca^{2+} imaging, we show that in immobile mice dentate granule cells generate sparse, synchronized activity patterns associated with entorhinal cortex activation. These population events are structured and modified by changes in the environment; and they incorporate place- and speed cells. Importantly, they are more similar than expected by chance to population patterns evoked during self-motion. Using optogenetic inhibition, we show that granule cell activity is not only required during exploration, but also during immobility in order to form dentate gyrus-dependent spatial memories.

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Poster

P851. Dentate Gyrus

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Topic: H.08. Learning and Memory

Support: NIH grant R01NS093866

Title: Novelty enhances granule cell double-spikes by disinhibition of recurrent excitation.

Authors: *W.-C. SHU[1,2], M. B. JACKSON[1];
[1]Neurosci., [2]Biophysics PhD program, Univ. of Wisconsin-Madison, Madison, WI

Abstract: As the principal cells of the dentate gyrus (DG), granule cells (GCs) play key roles in the filtering and processing of information as it enters the hippocampus. GCs exhibit distinct spatial-temporal firing patterns to encode, store, and recall features in the environment. In order to investigate how GCs contribute to information processing, we used a hybrid voltage sensor (hVoS) to image their electrical activity, and Cre driver mice to target the probe to GCs. In mature GCs targeted by transient Prox1-Cre activation in neonates, voltage imaging revealed that electrical stimulation of the perforant path activated

GCs, some of which responded with doublets, two spikes separated by an interval of 2-10 ms. The incidence of doublets increased with stimulus current. GCs in the suprapyramidal and infrapyramidal blades produce doublets with a similar frequency, which fell within the range of 16-22%. We performed pharmacological studies to investigate the balance between inhibition and excitation in doublet generation. Blockade of GABAergic transmission increased the incidence of doublets to 28-35%, and this increase was reversed by DCG-IV and WIN II. The action of DCG-IV and WIN II indicated that the recurrent excitation loop formed by GCs and hilar mossy cells (MCs) can contribute to the second spike of a doublet. However, GCs still generate doublets when recurrent excitation has been blocked, suggesting that intrinsic GC excitability also plays a role in generating the second spike. Imaging optical signals from GC dendritic trees suggested that the second spike of a doublet can be evoked by synaptic inputs. To investigate the impact of experience on doublets, we targeted the probe to GCs with a conditional Cre-driver coupled to the immediate early gene, c-fos, and placed animals in a novel environment. GCs activated by novelty exhibited a higher doublet incidence, and the interval became longer when $GABA_A$ receptors were blocked. Unlike doublets with a shorter interval (<6 ms), the long-interval doublets can be completely inhibited with DCG-IV and WIN II. The longer intervals modulated by recurrent excitation and inhibition may reflect a circuitry modification resulting from prior experience. In GCs from Prox1-Cre::hVoS mice exposed to a novel environment, the incidence of long-interval doublets was higher than in control Prox1 labeled GCs, but lower than in c-fos-Cre novelty-labeled GCs. The increase in the incidence of doublets following exposure to a novel environment suggests that doublets play a role in information storage.

Disclosures: W. Shu: None. **M.B. Jackson:** None.

Poster

P851. Dentate Gyrus

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Program #/Poster #: P851.07

Topic: H.08. Learning and Memory

Support: NIH R01 NS118440

Title: Post-learning sleep loss may block engram cell reactivation in the hippocampal dentate gyrus

Authors: *L. WANG[1], L. PARK[1], A. VEGA MEDINA[1], F. RAVEN[1], A. ENSING[1], S. J. ATON[2]; [2]Molecular, Cellular, and Developmental Biol., [1]Univ. of Michigan, Ann Arbor, MI

Abstract: Over a century of research suggests that sleep plays an important role in learning and memory consolidation. Studies have shown that hippocampus-mediated contextual fear memory (CFM) consolidation requires post-learning sleep. One possibility is that post-learning sleep benefits CFM by selectively reactivating engram neurons activated during fear learning. To study the effects of post-learning sleep on engram cells, we first labeled the engram cell populations in the hippocampal dentate gyrus (DG) that encode specific contexts. Using cFos-CreER mice, we find that engram populations activated during exploration of a specific environmental context can be reactivated during subsequent contextual fear conditioning (CFC) in the same context. Our preliminary data also suggests that post-CFC

sleep deprivation, which disrupts consolidation of CFM, may block the reactivation of engram neurons engaged during CFC in DG.

Disclosures: L. Wang: None. **L. Park:** None. **A. Vega Medina:** None. **F. Raven:** None. **A. Ensing:** None. **S.J. Aton:** None.

Poster

P851. Dentate Gyrus

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Title: Hilar mossy cell dopamine D2 receptors modulate spatial memory and anxiety-like behavior in mice

Authors: *M. GULFO[1], P. E. CASTILLO[1,2];
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Abstract: Expression from the dopamine D2 receptor (D2R) promoter is a hallmark feature of dentate gyrus hilar mossy cells (MCs), but the physiologic function of the MC D2R is unknown. MCs are uniquely positioned to shape dentate gyrus function and have been implicated in learning and mood disorders, but the mechanisms underlying their involvement are not well-understood. D2R signaling could modulate key aspects of MC function. To address this possibility, we assessed potential behavioral impacts of genetic MC D2R removal. We injected 3- to 4-month-old male and female floxed-Drd2 mice with AAV5-CaMKII-mCherry-Cre or AAV5-CaMKII-mCherry to generate MC D2R conditional knockout (cKO) and control mice, respectively, for behavioral testing. Results thus far indicate that conditionally knocking out D2Rs from MCs increases anxiety-like behavior and impairs spatial and contextual fear memory, with trends clearest in male mice. Specifically, relative to control mice, cKO mice displayed decreased center duration in the open field test and decreased open arm time in the elevated plus maze. In addition, while neither control nor cKO mice exhibited a deficit in the novel object recognition task, cKO mice exhibited a deficit in the novel object location task relative to control mice. Finally, control but not cKO mice were able to discriminate between safe and aversive contexts in a contextual fear learning assay. We are currently assessing the cellular mechanisms underlying the observed behavioral effects. Better understanding the MC D2R can help clarify mechanisms of MC function in normal physiology and disease states.

Disclosures: M. Gulfo: None. **P.E. Castillo:** None.

Poster

P851. Dentate Gyrus

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Topic: H.08. Learning and Memory

Support: National Institute of General Medical Sciences / National Institutes of Health, grant R01GM128183
College of Veterinary Medicine

Title: Cognitive dysfunction induced by chronic chemogenetic inhibition of somatostatin-positive interneurons in the dentate gyrus hilus

Authors: *J. LYU[1,2], R. NAGARAJAN[2], M. KAMBALI[2], M. WANG[1,2], U. RUDOLPH[2,1];
[1]Neurosci., [2]Comparative Biosci., Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: The cellular mechanisms leading to cognitive dysfunction in the elderly are not completely understood. In aged rodents, hyperactivity of DG granule cells and CA3 pyramidal cells and hypoactivity of CA1 pyramidal cells have been reported, and a reduction of somatostatin positive (Sst+) interneurons in the dentate gyrus (DG) hilus correlates with cognitive dysfunction. We wanted to test the hypothesis that chronic but not acute suppression of the activity of hilar Sst+ interneuron causes defined learning and memory deficits. An AAV vector expressing hM4D(Gi) was stereotaxically injected bilaterally into the DG hilus of Sst-Cre mice. The control groups were injected with an AAV vector lacking hM4D(Gi). Clozapine was administered to the mice to activate hM4D(Gi) and thus inhibit hilar Sst+ interneurons. The chronic treatment group received clozapine (0.1mg/kg/day) in the drinking water for 21 days before the first behavioral experiment and throughout testing and the acute treatment group was administered clozapine (0.1mg/kg i.p.) 30 minutes before behavioral experiments. We found that both chronic and acute chemogenetic inhibition (CCI and ACI, respectively) of Sst+ DG hilar interneurons increased the number of c-Fos+ neurons only in the DG hilus, but neither in the DG granule cell layer nor in CA3 or CA1. In contrast, SST expression was decreased after CCI but not after ACI. Likewise, compared to ACI, CCI resulted in a decreased recognition index in the novel object recognition test, and an increased path length and increased latency to find the hidden platform in the water maze, both for learning and reversal learning. Our data suggest a causal relationship between a chronic loss of activity of Sst+ interneurons in the DG hilus region and cognitive dysfunction. Furthermore, our results indicate that chronic suppression of the activity of hilar Sst+ interneurons leads to a reduction of SST expression, which has been observed in aging cognitive dysfunctional rodents. CCI but not ACI thus mimics at least some molecular and behavioral features of aging, which itself is a long-lasting process. CCI of DG hilar Sst+ interneurons may thus be further evaluated as an experimental model of aging-related processes in the hippocampus.

Disclosures: J. Lyu: None. **R. Nagarajan:** None. **M. Kambali:** None. **M. Wang:** None. **U. Rudolph:** None.

Poster

P851. Dentate Gyrus

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Program #/Poster #: P851.10

Topic: H.08. Learning and Memory

Title: Selective loss of early growth response-3 expression in adult dentate gyrus attenuates learning performance in male and female mice

Authors: *U. SASAKI[1], H. HAGIWARA[2], M. FURUTA[2], Y. OGURA[2], T. FUNABASHI[2];
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Abstract: Early growth response-3 (EGR3) is a transcription factor and is a member of a family of immediate-early growth response genes. It is suggested to be involved not only for regulation of genes associated with autoimmunity (Morita et al, 2016) but also for learning process (Gallitano et al, 2007; Meyers et al, 2018). In fact, the expression of EGR3 is found to be in the brain area related to memory such as the hippocampus (Crosby et al, 1992; Yamagata et al, 1994). Since EGR3 may affect brain development process, we tried to knockdown EGR3 during adult age as a site specific manner. To this end, we used Cre-Lox P system: hippocampus-specific EGR3 inactivation by adeno-associated virus (AAV) delivery of Cre recombinase. Male and female EGR3 floxed mice were injected AAV Cre-GFP into the dentate gyrus. Control mice received the injection of AAV GFP without Cre. Three weeks after the injection, mice were subjected to open field test and Y maze task. After the behavioral examinations, all mice were examined the immunocytochemistry using antibody to EGR3. AAV expression was examined by fluorescence microscopy. We revealed that Cre expression by AAV completely eliminated EGR3-immunoreactivity in the injected site. We confirmed that this was not because of cell loss since immunohistochemical staining of neuron-specific enolase was evident in AAV injected site. When mice confirmed AAV injection by fluorescence, we counted the number of EGR3-immunoreactive cells in the dentate gyrus. AAV-mediated Cre-GFP transfer into the dentate gyrus significantly decreased the number of EGR3-expressed cells in EGR3-floxed mice (approximately 50% reduction) compared to AAV-GFP injected mice, regardless of sex. In the open field test, the total distance and the spent time in the center in AAV Cre-GFP injected mice were not significantly different from those in AAV GFP injected mice, regardless of sex. However, in the Y maze test, the alternation score in AAV Cre-GFP injected EGR3 floxed mice was significantly decreased compared with AAV GFP injected mice, regardless of sex. In AAV Cre-GFP injected mice, however, the number of EGR3-immunoreactive cells loss was not clearly correlated with the degree of the impairment Y maze ability. We conclude that the attenuation of EGR3 expression in the dentate gyrus during adult is associated with learning disability but the number of EGR3 cells in the hippocampus is not simply correlated with memory function.

Disclosures: U. Sasaki: None. **H. Hagiwara:** None. **M. Furuta:** None. **Y. Ogura:** None. **T. Funabashi:** None.

Poster

P869. Place Cells V

Location: Virtual Only

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Program #/Poster #: P869.01

Topic: H.09. Spatial Navigation

Title: Sparse versus dense coding of very large environments in hippocampal subregions CA3 and CA1

Authors: *S. R. MAIMON, T. ELIAV, L. LAS, N. ULANOVSKY;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: The hippocampus is differentiated into distinct subregions, including areas CA1 and CA3, which differ markedly in their extrinsic and intrinsic anatomical connectivity. CA1 is largely a feedforward network with almost no intrinsic excitatory connections, whereas CA3 is a recurrent network of densely interconnected pyramidal neurons - which also projects to CA1. While the anatomical connectivity differs substantially between these two subregions, the basic firing properties of spatially-modulated place cells in CA1 and CA3 were found by previous studies to be surprisingly similar, consisting mainly of single place-fields with similar field-sizes and spatial information. We hypothesized here that perhaps the similar coding properties reported for CA1 and CA3 neurons stem from the small laboratory environment sizes that were used - and that perhaps under more naturalistic spatial scales of hundreds of meters or kilometers the coding schemes of these two areas might differ. Recently (Eliav*, Maimon* *et al*., *Science* 2021) we showed that CA1 place cells recorded in bats flying in a 200-meter long tunnel, exhibit multiple place fields with very different field-sizes for different fields. This multifield multiscale spatial code is fundamentally different from the single fields observed in small laboratory boxes. Here we compared these findings from CA1 to place cells in CA3 that we recorded in bats flying in the same long tunnel. Preliminary analyses showed a dramatic difference between these two subregions: Unlike CA1 place-cells, CA3 place-cells mostly had only single place-fields; however, the sizes of individual place-fields were similar between the two areas. Consequently, the spatial information was significantly higher for place-cells in CA3 versus CA1. These preliminary results suggest a fundamental functional difference in neural-coding between these two anatomical subregions of the hippocampus: Sparse coding in CA3 versus dense coding in CA1.

Disclosures: S.R. Maimon: None. **T. Eliav:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

P869. Place Cells V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P869.02

Topic: H.09. Spatial Navigation

Title: Natural switches in behavior rapidly modulate hippocampal position × distance coding

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Abstract: In the real world, both humans and animals dynamically and rapidly switch between different behaviors. However, neuroscience research typically studies the brain while the animal is performing *one* behavioral task at a time - and little is known about how brain circuits rapidly switch between different

natural behaviors. Navigation is a complex dynamic behavior that enables testing these kinds of behavioral switches: It requires the animal to know its own location within the environment, while also paying attention to incoming sudden events such as obstacles, predators or conspecifics. Here we set out to test how brief attentional switches to 'things out there' affect the representation of space in the hippocampus. To this end, pairs of bats flew in a 135-meter flight tunnel, alternating between flying alone and flying towards each other ('cross-over' events). During cross-overs, bats had to be attentive to the other bat in order to avoid collision. Indeed, bats increased their echolocation call rate and amplitude ~20 meters before the moment of cross-over, indicating that the bats were attentive during these events. We recorded the neural activity in hippocampal area CA1 and tracked the positions of the bats using wireless-electrophysiology and custom tracking devices. We found that during cross-overs, many CA1 neurons encoded the distance to the other bat: The neurons switched from allocentric coding (place tuning) to a conjunctive egocentric × allocentric coding (inter-bat distance × place tuning) - and then switched back to allocentric coding after the bats passed each other. These neuronal switches were very rapid, as fast as 100 ms. This switching was correlated on a trial-by-trial basis with the attention signal, as indexed by the bat's echolocation calls - suggesting that spatial attention and active-sensing are controlling these major switches in neural coding. Interestingly, we found that in place-cells, the different place-fields of the same neuron often exhibited very different tuning to inter-bat distance - creating a non-separable coding of allocentric position × egocentric distance. Theoretical analysis demonstrated that such a non-separable code leads to better decoding of distance. Together, our results suggest that attentional switches during navigation - which in bats can be measured directly by their echolocation signals - elicit very rapid dynamics of hippocampal spatial coding. More broadly, this study demonstrates that during natural behavior, neural circuits can rapidly and flexibly multiplex several computations, representing the relevant behavioral variables - to support behavioral flexibility.

Disclosures: A. Sarel: None. **S. Palgi:** None. **D. Blum:** None. **J. Aljadeff:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

P869. Place Cells V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P869.03

Topic: H.09. Spatial Navigation

Title: Object × position coding in the deep layers of the MEC in flying bats

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Abstract: A spatial environment is composed of its geometric layout, and the objects within it. These two classes of information - spatial geometric information on one hand, and information about objects on the other hand - have been shown to be coded in the medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC). Some neurons, like grid cells in MEC, encode positional information about the environment. Other neurons, like object-vector cells in the superficial layers of MEC and object-cells and trace-cells in the LEC, encode the presence of objects in the environment regardless of their location.

However, while the position of specific objects is important for navigation, little is known on how this intersection is encoded in the brain. Here we recorded from the medial entorhinal cortex of flying bats as they foraged for food in a 6×5×3 meter room, in which 6-11 landing-objects were placed at various heights. We found that a substantial fraction of cells in deep layers of the MEC fired at the vicinity of specific landing-objects at specific locations. These cells fired near the landing-object when the bat flew from or to the object, but not when it flew through the same location without engaging with the object. While most of these neurons coded for a single object in a single position, some coded for 2 or more objects. We speculate that these cells in the deep layers of the MEC combine object-vector information from the superficial layers of the MEC, which is then being spatially-modulated by hippocampal position-coding via the MEC-hippocampus-MEC loop that anatomically projects to the deep layers of MEC - and possibly together with object information coming from the LEC - to create a unique object × position coding in the deep layers of MEC.

Disclosures: G. Ginosar: None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

P869. Place Cells V

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Program #/Poster #: P869.04

Topic: H.09. Spatial Navigation

Support: Azrieli Fellows Program
ELSC Graduate Students Scholarship
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Title: Hippocampal Astrocytes Encode Reward Location

Authors: *A. DORON[1], A. RUBIN[2], A. BENMELECH-CHOVAV[1], N. BENAIM[1], T. CARMI[1], T. KREISEL[1], Y. ZIV[2], I. GOSHEN[1];
[1]The Hebrew Univ., Jerusalem, Israel; [2]Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Astrocytic calcium dynamics are involved in encoding of sensory information, and modulating them has been shown to impact behavior. Recent studies have implicated hippocampal astrocytes in memory processes, but their real-time calcium activity in awake mice has never been investigated. To this end, we chronically calcium imaged CA1 astrocytes using 2-photon microscopy when mice performed a spatial task. Specifically, we trained mice to run on a linear treadmill in order to proceed in a virtual environment and obtain water rewards. We find that astrocytic activity persistently ramps towards the reward location in a familiar environment, but not in a novel one. Using linear decoders, we accurately reconstructed mice location trajectories in a familiar environment from astrocyte activity alone. We could not do the same in the novel environment, suggesting that the spatial modulation of astrocytic activity is experience dependent. This is the first indication that astrocytes can encode location in spatial contexts, thus broadening their known computational abilities, and their role in cognitive functions.

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Poster

P869. Place Cells V

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P869.05

Topic: H.09. Spatial Navigation

Title: In search of neuronal replay sequences in the hippocampus of bats in a very large environment (200 meters)

Authors: *T. ELIAV, S. R. MAIMON, L. LAS, N. ULANOVSKY;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: In rodents, ensembles of hippocampal place-cells exhibit offline reactivations of neuronal sequences (termed replay) during rest and sleep - depicting sequences of experienced trajectories that occurred during movement. Recently, we found a multifield multiscale representation in the hippocampus of bats flying in a very large 200-meter tunnel (Eliav et al., Science 2021): Individual neurons exhibited multiple place-fields of diverse sizes, ranging from less than 1 meter to more than 30 meters, and the fields of the same neuron could differ up to 20-fold in size. This unexpected coding scheme opened intriguing questions regarding replay sequences in large naturalistic environments: Are there ultra-long compressed replay sequences during rest and sleep, as observed in rodents - but extending over dozens or hundreds of meters? Do individual replay sequences cover the entire environment or just parts of it, and in particular important locations? And how is the multifield multiscale representation manifested in such replay sequences - where each neuron could participate multiple times in each sequence, each time at a different location and with a different spatial scale? To investigate this, we applied here a clusterless state-space model (Denovellis et al., bioRxiv 2021) to decode sequential reactivations when bats were resting or sleeping in the 200-meter long tunnel. We then tested the spiking activity of single place-cells with respect to the decoded sequences. Here, we will present preliminary results from our analysis.

Disclosures: T. Eliav: None. **S.R. Maimon:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

P869. Place Cells V

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Program #/Poster #: P869.06

Topic: H.09. Spatial Navigation

Title: Hippocampal representations during natural social behaviors in a bat colony

Authors: *S. RAY, I. YONA, L. LAS, N. ULANOVSKY;
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Abstract: Highly-social animals, like humans, live in complex communities and interact with different individuals at times, locations and manner of their choosing. However, neurophysiological investigation of social responses is rarely conducted in rich settings that allows such affordances. To determine how the brain represents social information in a naturalistic setting, we constructed a bat cave for a colony of 5-10 Egyptian fruit bats of both sexes. The bats lived there 24x7, free to engage in any behaviors. Every day we conducted a ~3 hour recording session, which included tracking the bat's identities, their 3D positions and their social interactions using cameras and an RF-based positioning system, while performing wireless single-unit neural recordings from their hippocampus. Behavioral data analysis indicated that the session could be deconstructed into three distinct and interleaved phases: (1) Flight phase - bats were flying in the room, (2) Interaction phase - bats were engaged in social interactions, and (3) Observation phase - bats were in their roosts, observing other bats. Here we investigated how hippocampal CA1 neurons represent information when the animals' behavior is not experimentally constrained to a particular task. Preliminary results indicate that in the flight phase, the place-tuning of a subset of neurons was modulated by the presence or absence of conspecifics at take-off or landing locations. In the interaction phase, we identified and delineated several types of social interactions and found - (i) neurons responsive to a specific interaction type regardless of the identity of the conspecific, and (ii) neurons selective for both interaction type and individual identity. In the observation phase, while the bats were in the roost observing each other, we reasoned that the neurons could potentially represent multiple factors, which can be broadly categorized into three groups: (a) self-position or head direction, (b) allocentric locations of other bats, or (c) egocentric information about other bats. To glean a systematic understanding of the contribution of these factors to the neural representation, we utilized generalized additive models (GAM). Preliminary findings indicate that single neurons merge several streams of information, and simultaneously represent multiple factors - often combining factors related to self and others. Taken together, these findings suggests that dorsal CA1 neurons represent complex social and spatial information across multiple behavioral phases.

Disclosures: S. Ray: None. **I. Yona:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

P869. Place Cells V

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Program #/Poster #: P869.07

Topic: H.09. Spatial Navigation

Support: CIHR Grant

Title: Representation of 3D space in the hippocampus of freely moving marmosets

Authors: *D. B. PIZA[1], B. W. CORRIGAN[2], R. A. GULLI[3], L. E. MULLER[1], J. C. MARTINEZ-TRUJILLO[4];
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[3]Zuckerman Inst., Columbia Univ., New York, NY; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, Brain and Mind Institute, Univ. of Western On, London, ON, Canada

Abstract: The role of the hippocampus in representing space is widely supported. Neurons that increase their firing rate when an animal occupies a certain region, 'Place Cells,' have been thoroughly identified and studied in multiple species. This unique population of neurons has been thought to support a cognitive-map like representation of space in the brain; however, little is known about how these representations are formed in the common marmoset during free navigation in a 3D environment. Moreover, whether these representations are modulated by spatial view or movement kinematic has yet to be determined. In this work, we sought to identify the firing properties of neurons in the CA fields of the hippocampus while we register spatial and view information of freely navigating marmosets as they engage in a variety of foraging behaviors in 3D space. For this purpose, we habituated the experimental subjects to freely move inside a plexiglass recording chamber with four vertical levels while wearing affixed infrared reflective markers on top of skull implants that allowed for 6 degrees of freedom position and head direction camera tracking (Optitrack, Natural Point Inc, USA). Using MRI-guided neuro-navigation techniques, we chronically implanted 32ch microwire arrays in the hippocampus, and we were able to record single-unit activity during the aforementioned behaviors wirelessly. We analyzed data from 2 animals; spatial view and occupancy rate maps were constructed using 20cm3 bins. Spatial Information Content (SIC) was calculated independently for place and view for 200 total cells. SIC was higher for the spatial view than body position. We also found cells whose firing rate was highly correlated for both body velocity and head angular velocity.

Disclosures: D.B. Piza: None. **B.W. Corrigan:** None. **R.A. Gulli:** None. **L.E. Muller:** None. **J.C. Martinez-Trujillo:** None.

Poster

P869. Place Cells V

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Program #/Poster #: P869.08

Topic: H.09. Spatial Navigation

Support: NUS Memory Networks Program
Singapore Ministry of Education Tier 2 Research Fund
Singapore Ministry of Education Tier 3 Research Fund

Title: Independent influences of place and view in the hippocampus of the non-human primate

Authors: H. TAN[1], T. P. Y. NG[1], C. OWENS[1], C. LIBEDINSKY[1,2], S.-C. YEN[1,3];
[1]The N.1 Inst. for Hlth., [2]Dept. of Psychology, [3]Innovation and Design Programme, Fac. of Engin., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: The hippocampus and surrounding regions of the hippocampal formation are critical for spatial memory in multiple mammalian species. On a single-cell level in the rodent, pure selectivity for location (place cells) is most prevalent in the hippocampus proper, with some mixed selectivity for two or more spatial variables (e.g. conjunctive grid and head direction cells) in the surrounding areas. In the non-

human primate (NHP) hippocampus, however, evidence for pure place selectivity is scarce (Courellis et al., 2019; but see Rolls et al., 1999) with some studies finding greater proportions of mixed selectivity with spatial variables like location of gaze in space (Wirth et al., 2017; Mao et al., 2020). This may be true of the primate hippocampus, or be due to artifacts arising from linear track experiments where location and heading were confounded. To rule out the latter, we recorded hippocampal activity from a male NHP in a virtual navigation task where the directions of motion and view were not constrained by location, and employed a maximum likelihood approach (Burgess et al., 2005) to dissociate the independent contributions of spatial variables to cell firing rates. We recorded from 364 putative hippocampal neurons. Prior to accounting for independent influences of place and view, 68 cells emerged as selective, made up of 38 cells jointly selective for place and view, 20 selective exclusively for place, and 10 exclusively selective for view. After correcting for the influence of place on view and vice versa, the number of selective cells increased to 88, with 44 jointly selective for place and view, 12 exclusively selective for place, and 32 exclusively selective for view. Mixed selectivity remained the most prevalent mode of selectivity after isolating independent contributions of either spatial variable, suggesting that it could be a true property of the primate hippocampus.

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Poster

P869. Place Cells V

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Program #/Poster #: P869.09

Topic: H.09. Spatial Navigation

Title: Sensory Conflicts Induce Graded Remapping in Hippocampal Ensembles

Authors: *D. FETTERHOFF, A. SOBOLEV, C. LEIBOLD;
Dept. Biol. II, Ludwig-Maximilians-Universitat Munchen, Munchen, Germany

Abstract: An animal's spatial location in an environment can be inferred from multiple simultaneously available sources including allothetic (e.g. visual landmarks) and idiothetic (multisensory self-motion) cues. Which cues an animal preferentially utilizes to estimate its location may depend on task demands, experience, and idiosyncrasies and should be reflected in the hippocampal population activity. We recorded from CA1 place cells while Mongolian gerbils were navigating one-dimensional mazes in virtual reality, in which we introduced conflicts between task-irrelevant visual cues and reward-related movement patterns (turning direction). By introducing this conflict, we found that self-motion (turn type) was strongly over-represented, but responsiveness to visual cues, although task-irrelevant, elicited both rate and global remapping in both single cells and the recorded hippocampal ensemble. We propose that these types of remapping can be reconciled by considering global, partial, and rate remapping on a continuous scale on which the graded change of activity in the entire CA1 population can be interpreted as the expectancy of the animal about its spatial environment. This hypothesis is further supported by successful decoding of maze type in situations with identical sensory input.

Disclosures: D. Fetterhoff: None. **A. Sobolev:** None. **C. Leibold:** None.

Poster

P869. Place Cells V

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P869.10

Topic: H.08. Learning and Memory

Support: NSF Graduate Research Fellowship
Fulbright Research Fellowship

Title: The macroevolution of the mammalian hippocampus

Authors: *D. VANIER[1], P. MANGER[3], J. SMAERS[2];
[2]Anthrop., [1]Stony Brook Univ., Stony Brook, NY; [3]Anat., Univ. of the Witwatersrand, Johannesburg, South Africa

Abstract: Intro The evolution of map-like neural representations constituted a sea change in cognition which greatly enhanced navigation in early vertebrates. Over deep evolutionary time, the brain region supporting navigational representations, the hippocampus (HP), became pivotal to a host of cognitive processes ranging from declarative memory to divergent creativity. Characterizing the macroevolution of HP could reveal neuroanatomical changes that enable high-level HP-dependent abilities, including those possibly unique to humans. Here we model the evolution of the mammalian HP relative to brain and neocortex size across 435 species from 21 orders.
Methods A bivariate Bayesian evolutionary model was used to estimate where shifts in slope (covariance) and intercept (mean) of HP/brain occurred in the mammalian tree. Volumetric data from the literature and the genetic relatedness of species were used as input for the model. To confirm whether certain groups of species statistically differed in mean HP/brain (as predicted by the model), a phylogenetic least squares ANOVA was used. To determine if changes in mean HP/brain were driven by changes in HP or brain size, phylogenetic means for both traits were calculated using least-squares procedures to generate an ancestral to descendent ratio of change in mean size.
Results 12 shifts in the HP/brain scaling relationship resulted in 13 groups of species with distinct slopes or intercepts ($F=20.26$, $p<0.001$). Monkeys and apes ($b=0.70$), ferungulates ($b=0.66$), and fruit bats ($b=0.79$) indicate a decrease in slope of HP/brain as compared to their ancestral conditions ($b=0.90$, $b=0.89$, $b=0.93$, respectively). Other groups indicate negative (cetaceans, seals, manatees, elephants, other primates, other bats) or, rarely, positive (plains zebras, tapirs, elephant shrews) shifts in intercept alone.
Discussion Mammals with large brains, including those thought to possess exceptional memories such as great apes, exhibit decreases in HP relative to the brain which were driven by large changes in mean brain (neocortex). These evolutionary shifts imply fundamental changes to the developmental, genetic, and functional interactions of HP and the neocortex. In large-brained mammals, it thus seems likely that the emergence and expansion of neocortical association areas, and their interactions with HP, led to higher-level HP-dependent cognition. Different association areas, however, evolved via accretion in different lineages, and many human association areas only emerged in monkeys and apes. This suggests that, despite the conserved cytoarchitecture of HP, different mammals possess qualitatively different types of memory.

Disclosures: D. Vanier: None. **P. Manger:** None. **J. Smaers:** None.

Poster

P875. Cognitive Planning

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Program #/Poster #: P875.01

Topic: H.04. Executive Functions

Support: Becas de Doctorado Nacional, año 2015 of CONICYT 21150295
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Institut Universitaire de France (IUF)

Title: Long-range frontal theta phase modulation during cognitive planning

Authors: *M. DOMIC[1], M. IRANI[2], V. MEDEL[2], T. OSSANDÓN[2], *M. PERRONE-BERTOLOTTI[3]; [1]Univ. Católica del Norte, Antofagasta, Chile; [2]Pontificia Univ. Católica de Chile, Santiago, Chile; [3]Univ. Grenoble Alpes, Grenoble, France

Abstract: Cognitive planning (CP), the ability to develop a sequenced plan to achieve a goal, plays a crucial role in human goal-directed behavior. It has been suggested that cognitive control might result from frequency-specific interactions of specialized and widely distributed cortical regions due to the enriched rhythmic structure nature of the brain. We have previously demonstrated that CP induces a significant increase in the frontal midline theta (FMθ) power. It is suggested that the FMθ could interact with distant brain regions by modifying their local power amplitude in specific alpha and beta bands. Here, we specifically evaluated this using a phase to phase (weighted Phase Lag Index, wPLI) and phase-amplitude coupling approach. Our results show a robust increase in theta phase (4-8 Hz) connectivity during planning between frontal and widely distributed electrode sites. Additionally, we found that this frontal theta phase modulates frontal alpha amplitude (9-12 Hz) and frontal, central, and parietal low beta amplitude (13-20 Hz). These results support the idea that cognitive control implementation in the brain is performed via theta phase connectivity, which coordinates information processing (such as visuospatial analysis and motor control preparation). The prefrontal cortex performs this long-range coordination over disparate brain regions, modulating local alpha and beta amplitude.

Disclosures: M. Domic: None. **M. Irani:** None. **V. Medel:** None. **T. Ossandón:** None. **M. Perrone-Bertolotti:** None.

Poster

P875. Cognitive Planning

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P875.02

Topic: H.10. Human Learning and Cognition

Support: Neukom Institute for Computational Science

Title: Distinct, adjacent networks for place memory and scene perception in the human brain

Authors: *A. STEEL, B. D. GARCIA, A. MYNICK, Y. B. CHOI, C. E. ROBERTSON;
Psychology and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: How do visual and spatio-mnemonic systems interface during naturalistic scene perception? The reinstatement account posits that the same areas that perceive a stimulus are recruited during memory retrieval. Alternatively, in the context of scenes, recent studies suggest a transition from perception to memory moving anteriorly from the brain's scene perception areas. Here, we explicitly tested the reinstatement vs. anterior shift accounts of place memory using a combination of VR and fMRI. In Experiment 1 (N=14), we independently localized the three scene perception areas (parahippocampal place area, occipital place area, and medial place area/RSC) by comparing activation when participants saw images of scenes and faces. Then, in the same individuals, we localized areas that preferentially activated when participants recalled personally familiar real-world places (e.g., their house) versus faces (e.g., their mother). Remarkably, recall activity for personally familiar places was shifted anterior from, rather than co-localized with, category-selective scene perception areas in the brain (all $p<0.001$; Steel et al., 2021). To determine whether this anterior shift reflected the spatial aspects of memory and not episodic or semantic features, in Experiment 2 participants (N=11) studied 20 real-world places using head-mounted VR. VR affords exquisite stimulus control, enabling us to isolate the spatial component of memories. After training, we scanned participants during an explicit recall task and a passive perception task of the studied places. Here again, recall-related activity of learned VR environments was shifted anterior from the scene perception areas on all cortical surfaces. Moreover, the place memory areas were strongly recruited during recall and perception of VR environments, while the scene perception areas were not (all $p>0.001$). Finally, multivariate decoding analyses revealed robust representations of individual places in the place memory areas (all $p>0.01$). These findings validate the anterior shift account of place memory in contrast to reinstatement accounts. Moreover, they provide insight into the neural basis of visuospatial memory for naturalistic environments and, more broadly, the mechanisms by which stored knowledge about the world influences ongoing perception during naturalistic visual experience.

Disclosures: A. Steel: None. **B.D. Garcia:** None. **A. Mynick:** None. **Y.B. Choi:** None. **C.E. Robertson:** None.

Poster

P875. Cognitive Planning

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P875.03

Topic: H.10. Human Learning and Cognition

Title: Discrete scene snapshots prime perception of 360° space in immersive real-world scenes

Authors: *A. MYNICK, C. E. ROBERTSON, T. L. BOTCH, A. L. BURROWS, B. D. GARCIA; Dartmouth Col., Hanover, NH

Abstract: We experience our visual environment in discrete glances. How do we build a unified representation of a 360º visual environment? One possibility is that neighboring scene views become associated through concurrent activation during learning, enabling a single view to prompt reactivation of the surrounding environment. In this two-part study, we used Virtual Reality (VR) to ask whether a single view in an immersive panorama primes perceptual judgements of adjacent views in 360º space, and whether that priming is yoked to the spatial structure of a scene.
To examine whether a single view primes perceptual judgements of adjacent views in 360º space, subjects in Experiment 1 (N=21) learned 18 real-world panoramas using head-mounted VR. In a subsequent Priming Test, on each trial, subjects turned their head left or right to view a target image taken from a studied panorama (110º field-of-view), and made a perceptual (open/closed) judgement. Before target onset, a brief (300ms) prime image was presented directly ahead, either depicting: 1) an adjacent snapshot from the same panorama (Valid prime), 2) a snapshot from a different panorama (Different Scene prime), or 3) a grey box (Neutral prime).
We found an effect of priming condition on reaction time ($p<.001$): subjects made faster open/closed judgements when primed with an image from the same panorama (Valid prime condition) compared to Neutral ($p<.05$) and Different Scene primes ($p<.001$).
To examine whether perceptual priming is yoked to the 360º structure of a scene, subjects in Experiment 2 (N=21) performed a Priming Test with Valid, Neutral, and Spatially Incoherent primes. Spatially Incoherent primes were taken from the same panorama as the target, but targets were presented opposite their true location relative to the prime.
We found an effect of priming condition on reaction time ($p<.001$): subjects made faster open/closed judgements when primed with an image from the same panorama (Valid prime condition) compared to Neutral ($p<.001$) and Spatially Incoherent primes ($p<.001$).
To ensure spatial knowledge of the panoramas, all subjects completed an Explicit Memory Test, where on each trial they reported whether a snapshot had appeared on the left/right/front of a studied panorama. Performance was above chance ($p<.001$ in Experiments 1 and 2), indicating accurate spatial knowledge.
Taken together, we show that discrete views of a panorama prime each other in 360º space, and that priming is yoked to the spatial structure of a scene. These results suggest that reinstatement of unseen, adjacent views may play an important role in facilitating ongoing perception and maintaining a seamless sense of our 360º visual environment.

Disclosures: A. Mynick: None. **C.E. Robertson:** None. **T.L. Botch:** None. **A.L. Burrows:** None. **B.D. Garcia:** None.

Poster

P875. Cognitive Planning

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Program #/Poster #: P875.04

Topic: H.10. Human Learning and Cognition

Title: A cortical network representing visuospatial context in posterior cerebral cortex

Authors: *B. D. GARCIA, A. STEEL, K. GOYAL, A. MYNICK, Y. B. CHOI, C. E. ROBERTSON; Psychological & Brain Sci., Dartmouth Col., Hanover, NH

Abstract: How does the brain represent knowledge of the local visuospatial environment during naturalistic scene perception? Here, using controlled, naturalistic stimuli learned in head-mounted VR, we investigated where in the brain surrounding visuospatial context associated with a real-world scene is represented. We hypothesized that the place memory network, a set of cortical brain areas adjacent and anterior to the scene perception areas, would play a preferential role in representing visuospatial context. Participants (N=11) studied 20 real-world scenes using VR with varying spatial context. The Image Condition consisted of 45° of a panoramic environment (315° occluded). The Panorama Condition consisted of 270° of a panorama. Finally, the Street Condition consisted of a navigable environment made up of contiguous panoramas. Using fMRI, we examined neural responses when participants recalled (Exp. 1) and perceived discrete fields of view from each scene (Exp. 2). We first isolated neural regions that were selective for place memory and scene perception as described in Steel et al., 2021, and we assessed the relative sensitivity of these "place memory areas" and "scene perception areas" to the degree of spatial context associated with a scene during recall and perception. As predicted, all three of the place memory areas showed significant modulation by spatial context during both recall and perception (all $p>0.001$), with greater spatial context eliciting more activity in these areas. In contrast, spatial context did not modulate activity in the scene perception areas during recall (all $p>0.6$) or perception (all $p>0.4$). Intriguingly, spatial context did not impact hippocampal activity. Importantly, activity in control areas (V1 and FFA) was not impacted by spatial context (all $p>0.05$). Together, these results show that a specific cortical network represents spatial context in the brain and suggest that hippocampal responses may not reflect the spatial scale of an environment. This finding provides an important step towards articulating the neural structures underlying memory of navigable space.

Disclosures: B.D. Garcia: None. **A. Steel:** None. **K. Goyal:** None. **A. Mynick:** None. **Y.B. Choi:** None. **C.E. Robertson:** None.

Poster

P875. Cognitive Planning

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P875.05

Topic: H.10. Human Learning and Cognition

Support: NRF-2020R1A2C2007770
NRF-2020M3E5D9079913

Title: Representational changes in the ventromedial prefrontal cortex during memory integration

Authors: *W. KANG[1], S.-H. LEE[1,2];
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Abstract: Memory integration, a process of interconnecting related memories, is a basis of our adaptive behaviors. Prior memory studies have shown that the ventromedial prefrontal cortex (vmPFC) is engaged

in memory integration. However, it remains unclear how original memory traces change during the integration of new information into previous memory. Here we performed an event-related functional magnetic resonance imaging (fMRI) experiment to investigate the neural mechanism underlying memory integration. In the experiment, participants were asked to conduct two-phase learning and retrieval sessions. During the first phase of the learning session, they learned the first set of object pairs. After the first phase, they learned the second set of object pairs (second phase), which partially overlapped with the first set of object pairs. Using trial-by-trial similarity analyses, we found that the degree of shared representations for the first set of pairs in the vmPFC gradually decreased while that for the second set of pairs gradually increased during the second learning phase. Moreover, there was also a gradual increase in the degree of shared representations for the indirect association in the vmPFC. These results suggest that memory integration involves reorganizing related memory traces, including both existing and new memory traces in the vmPFC.

Disclosures: W. Kang: None. **S. Lee:** None.

Poster

P875. Cognitive Planning

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P875.06

Topic: H.04. Executive Functions

Support: NIMH R37 MH066078

Title: The Dual Mechanisms of Cognitive Control (DMCC) Project: A neuroimaging study of individual variation in cognitive control function

Authors: *T. S. BRAVER[1], A. KIZHNER[2], R. TANG[2], M. C. FREUND[2], M. F. SINGH[2], J. A. ETZEL[3]; [1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Psychological and Brain Sci., Washington Univ., St. Louis, MO; [3]Psychological and Brain Sci., Washington Univ., St.Louis, MO

Abstract: The Dual Mechanisms of Cognitive Control (DMCC) project provides a rigorous experimental test of a theoretical framework positing two key modes of control - proactive and reactive - that may reflect domain-general dimensions of individual variation). This framework is currently being evaluated through an on-going, larger-scale fMRI neuroimaging study (target N=200), that features a multi-session imaging protocol, composed of a novel cognitive control task fMRI battery, plus a comprehensive, out-of-scanner individual differences assessment. Study participants include both healthy young adults recruited from the Human Connectome Project, as well as monozygotic twin pairs. Participants are tested in a longitudinal design; each assessment wave includes 3 fMRI scanning sessions. In each fMRI session, 4 theoretically-optimized variants of well-established cognitive control paradigms are performed (plus resting-state scans): AX-CPT, Stroop, Cued Task-Switching, and Sternberg Working Memory. In the first session, tasks are performed under low-control Baseline conditions; the other two sessions task conditions encourage Proactive or Reactive control (counter-balanced order). Task fMRI scans follow a mixed blocked/event-related design, enabling estimates of both sustained and transient neural activity dynamics. A whole-brain ROI approach was used for analyses, relying upon well-established cortical parcellation

schemes. Additional analytic approaches, reported elsewhere, examined whole-brain neural modeling as a preprocessing step to filter intrinsic brain activity dynamics, multivariate pattern analyses to identify cognitive control neural coding, and neural fingerprinting approaches to assess twin similarity and test-retest reliability. Initial results based on 80 participants identified a neural signature of cognitive control involving parcels, involving the fronto-parietal and cingulo-opercular networks, that was domain-general (consistent across all four tasks), and also modulated in distinct fashion by the reactive and proactive conditions. A clear brain-behavior relationship was also observed, particularly in the reactive condition, such that individuals showing more efficient neural activity patterns also exhibited the strongest reactive-related enhancement of cognitive control function. The DMCC project is being conducted according to Open Science principles, so that data will be of maximal value to the scientific community. A subset of DMCC data is currently available at OpenNeuro (https://openneuro.org/datasets/ds003465); the full dataset will be made publicly available at project completion.

Disclosures: T.S. Braver: None. **A. Kizhner:** None. **R. Tang:** None. **M.C. Freund:** None. **M.F. Singh:** None. **J.A. Etzel:** None.

Poster

P875. Cognitive Planning

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Program #/Poster #: P875.07

Topic: H.04. Executive Functions

Support: NIH R03 AG065966
NIH R21 AG062395
NSF 1829473
NINDS K99NS115918

Title: Predictors and mechanisms of neurostimulation effects on cognitive control in aging.

Authors: *K. JONES[1], E. L. JOHNSON[2], A. GAZZALEY[3], T. ZANTO[1];
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Abstract: Background: Noninvasive transcranial electrical stimulation (tES) research is plagued with inconsistencies. Recent work suggests that neuroanatomical and neurophysiological variability alter tES efficacy. However, direct evidence is limited. Furthermore, the structural and functional mechanisms underpinning how tES affects learning remain poorly understood. **Objective**: We previously replicated effects of theta transcranial alternating current stimulation (tACS) on improving cognitive control in young adults. Here, we assess whether the same stimulation parameters have comparable effects in older adults (aged 60-80 years), a population known to have greater variability in neuroanatomy and neurophysiology. We hypothesized that variability in neuroanatomy and neurophysiology would predict tACS efficacy. We further sought to identify underlying mechanisms of behavioral gains through measuring EEG connectivity changes and the structural integrity of specific white matter tracts. **Methods**: tACS was applied to prefrontal cortex (F3-F4) while participants engaged in a gamified multitasking

intervention. Participants received either 6-Hz (theta) or 1-Hz (delta) tACS on three consecutive days (Tuesday-Thursday). To account for neuroanatomy, MRI data were used to form individualized models of the tACS-induced electric field (EF) in the brain. To account for neurophysiology, EEG data were used to identify individual peak theta frequency. Functional connectivity was assessed by measuring changes in phase-locking values (PLV) from the tACS-free baseline (Monday) at each tACS session and the one-day follow-up (Friday). Structural connectivity was measured used diffusion tensor imaging (DTI) collected at baseline. **Results**: In the theta tACS group, performance gains correlated with modeled EF and peak theta frequency. Together, these measures accounted for 54-65% of variance in performance gains, which were sustained for a month. Furthermore, performance gains were associated with a double dissociation in daily PLV changes, with theta tACS driving broadband (theta-beta) increases in PLV and delta tACS leading to reductions in PLV. The structural integrity of white matter tracks further predicted daily PLV changes, with maximal effects in inferior longitudinal and fronto-occipital fasciculi. **Conclusion**: These results demonstrate the importance of considering individual neuroanatomy and neurophysiology in tES research and begin to resolve inconsistencies across studies. Interventions should account for these differences and target underlying neural mechanisms of behavioral gains to reliably improve cognition in aging.

Disclosures: K. Jones: None. **E.L. Johnson:** None. **A. Gazzaley:** None. **T. Zanto:** None.

Poster

P875. Cognitive Planning

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Program #/Poster #: P875.08

Topic: H.04. Executive Functions

Support: NIMH R37MH087027
NIMH 5K99MH116100-02
Office of Naval Research Multidisciplinary University Research Initiatives Grant N00014-16-1-2832
MIT Picower Institute Faculty Innovation Fund
NIH EY029666

Title: A ubiquitous laminar motif of local field potential power across cortical areas, individual subjects and studies

Authors: *A. BASTOS[1], D. MENDOZA-HALLIDAY[2], N. LEE[2], M. LICHTENFELD[1], A. J. MAJOR[2], R. DESIMONE[3], E. K. MILLER[4];
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Abstract: The cerebral cortex is anatomically organized as a six-layered motif. This motif is preserved across all cortical areas and is thought to form the underlying architecture for a canonical cortical microcircuit that, with some variations, can be used by different areas to execute a diversity of functions. While this motif has been well described as a pattern of cytoarchitectonic differences across layers, little

is known about whether it can also be ubiquitously observed across cortex as a pattern of physiological differences across layers. Here, we report the discovery of such a physiological pattern in the power of neuronal oscillations. We analyzed electrophysiological recordings obtained using laminar probes implanted across layers in a variety of cortical areas (MT, V4, MST, LIP, 7A, right and left LPFC) in four macaque monkeys from two studies performed in different labs. We show that the relative power of local field potentials (LFP) oscillations across layers follows a characteristic pattern: Putative superficial layers (layers 2/3) have stronger power in the gamma (40-150 Hz) and delta/theta (1-6 Hz) bands than deeper layers. Putative deep layers (layers 5/6) have stronger alpha/beta (8-30 Hz) band power than superficial layers. We represented each laminar probe's relative power as a two-dimensional layer by frequency map. We then quantified the similarity between maps using image similarity analysis. We found that the relative power maps generalize across monkeys, areas, and studies. This suggests the presence of a ubiquitous physiological motif across cortex that represents a putative physiological signature of the canonical cortical microcircuit. Taking advantage of this motif, we propose a method for cortical layer identification in laminar electrophysiological recordings, and demonstrate its advantages compared to the current source density method.

Disclosures: A. Bastos: None. **D. Mendoza-Halliday:** None. **N. Lee:** None. **M. Lichtenfeld:** None. **A.J. Major:** None. **R. Desimone:** None. **E.K. Miller:** None.

Poster

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Program #/Poster #: P875.09

Topic: H.04. Executive Functions

Support: Jump ARCHES endowment through the Health Care Engineering Systems Center

Title: Effects of cardiovascular risk factors on prefrontal cortical activation during trail walking task: A dual task fNIRS study.

Authors: *A. BISHNOI, M. HERNANDEZ;
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Abstract: Cardiovascular measures such as heart rate (HR) and blood pressure are expected to change with age. However, the underlying mechanism by which impaired HR affects mobility and cognitive impairment remains unclear. HR reserve (HRR) is the difference between individual's maximum HR and resting HR, which has been shown to decrease with increased age. Impaired HRR in some older adults may result in reduced motor and cognitive abilities that may predispose them to an increased fall risk. Dual task (DT) paradigms have shown to measure this cognitive impairment while walking in older adults. Based on which, we designed the Instrumented trail walking task (TWT) to find this cognitive decline in older adults who are affected due to unknown cardiovascular impairments. This is the first study examining the effects of an instrumented TWT on prefrontal cortical (PFC) activation patterns evaluated by functional near infrared spectroscopy (fNIRS) among older adults with and without lower HRR (LHRR). We hypothesized that there would be an increase in activation going from an easier to a

more difficult task among older adults, particularly in those with LHRR, relative to those without LHRR. In this cross-sectional study, we examined 24 older adults with (LHRR: n=10; 70.2±4.71yrs; 1.02±0.23m/s) and without LHRR (HHRR: n=14; 60±8.14yrs; 1.17±0.17m/s). Participants completed baseline cognitive and motor testing before starting the paradigm on an instrumented treadmill. The DT paradigms consisted of four tasks: comfortable walking tasks (CW1 and CW2) and trail walking tasks (TWT-A with only sequential numbers and distractors and TWT-B with both sequential letters and numbers and distractors). The order of the tasks was CW1, TWT-A, CW2, TWT-B. Participants completed the TWTs under their comfortable walking speed with easier task first (TWT-A) and difficult task later (TWT-B). We found significant differences in age and gait speed between LHRR and HHRR ($p<0.05$). The results of the linear mixed model analysis with age as a covariate revealed trial (TR) ($p<0.01$) effects, and 2-way interaction among Cohort and TR ($p<0.0001$). Post hoc analysis confirmed these interactions between Cohort and Trial. We found significantly higher PFC activation i.e., higher oxyhemoglobin levels among both cohorts while going from TWT-A to TWT-B i.e., easier to difficult task. However, we found the use of higher activation in HHRR group, relative to LHRR, in TWT-B. This study confirms that the older adults had to use more attentional resources to do the difficult task, but that LHRR may be facing limitations in PFC recruitment, which merits further exploration.

Disclosures: A. Bishnoi: None. **M. Hernandez:** None.

Poster

P973. Software Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.02

Topic: I.07. Data Analysis and Statistics

Support: ERC starting grant #639272
Research Council of Norway #274306

Title: Nansen - an ecosystem of tools to provide a complete pipeline for analyzing two-photon microscopy data

Authors: *E. HENNESTAD, K. VERVAEKE, A. WITOELAR;
Univ. of Oslo, Oslo, Norway

Abstract: Two-photon microscopy is widely used to investigate brain functions. This technique produces vast amounts of images that require advanced and labour-intensive processing steps to extract neuronal signals. The complete analysis pipeline typically includes many steps such as brain motion correction (image registration), delineating neural structures of interest (image segmentation), and methods to infer neuronal spiking from the extracted signals. An increasing number of toolboxes have appeared that deal with these individual steps, but few of these provide a complete analysis pipeline. This often leaves the users with a significant amount of programming to incorporate a diverse set of toolboxes into their data analysis pipeline. Furthermore, these toolboxes often provide limited functionality for visualization and quality control. To tackle this problem, we have developed the “Neuroscience ANalysis Software ENsemble” (NANSEN). This package contains modules for building a complete processing pipeline and

exploring data using interactive graphical user interfaces. Currently available modules include existing toolboxes widely used by the neuroscience community, such as NoRMCorre, CaImAn and Suite2P. Because each toolbox has strengths and weaknesses for a specific step in the analysis pipeline, the user can choose what works best for their data. All these toolboxes are implemented as plugins, and as new toolboxes appear, they can be easily added. Importantly, to facilitate sharing and re-use data, we aim to make the data format compatible with the Neural Data without Borders (NWB) standard. The aim is to streamline the process for new users and provide powerful visualization tools for existing and advanced users. We further hope that this package can provide a common framework for further development of tools and analysis methods that can be shared widely within the neuroscience community.

Disclosures: E. Hennestad: None. **K. Vervaeke:** None. **A. Witoelar:** None.

Poster

P973. Software Tools II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.03

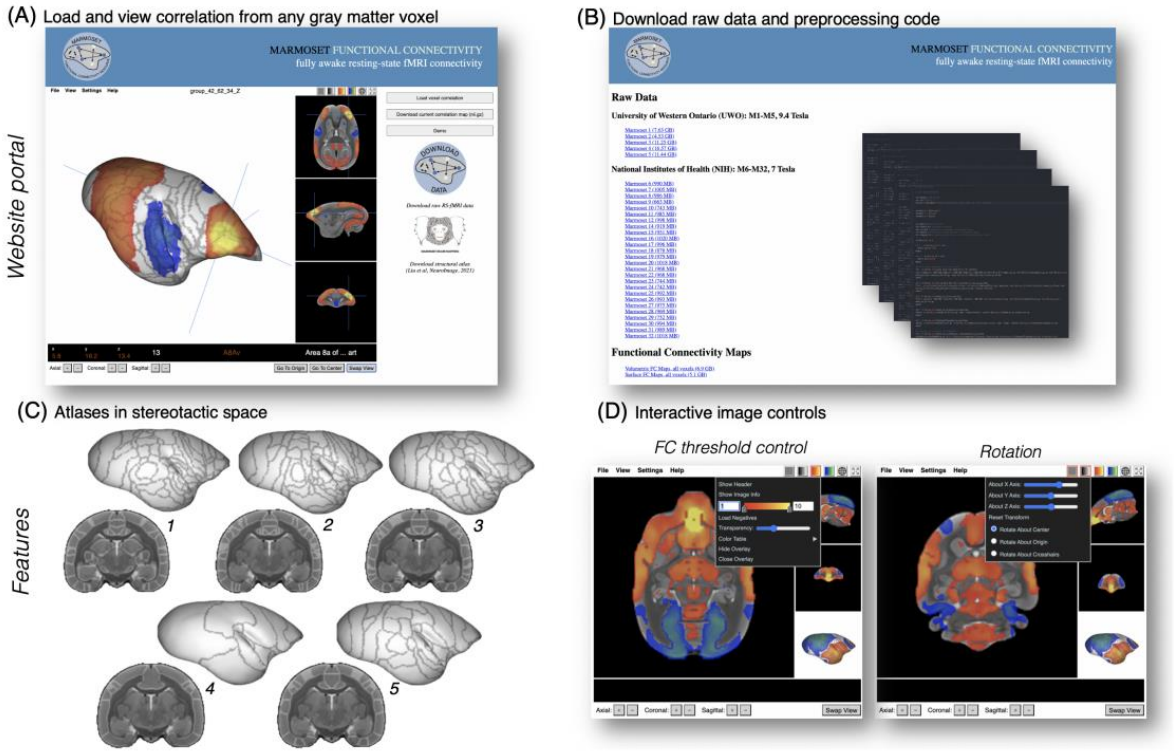
Topic: I.07. Data Analysis and Statistics

Support: Canadian Institutes of Health Research (FRN 148365, FRN 629 353372)
Pennsylvania Department of Health 631 Commonwealth Universal Research Enhancement (C.U.R.E.) Tobacco Appropriation Funds – 632 Phase 18 (SAP 4100083102)

Title: An Open Access Resource for Functional Brain Connectivity from Fully Awake Marmosets

Authors: *D. SCHAEFFER[1], L. KLASSEN[3], Y. HORI[5], X. TIAN[1], D. SZCZUPAK[1], C. C.-C. YEN[7], J. CLÉRY[5], K. GILBERT[4], J. GATI[4], R. S. MENON[6], C. LIU[8], S. EVERLING[9], A. C. SILVA[2];
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Abstract: The common marmoset (Callithrix jacchus) is quickly gaining traction as a premier neuroscientific model. However, considerable progress is still needed in understanding the functional and structural organization of the marmoset brain to rival that documented in long-standing preclinical model species, like mice, rats, and Old World primates. To accelerate such progress, we present the Marmoset Functional Connectivity Resource (marmosetbrainconnectome.org), consisting of over 70 hours of resting-state fMRI (RS-fMRI) data acquired at 500 µm isotropic resolution from 31 fully awake marmosets in a common stereotactic space. Three-dimensional functional connectivity (FC) maps for every cortical and subcortical gray matter voxel are stored in an online repository. Users can instantaneously view, manipulate, and download any whole-brain functional connectivity (FC) topology along with the raw datasets and preprocessing code. We expect that this resource will be of broad value, supporting novel hypotheses about the functional organization of the marmoset brain.



Disclosures: D. Schaeffer: None. **L. Klassen:** None. **Y. Hori:** None. **X. Tian:** None. **D. Szczupak:** None. **C.C. Yen:** None. **J. Cléry:** None. **K. Gilbert:** None. **J. Gati:** None. **R.S. Menon:** None. **C. Liu:** None. **S. Everling:** None. **A.C. Silva:** None.

Poster

P973. Software Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.04

Topic: I.07. Data Analysis and Statistics

Support: NIH R24-MH-114793

Title: The Brain Image Library: A Brain Data Archive for Microscopy

Authors: *A. ROPELEWSKI[1], A. WETZEL[1], G. HOOD[1], M. BRUCHEZ[2], A. WATSON[3], S. WATKINS[3];
[1]Pittsburgh Supercomputing Ctr., [2]Mol. Biosensor and Imaging Ctr., Carnegie Mellon Univ., Pittsburgh, PA; [3]Ctr. for Biologic Imaging, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The Brain Image Library (BIL) is a public resource serving the neuroscience community by providing a persistent centralized repository for microscopy data generated by brain researchers. BIL contains thousands of brain datasets including high-resolution data from the BRAIN Initiative Cell

Census Network. Data in BIL includes: whole brain datasets and their accompanying neuron tracings; whole brain datasets from cell counting experiments; datasets from spatial transcriptomics; datasets arising from multimodal experiments such as patch-seq; and data from other experimental modalities. BIL provides critical infrastructure that enables investigators to meet data sharing requirements such as those of the NIH BRAIN Initiative which requires data sharing for funding applications submitted after March 1, 2020 as well as the more broad National Institutes of Health data sharing policy effective in 2023. Deposited data in BIL does not need to have NIH funding, but does need to be relevant to the BRAIN Initiative.
BIL services include data transfer testing and network analysis assistance, LTO-7/8 tape processing and a visualization/computational enclave to allow researchers to process datasets in-place and share restricted and pre-release datasets. In addition, the BIL data is available on the Pittsburgh Supercomputing Center's Bridges2 supercomputer, which provides significant computational ability to process data in-place.

Disclosures: A. Ropelewski: None. **A. Wetzel:** None. **G. Hood:** None. **M. Bruchez:** None. **A. Watson:** None. **S. Watkins:** None.

Poster

P973. Software Tools II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.05

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1U19NS107464

Title: Brain platform: validating and sharing neurodata analysis pipelines

Authors: G. MAGNUSSON[1], ***Z. BOWEN**[1], M. DIEP[1], W. LOSERT[2];
[1]Fraunhofer Inst., College Park, MD; [2]Col. of Computer Mathematical and Natural Sci., Univ. of Maryland, College Park, MD

Abstract: Two-photon calcium imaging is one of the most powerful tools in modern neuroscience, however going from two-photon images to interpretable data requires pre-processing of images and post-processing of extracted signals. As a result, many algorithms and pipelines have been developed for the analysis of two-photon imaging data. While some algorithms and pipelines are published and publicly available, others are often home brewed and tweaked to fit the needs of individual researchers. Furthermore, the metadata associated with two-photon imaging data varies between different experimental setups. The vast differences in algorithm choices, pipeline parameter settings, and data sources combine to create an immense challenge of data reproducibility and collaboration. The BRAIN Platform is a tool that aims to reduce the friction of collaboration between researchers working on two-photon calcium imaging. The BRAIN Platform helps researchers share their algorithms as reusable modules, and then to combine and configure these modules as shareable workflows/pipelines. The BRAIN Platform implements an approach to evaluate the sensitivity and robustness of the configured pipelines; which can help guide researchers in selecting the appropriate parameter settings for the pipeline for their own specific data. The BRAIN platform has been developed as part of the BRAIN Initiative in

collaboration with 11 research labs, and as such comes with a set of validated modules and workflows. However, over time we hope to crowdsource more with help from the community. By making modules and workflows sharing easier, researchers can focus on developing and maturing their unique contribution while leveraging other parts of the analysis pipeline from the community. Furthermore, researchers can disseminate their analysis pipeline and results in a way that promotes repeatable, reproducible, and trustworthy analysis process.

Disclosures: G. Magnusson: None. **Z. Bowen:** None. **M. Diep:** None. **W. Losert:** None.

Poster

P973. Software Tools II

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Program #/Poster #: P973.06

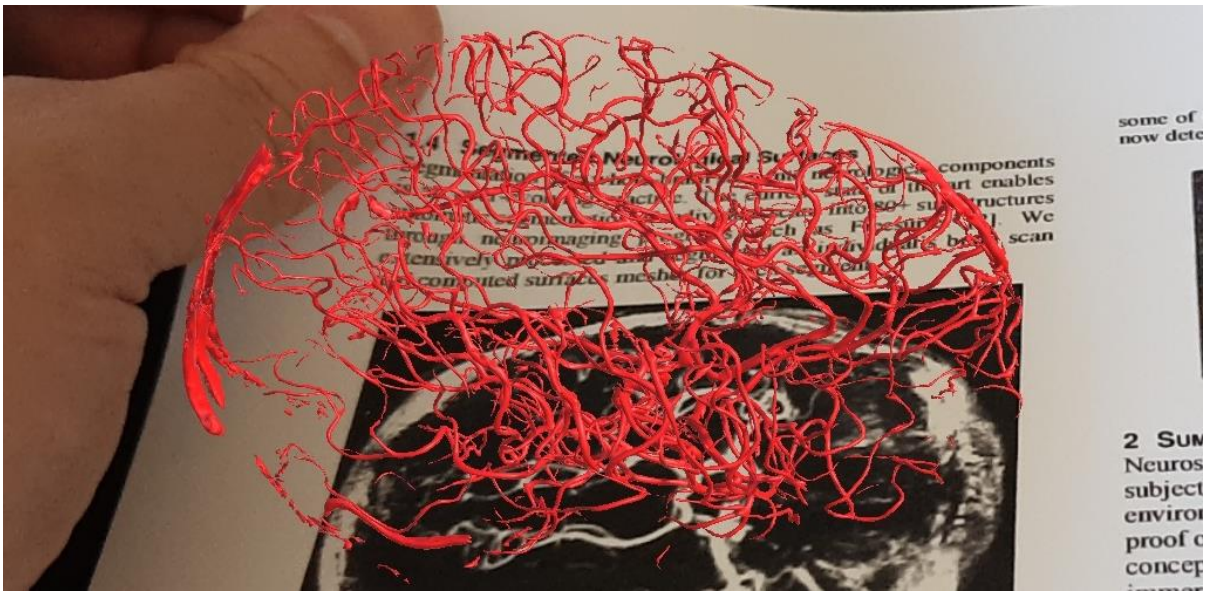
Topic: I.07. Data Analysis and Statistics

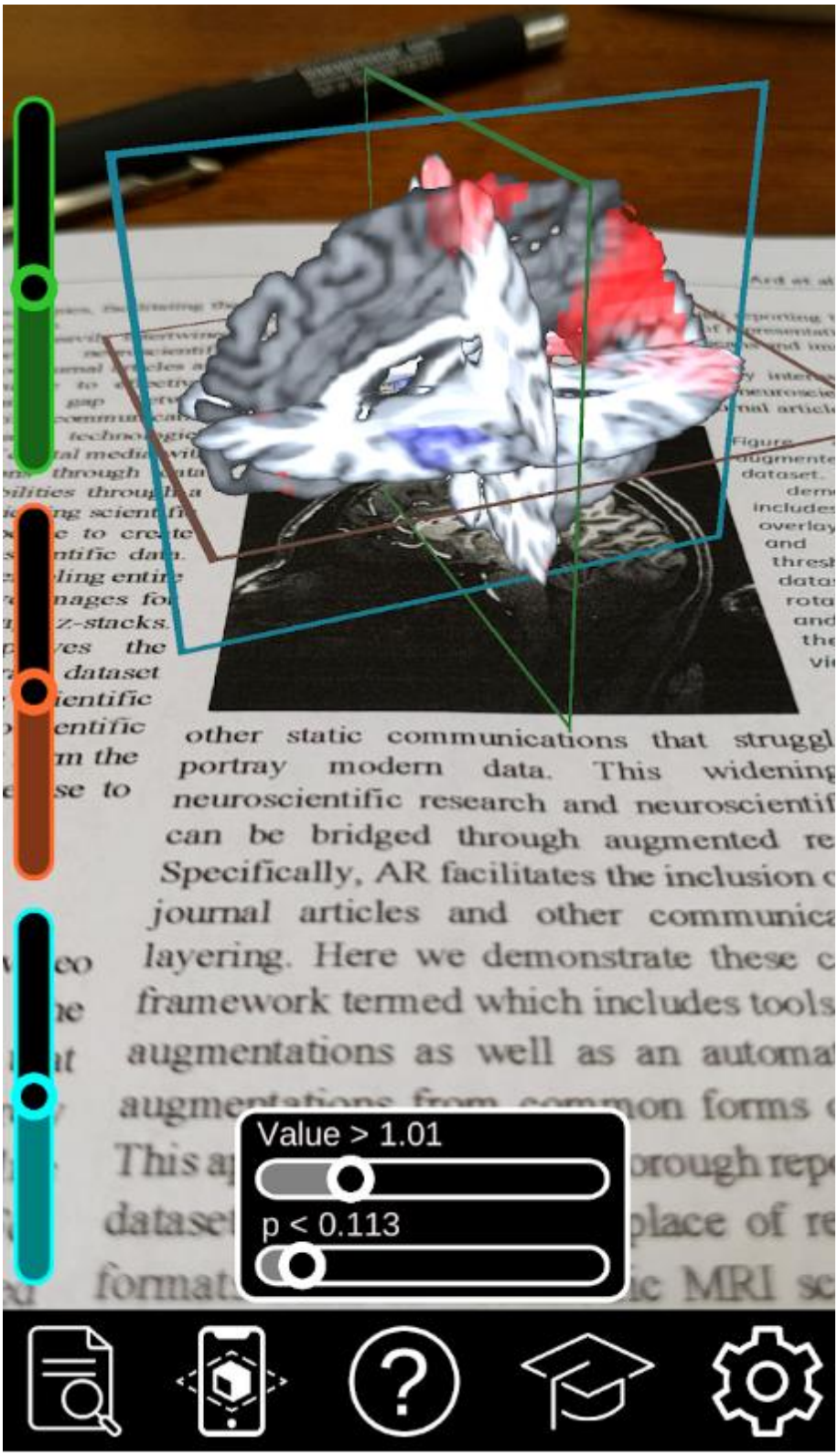
Support: NIH Grant P41EB015922
NIH Grant U54EB020406
Michael J. Fox Foundation's Parkinson's Progression Markers Initiative (PPMI – award # 8283.03)

Title: Community Accessible Augmented Reality Data Layering for Neuroscientific Communication

Authors: *T. ARD, A. W. TOGA;
USC Stevens Neuroimaging and Informatics Inst., Los Angeles, CA

Abstract: Neuroscientific research has become heavily intertwined with digital information, however neuroscientific communication remains largely based on journal articles and other static communications that struggle to effectively portray modern data. This widening gap between neuroscientific research and neuroscientific communication can be bridged through augmented reality (AR) technologies. Specifically, AR facilitates the inclusion of digital media with journal articles and other communications through data layering. Here we demonstrate these capabilities through a framework termed 'Schol-AR,' which includes tools for viewing scientific augmentations as well as an automated pipeline to create augmentations from common forms of neuroscientific data. This approach facilitates thorough reporting by enabling entire datasets to be viewed in place of representative images for formats such as volumetric MRI scans and image z-stacks. Furthermore, augmentation dramatically improves the comprehensibility of 3D data as well as overall dataset viewing and availability. Ultimately, augmenting scientific articles, posters, and other formats modernizes neuroscientific publication by merging the data and information that form the basis of neuroscientific research with the media we use to communicate.





Disclosures: T. Ard: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ardist Inc.. **A.W. Toga:** None.

Poster

P973. Software Tools II

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Program #/Poster #: P973.07

Topic: I.07. Data Analysis and Statistics

Support: NIMH DIRP

Title: Template and atlas-based processing pipeline for macaque MRI

Authors: *A. MESSINGER[1], P. PERKINS[1], B. JUNG[2], J. SEIDLITZ[3], C. SPONHEIM[4], D. GLEN[1], P. A. TAYLOR[1];
[1]NIH, Bethesda, MD; [2]Dept. of Neurosci., Brown Univ., Providence, RI; [3]Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [4]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: Non-human primate (NHP) functional neuroimaging research has been accelerated by recent advances and a greater availability of shared data. Consequently, there is a need for robust analysis tools designed for NHP neuroimaging with accompanying template spaces to standardize the localization of neuroimaging results. To this end, we have introduced a pipeline for processing structural and functional MRI data from the rhesus macaque (Jung et al., 2021). The pipeline includes the NMT v2, anatomical atlases, and software tools for aligning, processing, and analyzing structural and functional MRI data. The NMT v2 is a high-resolution population average brain template, with a stereotaxic orientation and coordinate system to facilitate surgical planning and standardized localization. Both the symmetric and asymmetric versions of the template include custom maps delineating the brain, each hemisphere, the cerebellum, and five different tissue types (cortical gray matter, subcortical gray matter, white matter, CSF, and blood vessels). Hierarchical atlases describing the anatomy of the cortex (CHARM, Jung et al., 2021) and subcortex (SARM, Hartig et al., 2021) at multiple levels of detail have been defined on the template for surgical planning, source localization, and volumetric and region of interest based analyses.The template and atlases have been integrated into the AFNI neuroimaging analysis software (Cox et al, 1996) to provide a comprehensive and robust pipeline for fMRI processing, visualization and analysis of NHP data. AFNI's new @animal_warper program can be used to efficiently align anatomical scans to the NMT v2 for (group) analysis in a standardized anatomy or for creating brain masks, atlases, and surfaces customized to an individual subject. AFNI's afni_proc.py program then integrates these alignment results with full fMRI processing using macaque-specific parameters: from motion correction through regression modeling. Both the @animal_warper and afni_proc.py programs generate reports and quality control images to facilitate assessment of their structural and functional outputs. Taken together, the NMT v2 and AFNI represent an all-in-one package for macaque functional neuroimaging analysis, as demonstrated with available demos for both task and resting state fMRI.

Disclosures: A. Messinger: None. **P. Perkins:** None. **B. Jung:** None. **J. Seidlitz:** None. **C. Sponheim:** None. **D. Glen:** None. **P.A. Taylor:** None.

Poster

P973. Software Tools II

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Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.08

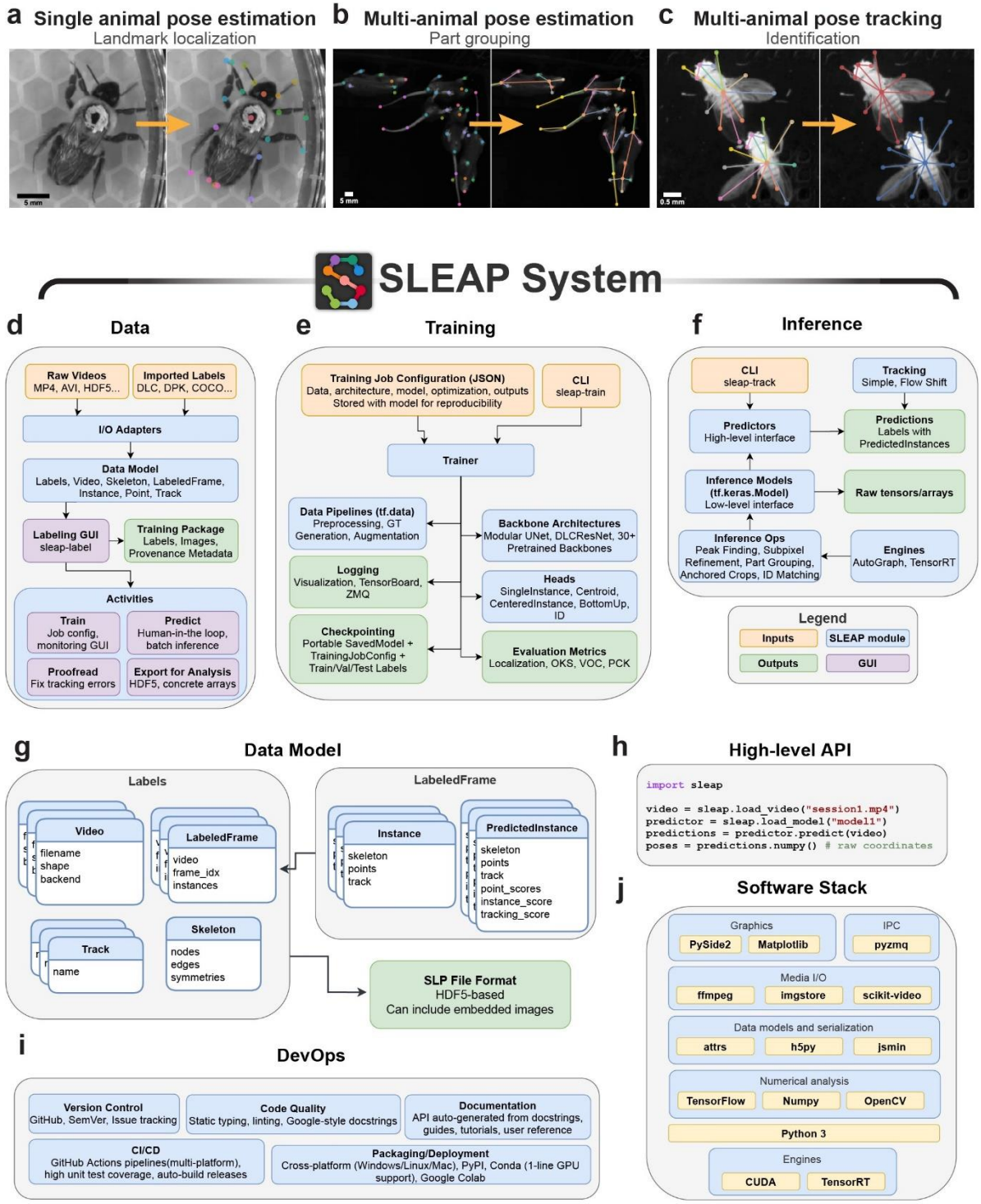
Topic: I.07. Data Analysis and Statistics

Support: NSF GRFP (DGE-1148900)
Princeton Porter Ogden Jacobus Fellowship
NIMH R00 MH109674
NIH DP2MH126375
Brain and Behavior Research Foundation award
Alfred P. Sloan Fellowship
Princeton Catalysis Initiative

Title: Sleap - a deep learning system for multi-animal pose tracking

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Abstract: The desire to understand how the brain generates and patterns behavior has driven rapid methodological innovation in tools to quantify natural animal behavior. While recent advances in deep learning and computer vision have enabled markerless pose estimation in individual animals, extending these to multiple animals presents unique challenges for studies of social behaviors or animals in their natural environments. Here we present SLEAP (Social LEAP Estimates Animal Poses), a machine learning system for multi-animal pose tracking. This system employs modern software engineering approaches to enable highly versatile and performant workflows for data labeling, model training and inference on new data. SLEAP features an accessible graphical interface, standardized data model, reproducible configuration system, over 30 model architectures, two approaches to part grouping, and two approaches to tracking. We applied SLEAP to 7 datasets across 4 species to systematically evaluate each approach and architecture, and we compare with other existing approaches. SLEAP achieves higher accuracy and speeds of more than 800 FPS, with latencies of less than 3.5 ms at full image resolution. This makes SLEAP usable for real-time applications, which we demonstrate directly by controlling social behaviors of one animal based on the tracking and detection of behaviors of its social partner.



Disclosures: T.D. Pereira: None. **N. Tabris:** None. **A. Matsliah:** None. **D.M. Turner:** None. **J. Li:** None. **S. Ravindranath:** None. **E.S. Papadoyannis:** None. **E. Normand:** None. **D. Deutsch:** None. **Z. Wang:** None. **G.C. McKenzie-Snith:** None. **C. Mitelut:** None. **M.D. Castro:** None. **J. D'Uva:** None. **M. Kislin:** None. **D.H. Sanes:** None. **S.D. Kocher:** None. **S.S. Wang:** None. **A.L. Falkner:** None. **J.W. Shaevitz:** None. **M. Murthy:** None.

Poster

P973. Software Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.09

Topic: I.07. Data Analysis and Statistics

Support: NIH 1R01MH124867
NIH 5U19NS104590
NIH 1R01MH124047

Title: Non-parametric vignetting correction tool improves detection of spatial transcriptomic transcripts

Authors: *B. Y. RAO[1,2], A. M. PETERSON[3,2], E. K. KANDROR[3], S. A. HERRLINGER[1,2], A. LOSONCZY[1,2,4], L. M. PANINSKI[5,3,6,7], A. H. RIZVI[3], E. VAROL[5,6,3,6];
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Abstract: Spatial transcriptomics techniques such as STARmap enable the subcellular detection of RNA transcripts within complex tissue sections. The data from these techniques are impacted by optical microscopy limitations, such as shading or vignetting effects from uneven illumination during image capture. Downstream analysis of these sparse spatially resolved transcripts is dependent upon the correction of these artefacts. We introduce a novel non-parametric vignetting correction tool for spatial transcriptomic images, which estimates the illumination field and background using an efficient iterative sliced histogram normalization routine. We show that our method outperforms the state-of-the-art shading correction techniques both in terms of illumination and background field estimation and requires fewer input images to perform the estimation adequately. As demonstration of the efficacy of our approach, we show that spatial transcriptomic volumes corrected by our method yield higher and more uniform gene expression spot-calling in a 20um section of dorsal rodent hippocampus. For example, RGS10, an enriched hippocampal gene, had over a five-fold increase in the number of gene-expression spots called with substantially more spots visualized in the periphery of the imaging FOV. Average gene expression spot-calling was increased by over three-fold from our method compared to the uncorrected image. Furthermore, many cell type specific genes such as CCK for interneurons and PLP1 for microglia that were undetectable in the uncorrected image were abundantly identified after application of our method enabling profiling the diversity of neural populations. Our method effectively corrects optical artefacts for downstream analysis of differential gene expression analysis, gene set enrichment, and other comparative genetic approaches. Python code and a demo file to reproduce our results are provided in the supplementary material and at this github page: https://github.com/BoveyRao/Non-parametric-vc-for-sparse-st

Disclosures: B.Y. Rao: None. **A.M. Peterson:** None. **E.K. Kandror:** None. **S.A. Herrlinger:** None. **A. Losonczy:** None. **L.M. Paninski:** None. **A.H. Rizvi:** None. **E. Varol:** None.

Poster

P973. Software Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 8:45 AM - 9:45 AM

Program #/Poster #: P973.10

Topic: I.07. Data Analysis and Statistics

Title: Cd-1 outbred mice produce less variable ultrasonic vocalizations than fvb inbred mice, while displaying a similar developmental trajectory

Authors: *M. BINDER, H. SHI, A. BORDEY;
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Abstract: The production of ultrasonic vocalizations (USVs) in neonatal mice is a critical means of communication that is used to elicit maternal care. Alterations in neonatal USV production is also an indicator of neurological deficits. However, USVs have been predominately assessed in inbred animals and are significantly understudied in outbred mice, even though outbred animals better represent the genetic diversity of humans and are used in several neurological disorder models. To determine the reproducibility of USVs across models, we compared male and female CD-1 (outbred) and FVB (inbred) mice on postnatal days (PD) 4,8,12,16, and 20. We found that CD-1 and FVB mice displayed a similar developmental trajectory of USVs. However, CD1 mice emitted more USVs on PD 12 than FVB mice. In addition, FVB mice emitted a longer duration of calls on PD 4 and 8 and a higher overall maximum and minimum frequency of USVs than CD-1 mice. No differences in mean amplitude were found between groups. We also detected numerous significant differences between outbred and inbred mice when comparing each groups' respective call type utilization. We next assessed the relative variability of mouse vocalizations between groups, finding that outbred mice were less variable than inbred mice. For the spectral and temporal characteristics of the USVs, variability was similar between groups. Altogether, we found that CD-1 outbred mice display a similar, if not lower, degree of variability than FVB inbred mice when assessing neonatal USVs.

Disclosures: M. Binder: None. **H. Shi:** None. **A. Bordey:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.01

Topic: B.10. Epilepsy

Support: NIH Grant R01-NS11198
NIH Grant F32-HD095567
American Epilepsy Society Postdoctoral Fellowship

Title: 4E-BP1 expression reverses aberrant HCN4 channel acquisition in mTOR hyperactive neurons

Authors: *L. H. NGUYEN, Y. XU, A. BORDEY;
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Abstract: Hyperactivation of mTOR signaling due to mutations in the mTOR pathway alters neuron structure and function, leading to intractable epilepsy. We previously found that mTOR hyperactive pyramidal neurons in layer (L) 2/3 medial prefrontal cortex have aberrant expression of functional HCN4 channels that are normally absent in L2/3 pyramidal neurons. The abnormal presence of these channels confers a unique mode of excitability in mTOR hyperactive neurons that is dependent on intracellular cyclic AMP levels and contributes to seizures. To identify the mTOR downstream processes leading to increased HCN4 levels, we investigated whether expressing 4E-BP1, a downstream regulator of cap-dependent translation that is inhibited by mTOR, would reduce HCN4 expression. We used *in utero* electroporation to co-express a constitutive active (CA) mTOR activator, $Rheb^{CA}$, with a tamoxifen-inducible, conditional 4E-$BP1^{CA}$ (c4E-$BP1^{CA}$) plasmid. Tamoxifen was administered in postnatal day (P) 12-16 mice to induce 4E-$BP1^{CA}$ expression. Whole-cell patch clamp recordings were obtained from L2/3 pyramidal neurons expressing control (BFP), $Rheb^{CA}$, or $Rheb^{CA}$+c4E-$BP1^{CA}$ in acute brain slices from P23-32 mice. $Rheb^{CA}$ neurons displayed increased membrane capacitance and conductance, as well as more depolarized resting membrane potentials (RMPs). c4E-$BP1^{CA}$ expression normalized the RMP and partially rescued membrane capacitance but not conductance. $Rheb^{CA}$ neurons displayed significantly larger hyperpolarization-induced inward currents, including HCN-mediated currents (termed I_h). Consistent with the function of I_h in maintaining the RMP at depolarized levels, larger I_h amplitudes were significantly correlated with more depolarized RMPs. No I_h was detected in either control or $Rheb^{CA}$+c4E-$BP1^{CA}$ neurons, suggesting that c4E-$BP1^{CA}$ expression abolished the abnormal I_h. Additionally, injections of hyperpolarizing current steps evoked a prominent I_h-mediated voltage sag in $Rheb^{CA}$ neurons, which was absent or minimal in control and $Rheb^{CA}$+c4E-$BP1^{CA}$ neurons. Immunostaining for HCN1-4 isoforms verified increased HCN4 levels in the $Rheb^{CA}$ condition which was eliminated by c4E-$BP1^{CA}$ expression, while no changes in HCN1-3 were detected across all groups. Overall, our findings demonstrate that aberrant acquisition of HCN4 channels in mTOR hyperactive cortical neurons is regulated downstream of mTOR by 4E-BP1-mediated cap-dependent translation.

Disclosures: L.H. Nguyen: None. **Y. Xu:** None. **A. Bordey:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

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Program #/Poster #: P097.02

Topic: B.04. Ion Channels

Support: Canadian Institutes of Health Research (CIHR) Foundation grant FDN-143337
FAPESP 2015/23467-7
FAPESP 2019/16765-2
CNPq

Title: Water deprivation amplifies hyperpolarization-activated inward current in vasopressinergic supraoptic neurons of rats.

Authors: E. F. SILVA[1], Z. S. THIROUIN[2], ***E. COLOMBARI**[1], C. BOURQUE[2];
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Abstract: Neurons of supraoptic nucleus (SON) express members of the cyclic nucleotide-gated family of ion channels like the hyperpolarization-activated and nucleotide-gated cation (HCN) channel that contribute to their electrical excitability and VP release. Here, we evaluated the role of hyperpolarization-activated inward current (I_H) in the control of electrical activity of vasopressinergic neurons of SON after water deprivation (WD). Electrophysiological recordings were performed through the patch-clamp technique using transgenic rats expressing enhanced green fluorescent protein (eGFP) under the control of VP promoter (VP-eGFP rats). Control (euhydrated) rats had continuous access to water and food, whereas WD rats had the water but not food removed for 48 h before initiating the experiments. The I_H was evaluated by bath application of ZD 7288 (a blocker of HCN channels). Under voltage-clamp, subtraction of current responses to hyperpolarizing steps was recorded in the absence and presence of ZD 7288 to investigate the properties of I_H, whereas voltage responses to depolarizing currents were recorded by current-clamp mode. The results showed that vasopressinergic neurons of SON from WD rats presented an amplified I_H (-0.836 ± 0.08 pA/pF, at -110 mV; $p<0.05$) compared with controls (-0.523 ± 0.09 pF/pA, at -110 mV). In addition, WD increased the number of spikes in vasopressinergic cells of SON at baseline (33 ± 5 total of spikes, *vs.* control: 10 ± 3 total of spikes; $p<0.05$), which was normalized after the selective block with ZD 7288 (20 ± 5 total of spikes, *vs.* baseline; $p<0.05$). Therefore, WD amplifies I_H in vasopressinergic SON neurons that contributes to their electrical excitability.

Disclosures: E.F. Silva: None. **Z.S. Thirouin:** None. **E. Colombari:** None. **C. Bourque:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.03

Topic: B.10. Epilepsy

Support: DST-INSPIRE
DBT-IISc

Title: Role of HCN Currents in Epileptiform Activity in Subicular Neurons

Authors: *M. ALFRED, S. K. SIKDAR;
Mol. Biophysics Unit, Indian Inst. of Sci., Bangalore, India

Abstract: Role of HCN Currents in Epileptiform Activity in Subicular Neurons
Monica Alfred and Sujit Kumar Sikdar
SKS Lab, MBU, Indian Institute of Science, Bangalore, India
Subicular neurons play a critical role in Temporal Lobe Epilepsy. While studies have shed light on how

synaptic conductances contribute to epileptiform activity in these neurons, it is still unclear how intrinsic conductances influence epileptic discharges. HCN channels play crucial role in pathophysiology by modulating the electrophysiological properties of neurons. To investigate the ability of intrinsic properties in a subicular neuron to generate epileptiform activity, we studied the effects of HCN currents (I_h) in 4-Aminopyridine magnesium-free epileptic model in various classes of subicular neurons. To study the modulation of epileptiform activity due to I_h in these neurons, we modeled subicular HCN currents in dynamic clamp that mimicked the effects of blocker and overexpression. We observed similar changes in input resistances with the subtraction and addition of currents in burst firing, regular firing and interneurons. However, the firing rate characteristics during epileptiform activity with the addition and subtraction of HCN channels in burst firing and regular firing differed from those observed in interneurons. The results indicate that burster cells majorly contribute to the epileptic firing characteristics due to HCN in subiculum. During the epileptiform activity, these bursters showed progressive loss of homeostatic compensation characterized by initial increase in sag followed by its decrease. The loss of homeostatic compensation incurred was found to be irreversible.These irreversible changes are also characterized by altered HCN channel kinetics. To study how these post-epileptic alterations govern neuronal excitability, we studied the electrophysiological profiles of subicular neurons with altered HCN current kinetics introduced through dynamic clamp in the presence of ZD7288. It was observed that the theta selectivity was modulated, and post-inhibitory rebound firing was evoked making the cell hyperexcitable. It is known that the stable neuronal network is homeostatically regulated by intrinsic excitability and synaptic currents. Attempts are being made to study the interaction between I_h and synaptic currents before and during the epileptiform activity in neurons with epilepsy-induced hyperexcitability.

Disclosures: M. Alfred: None. **S.K. Sikdar:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.04

Topic: B.10. Epilepsy

Support: NIH Grant R01 NS101596
NSF 1845348
NIH Grant R01 NS108874

Title: The persistent sodium channel blocker GS967 reduces hyperexcitability in Kcnq2 pyramidal neuron null neonatal mice ex vivo.

Authors: *B. HOU[1], S. SANTANIELLO[2], A. TZINGOUNIS[1];
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Abstract: KCNQ2 loss-of-function pathogenic variants could lead to a spectrum of neurological and neuropsychiatric disorders including Developmental and Epileptic Encephalopathy as well as Autism Spectrum Disorders. KCNQ2 channels are expressed early in development being critical regulators of

neonatal network excitability. Indeed, using mesoscale calcium imaging in acute slices from neonatal Kcnq2 conditional mice, we recently showed that Kcnq2 deletion from forebrain pyramidal neurons in the presence of elevated extracellular potassium led to multifocal activity across the neocortex and hippocampus. Surprisingly, the aberrant activity persisted in slices treated with synaptic glutamatergic and gabaergic blockers, but it was eliminated by the pan-sodium channel blocker TTX. In this study, we tested whether sodium channels with differing mechanisms of action could also dampen neuronal excitability of Kcnq2 null slices. To image calcium activity we used Emx1-cre::PCG5-tdT::Kcnq2$^{-/-}$ mice, mice that express GCamp5 in the presence of cre-recombinase. Similar to our earlier work, deletion of Kcnq2 from forebrain pyramidal neurons led to increased excitability across the forebrain in slice bathed with 8mM potassium. This activity was multifocal and, on many occasions, propagated across multiple forebrain subregions. Application of carbamazepine (60-100uM), a use-dependent sodium channel blocker, significantly dampened excitability across the whole forebrain with its greatest impact in the neocortex and lowest in the entorhinal cortex. Although carbamazepine decreased overall excitability it did not fully prevent propagation of activity across subregions. In contrast to carbamazepine, GS967 (2μM), a blocker of persistent sodium currents, was able to not only reduced excitability in Kcnq2 null mice, but also prevent signal propagation across regions. Thus, we propose that targeting the persistent sodium current might be beneficial in neurons and networks with Kcnq2 loss-of-function.

Disclosures: B. Hou: None. **S. Santaniello:** None. **A. Tzingounis:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.05

Topic: B.10. Epilepsy

Support: Marquette University Committee on Research
Department of Biological Sciences

Title: Changing roles of BK potassium channels in ictal activity and hippocampal parvalbumin neurons during early development in mice

Authors: *M. HUNSBERGER, B. MCDERMIT, M. MYNLIEFF;
Biol. Sci., Marquette Univ., Milwaukee, WI

Abstract: The BK potassium channel is a key regulator of neuronal firing and is implicated in neurological dysfunctions such as epilepsy. The BK antagonists, paxilline, has been shown to prevent seizure induction in adult animals with a history of seizures, but not in animals naïve to seizures. Comparison of our prior data to existing literature suggests that neurons from neonatal animals share hallmarks of BK channel function with neurons from more mature animals with a history of seizure induction. We tested the hypothesis that BK channel antagonists more effectively inhibit 0 Mg^{2+} induced seizure-like activity in hippocampal slices from immature mice than from more mature mice. We also characterized the developmental patterns of BK channel activity in CA1 excitatory pyramidal cells and CA1 region parvalbumin interneurons (PVIns), known to be major inhibitors of seizures.

We recorded local field activity in the CA1 region of hippocampal slices from mice aged P4 (postnatal day 4) to P15 days during perfusion with 0 Mg^{2+} aCSF with/without 1 µM paxilline. 0 Mg^{2+} aCSF evoked seizure-like discharges (SLDs) in 50% of P4-5 slices, 67% of P9-10 slices, and 14% of P14-15 slices. Paxilline decreased SLD rates to 17% and 33% in the P4-5 and P9-10 cohorts respectively, but increased SLD rates to 33% in P14-15 cohort. Paxilline delayed the onset of SLDs at all ages (two way ANOVA, Holm-Sidak multiple comparisons, P=0.04), and decreased SLD duration in P9-10 slices, from 13.1±2.2 to 5.0± 2.0 seconds, while not affecting SLD duration in P4-5 or P14-15 slices (two-way ANOVA, Holm-Sidak multiple comparisons, P=0.01).
Whole cell patch clamp in current clamp mode was used to record from hippocampal slices from mice with PV::TDtomato reporter for identification of PVIns. Preliminary data showed that PVIns in immature slices have fast firing rates, with firing rates in excess of 30 (P4-5), 70 (P9-10), and 100 (P14-15) Hz (1 s depolarization). A portion of PVIns in P5 slices fire no action potentials or fire a single slow action potential; this may be a quality issue of P4-5 slices or represent delayed maturation of PVIns. BK channel blockade with paxilline revealed that immature PVIns are more reliant on BK channels to maintain firing rates than pyramidal neurons. 1 µM paxilline induced more spike frequency adaptation in P10 PVIns than P10 pyramidal cells over the first 20 action potential pairs during a 1 s depolarization (two way ANOVA, P<0.001).
We found that blockade of BK channels decreased seizure-like activity in immature mice. Immature BK channel and PVIns may partly underlie heightened seizure susceptibility in neonates raising the possibility of targeting BK channels as in treating neonatal seizures.

Disclosures: M. Hunsberger: None. **B. McDermit:** None. **M. Mynlieff:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.06

Topic: B.10. Epilepsy

Support: Families of SCN2A

Title: A novel in vitro modeling system for SCN1A- Dravet Syndrome disease

Authors: *J. A. SIERRA DELGADO, C. N. DENNYS, A. HARTLAUB, F. ROUSSEL, X. ZHANG, S. SINHA RAY, K. C. MEYER;
Ctr. for Gene Therapy, Nationwide Children's Hosp., Columbus, OH

Abstract: SCN1A mutations lead to a heterogenous disease spectrum of epileptic disorders, with incomplete penetrance and variable expressivity. This spectrum encompasses familiar hemiplegic migraines, febrile seizures, and other infantile epilepsies, with Dravet Syndrome (DS) being the most severe manifestation. DS is characterized by prolonged myoclonic, hemi-clonic or generalized tonic-clonic seizures with early onset (1 -18 months) that are refractive to anti-epileptic drugs (AED). The disease manifestation depends on the type of mutation as well as other poorly understood disease modifiers. To date, most research focuses on the function and expression of the Nav1.1 sodium channel

on neurons, while little is known about the role of other cell types of the nervous system in disease progression, modulation of the disease phenotype and response to AEDs. To address this, we used a direct reprogramming method to generate neural progenitor cells (iNPCs) from primary fibroblasts derived from SCN1A-DS patients. We then differentiated the iNPCs into induced Astrocytes (iAs) to evaluate cellular pathways known to be affected by neurological disease. In addition to markers of cellular stress, we evaluated the metabolic profile of SCN1A-DS iAs as well as analyzed the impact of iAs on neuronal morphology and viability . We found cell-type and mutation specific metabolic profile of SCN1A-DS patient cells that were significantly different from controls. Co-culturing healthy mouse GFP+ neurons and patient iAs demonstrated that SCN1A-DS iAS induced a high degree of neuronal death. Pretreatment of select patient iAs with specific therapeutics prevented iAs mediated neurotoxicity. Interestingly, iAs that responded favorable to these therapeutics showed a specific mitochondrial energetic profile that upon treatment, was restored to healthy levels. Here we show for the first time that human SCN1A-DS iAs have aberrant mitochondrial activity, are toxic to neurons and can be implicated in disease pathology for SCN1A. Our results indicate that patient specific mutations may have a differential effect on the mitochondria and on the mitochondrial response to AEDs. We have developed two screen assays to evaluate both the impact of specific SCN1A mutations on disease pathologies as well as subgroup the patient population based on therapeutic response to a compound. This system allows detailed evaluation of the impacts of SCN1A-DS mutations on patients with diverse genetic backgrounds.

Disclosures: J.A. Sierra Delgado: None. **C.N. Dennys:** None. **A. Hartlaub:** None. **F. Roussel:** None. **X. Zhang:** None. **S. Sinha Ray:** None. **K.C. Meyer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Receiving royalties for Batten disease programs licensed to Amicus, Royalties from Kiadis. F. Consulting Fees (e.g., advisory boards); Receiving Grants, Royalties, Scientific Advisor for Alcyone Therapeutics.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.07

Topic: B.10. Epilepsy

Title: Sur1-trpm4 upregulation in epilepsy pathogenesis

Authors: *M. MOYER, R. SERRA, M. BACHANI, S. IVANOVA, V. GERZANICH, A. KSENDZOVSKY, M. SIMARD;
Neurosurg., Univ. of Maryland, Baltimore, MD

Abstract: Rationale: Current treatment for chronic epilepsy are inadequate. SUR1-TRPM4 is a depolarizing monovalent cation channel that is minimally expressed in the healthy human brain but is upregulated by hypoxia in traumatic brain injury and stroke. Furthermore, we recently described hypoxia-associated neuronal metabolic changes in chronic epilepsy. As such, we hypothesize that chronic seizures lead to neuronal Sur1-TRPM4 upregulation, which may facilitate seizures by increasing resting depolarizing sodium current. **Methods:** We used pentylenetetrazol (PTZ) kindling in mice as a model of chronic epilepsy. Mice were injected intraperitoneally with a sub-convulsive dose (35 mg/kg) of PTZ

every other day for 20 days, then monitored behaviorally (Racine scores) and with intracranial video electroencephalogram (EEG) for seizure activity. After kindling, immunohistochemistry was used to assess SUR1-TRPM4 expression in cerebral cortex and hippocampus of PTZ and control mice. SUR1-TRPM4 quantification was performed by counting cells that demonstrated a specific immunohistochemical signal, defined by an intensity greater than a threshold of 1.5x background intensity, within three 20x magnified fields per region. **Results:** PTZ-kindled mice had progressively worsening seizure severity over the course of induction, as evidenced by elevated Racine scores (Dose 1 average: 2.5; Dose 10 average: 4.75) and increased seizure frequency (Dose 1 average: 0 seizures/injection day; Dose 10 average: 1.25 seizures/injection day). SUR1-TRPM4 positive cell counts were increased in cortex (PTZ:49.9±11.3; Control:3.3±2.8; p=0.01) and hippocampus (PTZ=43.3±5.0; Control=2.2±0.7; p=0.002) of PTZ-kindled mice compared to controls. **Conclusions:** SUR1-TRPM4 is upregulated in chronic seizures. Future experiments will focus on evaluating HIF1α and NF-κB as upstream regulators, and assessing whether upregulation of SUR1-TRPM4 promotes seizures through its depolarizing effect on neuronal resting membrane potential. ![endif]>

Disclosures: M. Moyer: None. **R. Serra:** None. **M. Bachani:** None. **S. Ivanova:** None. **V. Gerzanich:** None. **A. Ksendzovsky:** None. **M. Simard:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.08

Topic: B.07. Synaptic Plasticity

Support: NIAAA grant P60-AA011605

Title: Effects of Interneuron-Selective HCN Channel Knockdown on Working Memory Performance in Female Sprague-Dawley Rats

Authors: *B. HUGHES[1], T. K. O'BUCKLEY[2], A. L. MORROW[3];
[1]Dept. of Psychiatry, [2]Bowles Ctr. for Alcohol Studies, [3]Psychiatry, Pharmacology, & Bowles Ctr. for Alcohol Studies, Univ. of North Carolina Sch. of Med., Chapel Hill, NC

Abstract: Chronic alcohol use elicits deficits in cognition and behavioral control that are associated with prefrontal cortical (PFC) dysfunction. Recently, we observed reduced excitability of inhibitory Martinotti cells in female rats after chronic ethanol exposure that correlated with reduced HCN channel-mediated current in these cells. In contrast, excitatory pyramidal neurons, also known to robustly express HCN currents, did not exhibit any change in excitability or HCN-mediated current after alcohol exposure. Previous studies have reported that cell-indiscriminant inhibition of PFC HCN activity facilitated working memory performance, indicating these channels act as potent regulators of cognitive function. On this basis, we hypothesized that the effects of alcohol exposure on Martinotti cell HCNs specifically contribute to the observed enhancements in working memory performance in female rats. To test this, we employed a multiplexed viral approach using a double-floxed miR-adapted shRNA targeting HCN channels that is co-infected with a Somatostatin-Cre virus. This system permits selective knock down of

HCN channels in somatostatin-positive interneurons, which include Martinotti cells, and preliminary electrophysiological characterization has demonstrated near-total knockout of HCN-mediated current in infected neurons. Based on these data, we conducted preliminary behavioral experiments using this approach, in which rats undergo training and testing on a delayed non-match-to-sample T-maze task 2-3 weeks post-infection. Initial observations demonstrate a strong trend toward enhanced working memory performance on this task in HCN-shRNA infected animals relative to scrambled control rats. After initial testing, we then exposed rats to water or ethanol (5 g/kg; intragastric gavage) for 15 days, and conducted a second test 24 hours after the last exposure. We again report a robust facilitation of working memory performance in both scram-shRNA and HCN-shRNA groups exposed to ethanol, although we presently lack sufficient n to determine an effect of HCN-shRNA infection on this enhancement. Additional experiments are currently underway to both increase animal numbers as well as further characterize the selectivity and penetrance of this viral knockdown system. Observations from these experiments will offer insight into whether alcohol effects on interneuron-expressed HCN channels mediate concomitant effects on cognitive function, and further demonstrate the suitability of this novel approach for interneuron-selective protein knockdown.

Disclosures: B. Hughes: None. **T.K. O'Buckley:** None. **A.L. Morrow:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.09

Topic: B.04. Ion Channels

Support: NIH Grant 1R21NS122347-01
NIH Grant 2R01NS057499-14

Title: Sex-specific regulation of neuropathic pain by microglial Orai1 channels

Authors: *K. DEMEULENAERE[1], S. TSUJIKAWA[1], M. CENTENO[1], M. M. MANESHI[1], M. TAPIES[1], M. YAMASHITA[1], K. STAUDERMAN[2], M. SALTER[3], V. APKARIAN[1], M. PRAKRIYA[1]; [1]Northwestern Univ. - Chicago, Chicago, IL; [2]CalciMedica, In., La Jolla, CA; [3]Hosp. for Sick Children Res. Inst., Toronto, ON, Canada

Abstract: Store-operated Orai1 channels are implicated in initiating inflammatory responses in many immune cells, yet much less is known about their role in regulating neuroinflammation that causes neuropathic pain. Spinal cord microglia play central role in directing inflammatory responses that underlie neuropathic pain. Here, we determine that Orai1 channels regulate microglia-mediated neuroinflammation and chronic pain in a sex-specific manner. Microglia deficient in Orai1 show reductions in ATP-evoked Ca^{2+} signaling and synthesis of pro-inflammatory cytokines including IL-6 and TNFa. Following nerve injury, male, but not female microglial Orai1 KO mice show mitigation of inflammatory cytokines and the pathological potentiation of glutamatergic neurotransmission in the spinal cord. Consistent with these cellular measures of neuroinflammation, male but not female microglial Orai1 KO mice are protected against pain hypersensitivity. A small-molecule Orai1 antagonist, CM4620, also mitigates

hypersensitivity in male but not female Orai1 KO mice. These findings identify Orai1 channels as a critical checkpoint for the sex-specific regulation of microglial neuroinflammation underlying neuropathic pain.

Disclosures: K. DeMeulenaere: None. **S. Tsujikawa:** None. **M. Centeno:** None. **M.M. Maneshi:** None. **M. Tapies:** None. **M. Yamashita:** None. **K. Stauderman:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Provided small molecule inhibitor for in vivo and in vitro studies. **M. Salter:** None. **V. Apkarian:** None. **M. Prakriya:** None.

Poster

P097. Ion Channels: Modulation, Behavior, and Disease

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P097.10

Topic: B.04. Ion Channels

Support: NIH-NIDA RO1DA046476
Kempner Foundation Postdoctoral Fellowship

Title: Cue-induced recall for cocaine or morphine self-administration increases ryanodine 2 (RyR2) phosphorylation in the prefrontal cortex

Authors: *K. R. BARBER[1], B. M. LOPEZ[1], P. CULVER[2], V. S. VIZCARRA[1], L. MAJUTA[1], C. DIEZEL[1], R. PARMAR[1], A. C. RIEGEL[1];
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Abstract: Ryanodine receptors (RyRs) are intracellular calcium (Ca2+) release channels important for long-term potentiation, dendritic spine remodeling, and learning/memory formation. In the CNS, the type-2 RyR channel (RyR2) localized to the endoplasmic reticulum is subject to activity-dependent phosphorylation and transcriptional regulation. In the hippocampus, chronic overactivation/hyperphosphorylation of RyR2 (RyR2*P*) at a serine residue 2808 also produces a pathological posttranslational modification associated with the persistent leak of Ca2+ from intracellular stores, alterations in synaptic plasticity, and cognitive disease. In the prefrontal cortex (PFC) area 32V (A32V; formerly prelimbic) a region important for relapse/drug-seeking, the relevance of RyR2*P* is not yet defined. However, addictive drugs, including stimulants and opiates, are known to result in hyperphosphorylation. Prior PFC studies suggest that the contextual memory formation associated with non-contingent drug-induced plasticity increases unphosphorylated RyR2 content. In the present study, we evaluated if drug-seeking in rats with a history of contingent drug self-administration impacted RyR2*P* in A32. We trained male Sprague Dawley rats to chronically (14d) self-administer either drug cocaine (0.5 mg/kg i.v.) or morphine (1mg/kg i.v.) or natural (sucrose; 45 mg) rewards and then performed a single 'recall' test to engage reward-seeking PFC neuron ensembles, without the confounding ingestion of the reward itself. At 90 minutes of 'recall,' the rats underwent cardiac perfusion for later brain sectioning and immunohistochemical analysis. The phospho-antibody directed against the serine residue 2808 of RyR2*P* showed robust expression in the cytosol and specifically apical dendrites of a heterogeneous population of A32 Layer 5 pyramidal cells. A subpopulation of these A32 cells

expressing RyR2*P* was also colocalized with the intermediate early gene product c-fos (RyR2*P*+/Fos+). Manual quantification of A32V indicated a similar RyR2*P*+/Fos+ expression with recall for cocaine or morphine, which was ~twice that of sucrose. This difference in the colocalization expression was not evident in more dorsal regions. Ongoing studies using RNAscope are visualizing the parallel changes in gene expression. Taken together, these data indicate that the neuronal activation in the PFC during drug-seeking is not randomly distributed and is associated with greater RyR2*P* expression for drug-seeking behaviors, rather than natural rewards. Consequently, overactivation of RyR2*P* at serine 2808 may contribute to the ensemble activity of PFC neurons during relapse to drug-seeking.

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Poster

P097. Ion Channels: Modulation, Behavior, and Disease

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Program #/Poster #: P097.11

Topic: B.04. Ion Channels

Support: NIH grant R15GM12401

Title: Voltage-gated calcium channel inactivation determines the extent of channel inhibition by small RGK GTPases

Authors: *Z. BURAEI[1], R. LEVENSON-PALMER[2], S. ALLAM[1], B. CERNUDA[3], G. SUPPA[4], S. DOBBINS[5], Z. CHIA CHANG[1], S. KAUR[1], J. YANG[6];
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Abstract: Voltage-gated Ca2+ channels (VGCC) directly control muscle contraction and neurotransmitter release, and slower processes such as cell differentiation, migration, and death. They are potently inhibited by RGK GTP-ases (Rem1, Rem2, Rad and Gem/Kir), which decrease Ca2+ channel membrane expression, as well as directly inhibit membrane-resident channels. The mechanisms of membrane-resident channel inhibition are difficult to study because RGK-overexpression causes complete or near complete channel inhibition. Using titrated levels of Gem expression in Xenopus oocytes to inhibit WT P/Q-type calcium channels by ~50%, we show that inhibition is dependent on channel inactivation. Interestingly, fast-inactivating channels, including Familial Hemiplegic Migraine mutants, are more potently inhibited than WT channels, while slow-inactivating channels, such as those expressed with the β2a auxiliary subunit, are spared. We found similar results in L-type channels, and, remarkably, Timothy Syndrome mutant channels were insensitive to Gem inhibition. Further results suggest that RGKs slow channel recovery from inactivation and identify RGKs as likely modulating factors in channelopathies.

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Poster

P097. Ion Channels: Modulation, Behavior, and Disease

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Program #/Poster #: P097.12

Topic: F.08. Biological Rhythms and Sleep

Support: DBT/Wellcome Trust India Alliance [Senior Fellowship No. IA/S/16/2/502727]
Department of Biotechnology through the DBT-IISc partnership program
Revati and Satya Nadham Atluri Chair Professorship
Kishore Vaigyanik Protsahan Yojana

Title: Ion-channel degeneracy and plasticity manifolds govern the emergence of circadian oscillations of neuronal intrinsic properties in the suprachiasmatic nucleus

Authors: *H. NAGARAJ, R. NARAYANAN;
Indian Inst. of Sci., Bangalore, India

Abstract: Organismal adaptation to the day-night cycle is achieved by circadian oscillators in most organs, which are synchronized by the suprachiasmatic nucleus (SCN). Neurons in the SCN undergo autonomous oscillations in their intrinsic physiological properties through changes in a subset of ion channels they express. However, it is not known if characteristic physiology of SCN neurons could be achieved through multiple ion-channel combinations or if there are several routes to achieve the circadian transitions in their physiological properties. In this study, we first employed an unbiased stochastic search (spanning 13 parameters involving 11 SCN neuronal ion channels) to construct a biophysically realistic population of SCN neurons with day-like phenotypes. We generated 30,000 models and found a subset of 128 valid models that manifested 9 different characteristic signatures of day-like SCN neurons. We found these valid models to manifest ion-channel degeneracy, whereby disparate ion-channel combinations were able to elicit similar characteristic functional outcomes, also expressing weak pairwise dependencies across model parameters. We next chose 20 day-like neuron models and subjected a specific subset of 6 ion channels to physiologically established directions of transitions, with transition magnitudes defined by an unbiased stochastic search algorithm. We validated these transitions employing 9 night-like physiological features, and found 719 valid night-like SCN models that manifested ion-channel degeneracy. We performed nonlinear dimensionality reduction analyses on these transitions and found the manifestation of *plasticity manifolds*, structured low-dimensional manifolds in the space of all permitted changes, underlying day-to-night transitions. Finally, towards completing the circadian cycle, we picked 26 night-like neurons and performed an unbiased stochastic search on the magnitude of changes in the same subset of 6 ion-channel conductances, with directions of changes opposite to those for day-to-night transitions. Validation against day-like phenotypes yielded 1184 valid transitions, with the emergent day-like neurons showing ion-channel degeneracy but with a notable absence of structured plasticity manifolds in the associated transitions. These results pointed to the possibility that night-to-day transitions might have greater flexibility relative to their day-to-night counterparts. Together, our analyses demonstrate the expression of ion channel degeneracy in SCN neurons and points to the existence of structured plasticity manifolds in defining ion-channel transitions during circadian oscillations.

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Poster

P100. Presynaptic Organization

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Program #/Poster #: P100.01

Topic: B.05. Neurotransmitter Release

Support: NIH Grant 5R01NS107506-2

Title: Heterogeneous Populations of Synapses Contribute to Globally Stable Output of the Drosophila Larval Neuromuscular Junction

Authors: *K. AGHI[1], R. LI[2], R. SCHULTZ[1], Z. L. NEWMAN[2], E. Y. ISACOFF[1,2];
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Abstract: Glutamate-releasing motor neuron connections to the fruit fly larval muscle are diverse in their synaptic communication properties. Two distinct motor neurons types (Ib and Is) form the neuromuscular junction (NMJ), each containing hundreds of sites of neurotransmitter release. There is great heterogeneity between synapses in the probability (Pr) that an action potential will evoke release of neurotransmitter under low frequency stimulation (0.2 Hz) that reflects basal transmission (ranging from $\leq$0.005 to 0.5). A portion of the variance in Pr can be explained by synapse-to-synapse differences in the quantity of three elements of the presynaptic release machinery: the scaffolding protein, ELKS/CASK homolog, Bruchpilot, the voltage-gated Ca^{2+} channel, Cacophony, and the SNARE protein interacting protein Complexin. Our central hypothesis is to ask if the relative locations of synapses is a critical factor in setting basal Pr, We used a k-Nearest Neighbor (k-NN) framework of analysis to relate distances between synapses to release behavior. Our finding is that Pr is randomly distributed in space across synapses: there is neither a relationship between synapse spacing and Pr, nor the Pr of a synapse and that of its neighbor. We asked how Pr changes with elevated stimulation frequency. While we observed the expected behavior that synapses with low basal Pr tended to facilitate or and synapses with high basal Pr tended to depress, we observed many relatively high Pr synapses that were stable or facilitated and many low Pr synapses that were stable or depressed. Remarkably, despite the great diversity in the balance between facilitation and depression across synapses, transmission the distribution of Pr in the population of synapses was globally stable, providing a constant safety factor for transmission. We are now asking whether fast feedback contributes to the diversity of frequency-dependent changes in Pr and are focusing on the presynaptic metabotropic glutamate receptor (DmGluRA).

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Poster

P100. Presynaptic Organization

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Program #/Poster #: P100.02

Topic: B.05. Neurotransmitter Release

Support: MH-104536
NS-40296
The Picower Foundation

Title: Characterization of Molecular Mechanisms that Contribute to Functional Synaptic Diversity Between Tonic and Phasic Motoneurons

Authors: *S. K. JETTI[1], A. B. CRANE[1], Y. AKBERGENOVA[1], C. A. WHITTAKER[2], N. A. APONTE-SANTIAGO[1], *J. T. LITTLETON[1];
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Abstract: Synapses exhibit striking diversity in morphology, synaptic strength, response kinetics, and short-term plasticity. Although extensive progress has been made in characterizing mechanisms of synaptic transmission, the molecular logic that specifies functional synapse diversity remains poorly understood. Synaptic transmission differences between neuronal classes is likely secondary to differences in gene expression programs as well as changes in the nanoscale organization of key synaptic proteins. Larval *Drosophila* Tonic and phasic motoneurons show multiple distinctions in synaptic connectivity and synaptic release properties, providing an attractive neuronal subpopulation to examine molecular and structural differences that contribute to these features. To further examine how their unique synaptic differences arise, we used GAL4 drivers for tonic Ib and phasic Is motoneuron subtypes. We combined single neuron isoform Patch-Seq, STED nanoscopy, synaptic GCaMP imaging, optogenetics, and electrophysiology to characterize a subset of Ib and Is motoneurons innervating a common postsynaptic muscle target. We confirmed physiological differences in synaptic physiology at these two distinct synapses using synaptic GCaMP imaging, optogenetics, and electrophysiological analyses. In addition, STED nanoscopy revealed differential active zone organization of key proteins between Ib and Is motoneurons that also likely contribute to their unique differences in synaptic transmission. A collection of several hundred differentially expressed loci were identified by isoform Patch-Seq. RNAi knockdown was coupled with morphological analysis and cell-type specific optogenetics to screen these candidates for roles in establishing diversity in tonic and phasic synaptic transmission. Although the screen is ongoing, multiple differentially expressed loci that contribute to differences in tonic versus phasic synaptic properties have already been identified. These include the AZ proteins RIM and Rbp, the extracellular matrix components Ana, synaptic cleft protein Hig, the cyclic nucleotide gated-channels, and the calcium-binding protein Cbp53E. In addition, tonic and phasic motoneurons differentially express a large repertoire of cell adhesion and axonal pathfinding proteins, as well as G-protein coupled neuromodulatory receptors. These findings indicate the unique nanoscale organization of AZs, together with differences in molecular programs that regulate several synaptic properties, contribute to functional differences between phasic and tonic motoneurons.

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Poster

P100. Presynaptic Organization

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P100.03

Topic: B.05. Neurotransmitter Release

Title: Structural and functional analysis of TRAPP complexes in the Drosophila larval central nervous system and neuromuscular junction

Authors: *L. LIANG, R. THAKUR, K. M. O'CONNOR-GILES;
Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: Communication in the nervous system is the basis for behaviors such as movement and cognitive functions including learning and memory. Synapses are the sites of this communication between neurons. In presynaptic neurons, neurotransmitter filled synaptic vesicles are docked near calcium channels for efficient neurotransmission upon arrival of an action potential. Yet, little is known about how synaptic vesicles are recruited and positioned at the presynaptic membrane to achieve this organization. Ultrastructural analysis of synapses across species shows the presence of protein tethers linking synaptic vesicles to other vesicles and to active zone membranes. However, the composition of these tethers remains unknown.
The Transport Protein Particle (TRAPP) is a multi-subunit protein complex that has been identified to tether endoplasmic reticulum-derived vesicles to vesicular tubular clusters. Mutations in TRAPP subunits have been implicated in motor dysfunction, intellectual disability, and developmental delay. However, a potential role for TRAPP in tethering synaptic vesicles at synapses remains unexplored. We find that core TRAPP subunits are expressed in the *Drosophila* larval ventral nerve cord and at the neuromuscular junction, where we observe co-localization with synaptic vesicles. Functionally, we find that knocking down some, but not all, TRAPP subunits leads to decreased levels of synaptic vesicle proteins as well as components of the active zone cytomatrix, a conserved complex of proteins implicated in the organization of synaptic vesicles at synapses. We propose that TRAPP complexes play an important role in synaptic vesicle recruitment and neurotransmission, and that studying their function will provide new insights into long-standing questions about synaptic vesicle trafficking.

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Poster

P100. Presynaptic Organization

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Program #/Poster #: P100.04

Topic: B.05. Neurotransmitter Release

Support: Pilot Project grant from Albert Einstein college of Medicine

Title: Calcium channel localization and function are altered in worms carrying patient CACNA1A mutations

Authors: *M. ZULUAGA-FORERO[1,2], Y. DONG[3], J. BAI[3], P. T. KURSHAN[1];
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Abstract: Mutations in the P/Q-type voltage-gated calcium channel (CACNA1a) in humans are associated with diseases ranging from motor disorders such as episodic ataxia type 2 (EA2) to familiar hemiplegic migraine type 1 (FHM1) to cognitive dysfunction including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). These channels are expressed in both the somatodendritic compartment and at presynaptic terminals, however, the mechanistic links between different mutations and their roles in *neuronal excitability* versus *synaptic transmission* are not well understood. We use the nematode *C.elegans* due to its lack of gene redundancy, genetical tractability, and simplified nervous system, to elucidate changes in presynaptic calcium channel localization and functional defects produced by these mutations. The worm has only one ortholog of the channel (UNC-2) expressed in its nervous system that shares high homology with the human protein. We have found that worms carrying several patient-derived mutations show various defects in channel localization at pre-synapses as well as altered synaptic function, assessed using both electrophysiological and behavioral readouts. Interestingly, some channel mutations lead to decreased synaptic localization yet have increased acetylcholine release (as assessed by aldicarb sensitivity), miniature EPSC frequency, and behavioral hyperactivity. Single-molecule localization, additional mutations, and interactions with other presynaptic proteins are being evaluated to assess the impact of mutations associated with a range of disorders on presynaptic morphology and synaptic function.

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Poster

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Topic: B.05. Neurotransmitter Release

Support: DFG CRC166 project B6
IZKF-Projekt Z-3/69

Title: Three-dimensional nanoscopy of defined active zones lacking RIM1α in hippocampal mossy fiber synapses

Authors: *K. LICHTER[1,2,3,4], M. PAUL[2], M. PAULI[2], P. KOLLMANNSBERGER[5], C. STIGLOHER[3], M. HECKMANN[2], A.-L. SIRÉN[1];
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Hlth., Würzburg, Germany; [5]Ctr. for Computat. and Theoretical Biology, Univ. of Würzburg, Würzburg, Germany

Abstract: Hippocampal mossy fiber (MF) synapses play a key role in information processing and express unique presynaptic plasticity (Salin et al., PNAS 1996, 93:13304-09). The cytomatrix of proteins at active zones (AZs), specialized presynaptic sites for vesicle release, precisely facilitate temporal and spatial interaction to transform action potentials into chemical synaptic transmission. While morphological complexity of MF boutons (MFBs) has been well documented with classical transmission and scanning electron microscopy (EM), functional EM techniques only recently allowed to further investigate how presynaptic architectural complexity may be coupled with functional properties of synaptic transmission at MFBs (Borges-Merjane et al., Neuron 2020, 105:1-15; Imig et al., Neuron 2020, 108:843-60). Therefore, several aspects of the three-dimensional AZ architecture in MFBs, its alteration in plasticity and the contribution of single AZ proteins to it, remain to be elucidated. The Rab3a-interacting molecule (RIM) protein family contributes to vesicle exocytosis at presynaptic membranes. In electrophysiological experiments, hippocampal MFBs lacking the RIM1 isoform RIM1α express impaired presynaptic plasticity (Castillo et al., Nature 2002, 415: 327-30). Ultrastructural studies have emphasized a morphological involvement of RIM1α and equivalent protein homologues to AZ architecture in artificial synaptic preparations, e.g. synaptosomes (Fernanández-Busnadiego et al., J Cell Biol 2013, 201:725-40), and in synapses of other organisms, e.g. *C. elegans* (Stigloher et al., J Neurosci 2011, 31:4388-96).
We carried out rapid cryo-immobilisation of acute brain slices from adult RIM1α$^{-/-}$ mice and performed electron tomography of synapses in giant MFBs to spine head CA3b pyramidal neurons, standardized in brain level and hemisphere. 3D stereogeometric analyses of 60 reconstructed electron tomograms of AZs in RIM1α$^{-/-}$ and wild type RIM1α$^{+/+}$ mice facilitated novel ultrastructural contributions of RIM1α on synaptic nano-architecture. Beside structural complexity, our approach uncovers an immense structural heterogeneity within AZs of hippocampal MFBs in both phenotypes. In addition, three-dimensional nano-architecture of RIM1α deficient AZs shows significant differences to wildtype AZs in AZ area expansion, SV pool organization and differentiation of docking states within less than 5 nm to the presynaptic membrane.

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Poster

P100. Presynaptic Organization

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Program #/Poster #: P100.06

Topic: B.05. Neurotransmitter Release

Support: MOH- 000225

Title: Two mechanisms of synaptic vesicle clustering by synapsins: roles of liquid-liquid phase separation and oligomerization

Authors: *S.-H. SONG, G. J. AUGUSTINE;
Lee Kong Chian Sch. of Medicine, NTU, Singapore, Singapore

Abstract: Synapsins are synaptic vesicle (SV) proteins that participate in SV trafficking by making a cluster of SVs that constitutes a SV reserve pool (RP). We compared two molecular mechanisms that are proposed to allow synapsins to cluster SVs: liquid-liquid phase separation (LLPS), which could cluster SVs by creating synapsin condensates within the presynaptic terminal (Science 361: 604); and oligomerization, which could cluster SVs because synapsins can bind both to SVs and to other synapsin molecules (Science 259: 780). *In vitro*, all synapsin isoforms can create LLPS, with the size of their condensates well-correlated with the length of their intrinsically disordered regions. This process is inhibited by ATP, with half-maximal inhibition occurring at 1.7 mM. In the presence of 5 mM ATP, synapsin can still create macromolecular structures; these are caused by oligomerization, because they get smaller with synapsins harboring point mutations that impair oligomerization. Although both mechanisms can cluster SVs *in vitro*, synapsin oligomerization is more effective than LLPS: in 5 mM ATP, which favors oligomerization, SV clusters are larger and SVs better co-localize with synapsin. We also examined the roles of these two mechanisms at synapses from cultured neurons from synapsin triple-knockout mice. At GABAergic synapses, expression of synapsin 2a mutants that prevent oligomerization still clusters SVs and supports normal GABA release. However, at glutamatergic synapses, these synapsin 2a mutants accelerate the rate of synaptic depression, indicating a defect in mobilization of SV from the RP. This contrasts with expression of wild-type synapsin 2a, which rescues synaptic depression and SV mobilization from the RP (J. Neurosci. 28: 10835). In summary, both LLPS and oligomerization contribute to synapsin-dependent trafficking of SV. Remarkably, the relative roles of these two processes differ at excitatory and inhibitory synapses.

Disclosures: S. Song: None. **G.J. Augustine:** None.

Poster

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Program #/Poster #: P100.07

Topic: B.05. Neurotransmitter Release

Support: NIH/NINDS RO1 NS104999

Title: Proximity Labeling Reveals NMDA Receptors Localized on the Presynaptic Terminal of Parvalbumin Interneurons in the Mouse Cortex

Authors: *A. S. BATTISON[1], J. L. BALSBAUGH[2], J. C. LIDDLE[2], C. B. O'CONNELL[3], J. J. LOTURCO[1];
[1]Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT; [2]Univ. of Connecticut Proteomics and Metabolomics Facility, Storrs, CT; [3]Univ. of Connecticut Advanced Light Microscopy Facility, Storrs, CT

Abstract: We present a method for obtaining cell-type specific local proteomes in fixed mouse tissue using an antibody based proximity labeling method. We focus our analysis on the three major GABAergic

cell types in the cortex, Parvalbumin (PV), Somatostatin (SST) and Vasoactive Intestinal Peptide (VIP). To achieve cell type specificity in our proximity labeling we cross a PV, SST, or VIP-Cre mouse line to a TdTomato-Synaptophysin reporter mouse, resulting in offspring that have a novel TdTomato antigen in the presynaptic terminal exclusively in our cell type of interest. We use the TdTomato antigen as the basis for proximity labeling which results in biotinylation of proteins that are in the vicinity of our target cell. These proteins are isolated with a streptavidin pull-down, and prepped for mass spectrometry (LC-MSMS). Results show that we are able to detect local presynaptic proteomes of the three major GABAergic interneuron subtypes, and further analysis of the parvalbumin (PV) presynaptic terminal suggests the presence of presynaptic NMDA receptors on that cell type alone. Through superresolution microscopy and electrophysiology we investigate the presence and function of these presynaptic NMDA receptors on parvalbumin cortical interneurons.

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Poster

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Topic: B.05. Neurotransmitter Release

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MCDB Neurodegenerative Disease Fund

Title: A tale of two NTs: structure and function of dual glutamatergic-GABAergic neurons in major depressive disorder

Authors: *D. WHITE, M. STOWELL;
MCDB, Univ. of Colorado Boulder, Boulder, CO

Abstract: Dissecting the Regulation of Disparate Synaptic Vesicle Pools in the LHb. The equilibrium of excitatory and inhibitory neurotransmission is critical for normal brain function and disruptions in this balance can result in several devastating neurological disorders. While most neurons in the brain release a single primary neurotransmitter, certain populations are capable of releasing two neurotransmitters. These “dual-release” neurons often transmit ostensibly competitive molecules but manage to regulate vital neurological processes. In particular, GABA and GLUT dual-release neurons in the lateral habenula (LHb) are involved in mood regulation. Aberrant release at the LHb is associated with major depressive disorder (MDD), but the mechanism underlying this relationship is unknown. To investigate the role of LHb dual-release neurons in the pathology of MDD, we have combined optical imaging, CyTOF and EM to investigate the murine LHb. Characterizing the spatial arrangement of GLUT and GABA is critical for understanding how dual-release is regulated at the molecular level. Super-resolution STORM imaging allows nanoscale visualization of the pre-synaptic terminal. This resolution is sufficient to distinguish between populations of GLUT and GABA vesicles, as well as vesicles that contain both transporters.

Additionally, both isolated synaptosomes and pre-synaptic vesicles are used with CyTOF to investigate the proportional load of GABA vs GLUT in the LHb. Here we present preliminary data that suggests there is complex molecular regulation and distribution of GABA and GLUT synaptic vesicles in the LHb and points towards potential targets for the treatment of MDD.

Disclosures: D. White: None. **M. Stowell:** None.

Poster

P100. Presynaptic Organization

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P100.09

Topic: B.05. Neurotransmitter Release

Support: FONDAP 15150012
NIH AG067333
NIH 1S10 OD016281-01

Title: Ketogenic diet effects at short-, medium and long-term on cortical synaptic proteome in aging mice

Authors: *D. ACUNA[1], A. ACEVEDO[2], C. OLMOS[1], C. WEHRFRITZ[3], S. SHAH[3], B. SCHILLING[3], J. C. NEWMAN[3], C. GONZÁLEZ-BILLAULT[1,3,2];
[1]Biol., Univ. de Chile, Santiago, Chile; [2]Inst. of Nutr. and Food Technology, (INTA), Santiago, Chile; [3]Buck Inst. for Res. on Aging, Novato, CA

Abstract: Aging is a complex process affecting brain function progressively over time with increased risk of cognitive decline and neurodegenerative diseases. Cerebral cortex is particularly vulnerable to age due to significant molecular changes in neurons such as energy metabolism decline, loss of proteostasis and synaptic dysfunction. Recent studies found that long-term treatments with ketogenic diet (KD) preserve memory and motor function in old mice, however the precise molecular mechanisms involved and duration of treatment that is required remain to be elucidated. Therefore, we investigated how KD administration at short- (1 week), medium- (6 weeks) and long- term (12 months) affects the cortical synaptic proteome in C57BL/6 mice. We performed mass spectrometric analysis using a label-free, data-independent acquisition (DIA) approach to analyze pre-synaptic and post-synaptic preparations from animals at the end of the treatment period (24-26 months old). Bioinformatic analysis revealed increased expression of presynaptic proteins involved in actin cytoskeleton, mitochondria, synaptic vesicle cycle and cAMP pathways in old mice treated with KD at long and medium-term, whereas modest changes in the postsynaptic proteome were identified at short-term administration. Additionally, these findings were corroborated by dendritic spine morphology analysis and synaptic contacts counting in cortical brain slices. Overall, we show that KD predominantly modulates the presynaptic proteome of cortical synapses through the activation of key specific molecular pathways involved in energy supply and synaptic organization, preserving their function in aging mice.

Disclosures: D. Acuna: None. **A. Acevedo:** None. **C. Olmos:** None. **C. Wehrfritz:** None. **S. Shah:** None. **B. Schilling:** None. **J.C. Newman:** None. **C. González-Billault:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.01

Topic: B.07. Synaptic Plasticity

Support: Forschungskredit grant, University of Zurich
International Postdoc grant (2018-06813), Swedish Research Council
European Research Council Starting grant (SynDegrade-679881)
Swiss National Science Foundation Assistant Professor grant (PP00P3–15)

Title: Distinct molecular pathways govern presynaptic homeostatic plasticity

Authors: *A. NAIR, P. MUTTATHUKUNNEL, M. MUELLER;
Univ. of Zurich, Zurich, Switzerland

Abstract: Presynaptic homeostatic plasticity (PHP) stabilizes synaptic transmission by counteracting impaired neurotransmitter receptor function through increased presynaptic release. PHP is thought to be triggered by impaired receptor function, and to involve a stereotypic signaling pathway. However, here we demonstrate that different receptor perturbations that similarly reduce synaptic activity result in vastly different responses at the Drosophila neuromuscular junction. While receptor inhibition by the glutamate receptor (GluR) antagonist γ-DGG is not compensated by PHP, the GluR inhibitors PhTx-433 and Gyki induce compensatory PHP. Intriguingly, PHP triggered by PhTx and Gyki involve separable signaling pathways, including inhibition of distinct GluR subtypes, differential modulation of the active-zone scaffold Bruchpilot, and short-term plasticity. Moreover, while PHP upon Gyki treatment does not require genes promoting PhTx-induced PHP, it involves presynaptic Protein Kinase D. Thus, synapses not only respond differentially to similar activity impairments, but achieve homeostatic compensation via distinct mechanisms, highlighting the diversity of homeostatic signaling.

Disclosures: A. Nair: None. **P. Muttathukunnel:** None. **M. Mueller:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.02

Topic: B.07. Synaptic Plasticity

Support: NIH-F31 1F31NS122424-01
NIH R01 NS078179

Title: Dynamic regulation of calcium channels and their auxiliary subunits at the Drosophila neuromuscular junction

Authors: A. T. MEDEIROS[1], S. J. GRATZ[1], A. DELGADO[1], K. M. O'CONNOR-GILES[2];
[1]Dept. of Neurosci., [2]Neurosci., Brown Univ., Providence, RI

Abstract: Nervous systems must be plastic to maintain effective communication within dynamic environments. Communication between neurons relies on calcium-dependent neurotransmitter release at specialized areas of synapses called active zones. Calcium channels are critical mediators of neurotransmitter release, but how they modulate synaptic activity to keep communication within established parameters is incompletely understood. We have investigated calcium channel dynamics during homeostatic plasticity, a conserved mechanism for stabilizing the activity of a neuron around an established set-point. In *Drosophila* the application of Philanthotoxin, a wasp toxin that blocks postsynaptic glutamate receptors, induces presynaptic homeostatic potentiation (PHP) within minutes. During PHP, neurotransmitter release is increased to compensate for glutamate channel impairment and maintain effective communication. PHP is achieved through an increase in the probability of release thought to involve both an increase readily-releasable synaptic vesicles and calcium influx. We have found that the sole *Drosophila* CaV2 calcium channel Cacophony (Cac) is rapidly recruited to active zones within 10 minutes of Philanthotoxin challenge, indicating that synaptic calcium channel levels can be dynamically regulated on rapid time scales to influence synaptic probability of release. However, calcium influx depends not only on the pore forming α_1 subunit, but also auxiliary subunits that impact the trafficking, organization, and function of the channel. CaV2 channels are composed of an α_1 subunit, a β subunit, and an $\alpha_2\delta$ subunit, each of which is encoded by multiple genes and/or alternative isoforms. While we know that the α_1 subunit, Cac, is rapidly trafficked to the synapse to aid in potentiation, it is unknown how these auxiliary subunits are modulated to influence channel trafficking and membrane insertion at active zones. To address this question, we used CRISPR gene editing to create endogenously tagged lines of the *Drosophila* β and $\alpha_2\delta$ subunits. We have confirmed normal channel function in our tagged lines. We find that subunits localize to synapses with both overlapping and unique cellular patterns. In ongoing studies, we are investigating the dynamic regulation of channel composition during PHP. Using our genetic toolset to characterize calcium channel complex dynamics will enable us to understand how channel levels, sub-synaptic localization, and subunit composition are modulated to tune synaptic probability of release.

Disclosures: A.T. Medeiros: None. **S.J. Gratz:** None. **A. Delgado:** None. **K.M. O'Connor-Giles:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.03

Topic: B.07. Synaptic Plasticity

Support: SNSF grant P2FRP3_178089 to FJBG
SNSF grant P400PB_191080 to FJBG

NIH/NINDS grant R35NS097212 to GWD

Title: Mechanisms of Presynaptic Homeostatic Plasticity at a Central Cholinergic Synapse in Drosophila

Authors: *F. J. BERNARDO-GARCIA, G. W. DAVIS;
Univ. of California San Francisco, San Francisco, CA

Abstract: Synaptic homeostasis refers to a set of adaptive physiological mechanisms that ensure robust, reliable information transfer at synaptic connections. Presynaptic homeostasis (PHP) is the process by which neurons adjust the release of neurotransmitter to offset disruptions that impair synapse integrity and function, including the effects of synapse degeneration. Large-scale forward genetic screens in *Drosophila* have revealed highly conserved molecular mechanisms of PHP, operating at neuromuscular junctions in fly and mouse. By contrast, little is known about the expression or molecular mechanisms of PHP at central synapses in any organism. Here, we establish for the first time that PHP occurs at a cholinergic synapse in the *Drosophila* adult central nervous system. This system is amenable to forward genetic screens. We demonstrate that PHP can be rapidly induced within minutes, and is persistently expressed, paralleling observations at the *Drosophila*, mouse and human NMJ. However, emerging molecular mechanisms appear to be distinct from those observed in the peripheral nervous system. Furthermore, distinct molecular mechanisms appear to govern the rapid induction (minutes) versus sustained expression (days) of PHP. These data highlight the relevance of PHP to the maintenance of robust information transfer at central synaptic connections. Novel mechanisms and a model for PHP at a cholinergic central synapse will be presented.

Disclosures: F.J. Bernardo-Garcia: None. **G.W. Davis:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.04

Topic: B.07. Synaptic Plasticity

Support: NIMH Grant R01

Title: The mTOR protein interaction network responds to homeostatic scaling and is disrupted in Shank3 knockout mice

Authors: *D. WEHLE[1], W. E. HEAVNER[2], S. E. P. SMITH[1];
[1]Univ. of Washington Grad. Program In Neurosci., Seattle, WA; [2]Natl. Inst. of Neurolog. Disorders and Stroke, Washington D.C, DC

Abstract: While Autism spectrum disorder (ASD) is a heterogenous disorder with a wide array of causative mutations implicated, animal modeling studies of many implicated genes have identified shared mechanisms and deficits. One such common disfunction lies in a form of synaptic plasticity called homeostatic scaling, a non-Hebbian form of plasticity that allows a neuron to maintain its firing rate within a useful dynamic range despite changes in overall network excitability. Another common

dysfunction in ASD involves disruption in the PI3K-AKT-mTOR signal transduction pathway, which itself is implicated in homeostatic scaling. Here, to relate disruptions in mTOR signaling with disruptions in homeostatic plasticity, we investigated the activity of an mTOR protein interaction network (PIN) during homeostatic scaling in wildtype and ASD-model mice. We treated p16 to p20 cultured cortical neurons with tetrodotoxin (TTX) to induce upscaling and bicuculine (BIC) to induce downscaling. We then observed the response of a PIN composed of proteins involved in mTOR signal transduction using a novel Qualitative Multiplex Immunoprecipitation (QMI) antibody panel. We found extensive re-arrangement of protein complexes containing PI3K, mTORC1/2, TSC, FMRP and EIF4E/G, among others. The protein complexes altered by up- vs. down-scaling partially overlapped; both up- and down-scaling induced similar changes in interactions involving the EIF4 complex, while down scaling produced unique protein network changes involving TSC and mTORC1/2 complexes and up scaling induced a small set of unique interactions involving EIF4, AKT, p70S6K, and TSC. Next, we compared frontal cortical tissue from unmanipulated Shank3B KO and wildtype adult mice using QMI. We identified genotype-dependent differences in the mTOR PIN, including downregulation of a complex containing EIF4E and EIF4G, which suggested downregulated protein synthesis in Shank3 animals. Using Puromycin labeling of newly synthesized proteins, we confirmed downregulation of basal levels of protein synthesis in Shank3 cortex. Finally, we induced homeostatic scaling in Shank3B wildtype and mutant cortical cultures to compare genotype-dependent responses to scaling in the mTOR PIN. Overall, our results indicate that homeostatic scaling induces changes in mTOR and EIF4-related protein complexes, implying that mTOR signaling may mediate homeostatic scaling. The mTOR PIN, specifically EIF4 interactions, are dysregulated in the Shank3 knockout model, which may link molecular mTOR signaling deficits to the altered synaptic plasticity observed in this model of ASD.

Disclosures: D. Wehle: None. **W.E. Heavner:** None. **S.E.P. Smith:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.05

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R35 NS111562
SFARI Award 345485

Title: A phosphorylation switch in Shank3 bidirectionally regulates homeostatic synaptic scaling

Authors: *C.-H. WU[1], V. TATAVARTY[1], P. M. JEAN BELTRAN[2], A. A. GUERRERO[1], H. KESHISHIAN[2], K. KRUG[2], S. A. CARR[2], J. R. COTTRELL[3], G. TURRIGIANO[1];
[1]Dept. of Biol., Brandeis Univ., Waltham, MA; [3]Stanley Ctr. for Psychiatric Res., [2]Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Synaptic scaling is an important form of homeostatic plasticity that bidirectionally adjusts postsynaptic weights in response to perturbation of neuronal activities. It maintains stable neuronal firing by globally changing the synaptic accumulation of GluA2-containing AMPA receptors. Up to date, how

synaptic GluA2 is regulated during scaling remains incompletely understood. Phosphorylation is a posttranslational modification that regulates many forms of synaptic plasticity and likely mediates the molecules crucial for synaptic scaling. Src homology 3 (SH3) and multiple ankyrin repeat domains 3 (Shank3) is a postsynaptic scaffold protein enriched in excitatory synapses. It interacts with various cellular factors within the postsynaptic density (PSD) and engages in local signaling pathways important for synaptic transmission. Mutations and deletion of the *SHANK3* gene have been associated with neurodevelopmental disorders, including intellectual disability autism spectrum disorders (ASD). Our lab previously demonstrated that Shank3 is indispensable for the expression of synaptic scaling.Nonetheless, it is unknown how Shank3 facilitates synaptic scaling and whether phosphorylation is involved in the process. Here we aim to investigate changes in the phosphoproteome after pharmacologically inducing bidirectional synaptic scaling in cultured rodent cortical neurons. Our quantitative mass spectrometry analysis revealed widespread and temporally complex changes at many phosphosites, with strong enrichment for synapse-associated proteins. We further identified Shank3 among the molecules that showed opposite changes in phosphorylation during scaling up and down. We found that Shank3 was stably hypophosphorylated during activity blockade, which was maintained by increased activity of protein phosphatase 2A (PP2A). Using pharmacological and genetic approaches, we then showed that the hypophosphorylated state of Shank3 supported the synaptic abundance of both Shank3 and GluA2 through the PP2A-dependent process. Lastly, we conducted imaging and electrophysiological experiments and demonstrated that overexpressing Shank3 phospho-mutants ablated scaling-induced changes in postsynaptic strength in a direction-specific manner. This work demonstrates that PP2A-dependent hypophosphorylation of Shank3 is essential for scaling up, and suggests that widespread changes in the phosphoproteome are instrumental in reconfiguring postsynaptic sites during homeostatic synaptic plasticity.

Disclosures: C. Wu: None. **V. Tatavarty:** None. **P.M. Jean Beltran:** None. **A.A. Guerrero:** None. **H. Keshishian:** None. **K. Krug:** None. **S.A. Carr:** None. **J.R. Cottrell:** None. **G. Turrigiano:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.06

Topic: B.07. Synaptic Plasticity

Support: NIMH grant R01MH113545

Title: Widespread remodeling of synaptic protein interaction networks following homeostatic plasticity requires Homer1 and Shank3

Authors: W. E. HEAVNER, J. D. LAUTZ, H. E. SPEED, E. P. GNIFFKE, J. P. WELSH, N. A. BAERTSCH, ***S. SMITH**;
Univ. of Washington, Seattle, WA

Abstract: Neurons maintain constant levels of excitability using homeostatic scaling, which adjusts relative synaptic strength in response to large changes in overall activity. While previous studies have

catalogued the transcriptomic and proteomic changes associated with scaling, the resulting alterations in synaptic protein interaction networks (PINs) are less well understood. We monitored a glutamatergic synapse PIN composed of 380 binary interactions among 21 protein members to identify protein complexes altered by synaptic scaling. In cultured cortical neurons, we observe widespread bidirectional PIN alterations with up- versus downscaling. In the barrel cortex, the PIN response to 48 hours of sensory deprivation exhibits characteristics of both upscaling and downscaling, consistent with emerging models of excitatory/inhibitory balance in cortical plasticity. Mice lacking *Homer1* or *Shank3* do not undergo normal PIN rearrangements, suggesting that they serve as structural hubs for synaptic homeostasis, which may be disrupted in Autism Spectrum Disorders (ASDs). Our approach demonstrates how previously identified RNA and protein-level changes induced during homeostatic scaling translate into functional PIN alterations that mediate changes in neuronal excitability.

Disclosures: W.E. Heavner: None. **J.D. Lautz:** None. **H.E. Speed:** None. **E.P. Gniffke:** None. **J.P. Welsh:** None. **N.A. Baertsch:** None. **S. Smith:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.07

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01N2085164

Title: Electrophysiological analysis of conserved sleep factors reveals that calcineurin signaling regulates homeostatic synaptic plasticity

Authors: *N. ARMSTRONG, C. FRANK;
Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: The ability of synapses to maintain physiological levels of evoked neurotransmission is essential for neuronal stability. Defective neurotransmission can result in a plethora of chronic disorders like forms of epilepsy and migraine or disturbed routine behaviors, like sleep. A variety of perturbations can disrupt neurotransmission, but synapses often compensate for disruptions to stabilize activity levels, using forms of homeostatic synaptic plasticity. Presynaptic homeostatic potentiation (PHP) is one such mechanism. In PHP, neurotransmitter release increases in response to challenges to the synapse, resulting in the maintenance of evoked neurotransmission. We hypothesized that conserved proteins known to control sleep (a homeostatic process) might have conserved roles in functional synapse stability. Using the *Drosophila melanogaster* neuromuscular junction (NMJ) as a model synapse that expresses PHP, we tested the ability for the synapse to express PHP when it lost conserved sleep factors. One core finding of this approach was that multiple calcineurin components are necessary either for the rapid induction or chronic maintenance of PHP in neuron, muscle, or glia. Overexpression of a calcineurin regulator, *sarah* (*sra*), in either neuron or muscle results in chronic PHP deficits. Interestingly, the PHP deficit observed in animals with a muscle-specific overexpression of *sra* can be partially rescued using the calcineurin inhibitor, FK506. Additional data suggest that tissue-specific expression of genes encoding either the

regulatory subunit of calcineurin or encoding the catalytic subunit are necessary for PHP.Prior work suggests that intracellular calcium signaling mediated by IP_3 receptors and Ryanodine receptors is required for the maintenance of PHP, but it is unclear what the mechanism is by which IP_3R and RyR – or downstream intracellular calcium signaling – function to maintain PHP. Our current findings suggest that calcineurin signaling could be driving this function across multiple tissue types and over different temporal phases of PHP expression.

Disclosures: N. Armstrong: None. **C. Frank:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

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Program #/Poster #: P116.08

Topic: B.07. Synaptic Plasticity

Support: Swiss National Science Foundation Assistant 571 Professor grant (PP00P3–15)
European Research Council Starting grant 572 (SynDegrade-679881) to MM

Title: The E3 ligase Thin controls homeostatic plasticity through neurotransmitter release repression

Authors: *M. BACCINO-CALACE, K. SCHMIDT, M. MÜLLER;
Univ. of Zurich, Zurich, Switzerland

Abstract: Synaptic proteins and synaptic transmission are under homeostatic control, but the relationship between these two processes remains enigmatic. Here, we systematically investigated the role of E3 ligases, key regulators of protein degradation-mediated proteostasis, in presynaptic homeostatic plasticity (PHP). An electrophysiology-based genetic screen of 157 E3 ligase-encoding genes at the *Drosophila* neuromuscular junction identified *thin*, an ortholog of human *tripartite motif-containing 32 (TRIM32)*, a gene implicated in several neural disorders, including Autism Spectrum Disorder and schizophrenia. We demonstrate that *thin* functions presynaptically during rapid and sustained PHP. Presynaptic *thin* negatively regulates neurotransmitter release under baseline conditions by limiting the number of release-ready vesicles, independent of gross morphological defects. We provide genetic evidence that *thin* controls release through *dysbindin*, a schizophrenia-susceptibility gene required for PHP. Thin and Dysbindin localize in close proximity within presynaptic boutons, and Thin degrades Dysbindin in vitro. Thus, the E3 ligase Thin links protein degradation-dependent proteostasis of Dysbindin to homeostatic regulation of neurotransmitter release.

Disclosures: M. Baccino-Calace: None. **K. Schmidt:** None. **M. Müller:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.09

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS085164

Title: Chaperones HSP26 and 27 promote the induction of homeostatic synaptic plasticity by regulating protein aggregates

Authors: *C. FRANK, **B. MALLIK**;
Univ. of Iowa, Iowa City, IA

Abstract: Accumulation of toxic proteins in muscle has been linked with the onset of pathophysiological conditions, which in many cases, are characterized by altered muscle function and synapse loss. Heat shock proteins (HSPs) help protein folding and resolution of unfolded proteins, thereby reducing stress caused by protein aggregation. While most heat shock proteins are expressed in neurons, their functional relevance in muscle is largely unknown. Here we describe a role for muscle heat shock proteins in inducing the expression of a form of homeostatic synaptic plasticity. At the *Drosophila melanogaster* neuromuscular junction, perturbation of postsynaptic glutamate receptors activates retrograde signaling which precisely increases neurotransmitter release to restore baseline synaptic strength. This signaling can be induced in as little as 10 minutes with the drug Philanthotoxin-433 (PhTx). Moreover, increased transmitter release is associated with molecular signatures, like increased active zone protein material. We performed a reverse genetic screen to identify factors in the postsynaptic compartment necessary to generate retrograde homeostatic signaling. This approach helped us to identify heat shock proteins 26 and 27 (HSP26 and 27) . When these factors are genetically depleted, there is a failure in the acute, 10-minute induction of synaptic homeostasis. By contrast, after chronic genetic perturbation of glutamate receptors or extended incubation of PhTx in an open NMJ preparation (~ 45 minutes) the synapse is able to express and maintain homeostatic signaling, even in the absence of *hsp26* or *27* function. Interestingly, transgenic expression of human disease PolyQ repeat proteins in the muscle (such as human Huntington *HTT46Q* or *HTT72Q*) phenocopies the homeostatic induction timing defects of *hsp26* and *27* gene loss. Moreover, muscle overexpression of *hsp26* and *27* in the genetic background of these PolyQ-expressing flies restores the successful 10-minute induction of synaptic homeostasis. This restoration includes NMJ function, and it includes restoration of molecular signatures, like increased presynaptic active zone material after homeostatic induction. Together our findings support the model that protein aggregation in muscle slows the induction of homeostatic signaling. In the context of modeling human disease, our data could shed light on the consequences that protein aggregation may have on neuroplasticity and downstream neurophysiological function.

Disclosures: C. Frank: None. **B. Mallik:** None.

Poster

P116. Homeostatic Plasticity: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P116.10

Topic: B.10. Epilepsy

Support: NINDS

Title: Activity-dependent Regulation of the PARbZIP transcription factor family in mouse cortical neurons.

Authors: *E. A. BARRIOS[1], V. VALAKH[1,4], M. SHA[2], S. B. NELSON[3];
[1]Biol., [3]Dept Biol MS#008, [2]Brandeis Univ., Waltham, MA; [4]Stanley Ctr. for Psychiatric Res., Broad Inst. of Harvard and MIT, Cambridge, MA

Abstract: Homeostatic plasticity requires gene transcription. However, little is known about how gene expression regulates this form of plasticity. We found that in organotypic slice cultures following prolonged activity deprivation, expression of the members of the PARbZIP transcription factor family (TEF, HLF, DBP) are robustly increased. Knockout of these PARbZIP TFs causes seizures in mice. In the absence of these TFs homeostatic response to activity deprivation is increased in cortical slice cultures. Together, these findings suggest that PARbZIP TFs normally constrain homeostatic plasticity. These TFs are regulated by circadian clock genes, and since components of the molecular clock have also been implicated in epilepsy, we tested the role of the clock genes in activity-dependent PARbZIP regulation. Knockout of the obligate clock gene Bmal1 reduced PARbZIP expression and impaired their elevation during activity deprivation. We also tested whether translation of other TFs are required for the elevation of PARbZIPs following activity deprivation. Blocking translation with cyclohexamide did not prevent the elevation of PARbZIP expression during activity deprivation. This implies that PARbZIPs function as immediate early genes that recognize a fall rather than an elevation in activity.

Disclosures: E.A. Barrios: None. **V. Valakh:** None. **M. Sha:** None. **S.B. Nelson:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

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Program #/Poster #: P118.01

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R25 NS 80686-10/11
Vulnerable Brain Project

Title: Ketamine reduces depression-like behavior of mice resulting from single housing during adolescence and alters the proportion of postsynaptic spines in layer 1 of prefrontal cortex with drebrin immunoreactivity

Authors: *E. MAKOWICZ[1], C. J. AOKI[2];
[1]City Univ. of New York At Hunter Col., New York, NY; [2]Ctr. Neural Sci., New York Univ., New York, NY

Abstract: Ketamine, an NMDA receptor (NMDAR) antagonist, has been shown to alleviate depression symptoms more rapidly and for longer than the traditional anti-depressants targeting the monoamine systems. Ketamine's longer-lasting effect may be due, in part, to increasing BDNF levels and

synaptogenesis in cortex. The current study aimed to elucidate further the mechanism by which ketamine could reduce depressive-like behavior, elicited by single-housing (SH) of male mice during adolescence. We hypothesized that ketamine alleviates depression through synaptogenesis involving drebrin, an F-acting binding protein enriched in spines and previously shown to aid the activity-dependent trafficking of NMDARs into spines and to localize them over postsynaptic densities (PSDs). Depressive-like behavior was quantified based on immobility during two forced swim test[c1] s (FST) administered one week apart, with the 2nd FST preceded 1-3 days by an IP injection with ketamine (10 mg/kg BW) versus saline. Since the[c2] effects of ketamine are reported to result in neuroanatomical changes in layer 1 of the prefrontal cortex, (PFC), we quantified the proportion of postsynaptic spines with and without drebrin-immunoreactivity here by electron microscopic immunocytochemistry (EM-ICC). FST revealed individual differences in immobility prior to ketamine injection: not all of the SH animals exhibited decreased immobility, relative to group-housed mice (9 out of 16). A significant ketamine effect, measurable as reduced immobility, was detected upon SH animals (SH-K, N=16), relative to saline-injected SH littermates (SH-S, N=15) ($p=0.02$). EM-ICC data showed reduced proportion of spines exhibiting intense levels of drebrin in the cytoplasm of the SH-K group, relative to the SH-S group, indicating that ketamine reduced drebrin-mediated trafficking of synaptic proteins between spines and dendritic shafts. Conversely, a more discrete drebrin immunoreactivity over PSDs was observed among spines in the SH-K group, relative to the SH-S group. We have shown previously that this is indicative of increased anchoring of NR2B-containing NMDARs at the synaptic cleft. These findings support the idea that ketamine promotes anti-depressive behavior by altering the drebrin-mediated spine-shaft trafficking of synaptic proteins in layer 1 of PFC.

Disclosures: E. Makowicz: None. **C.J. Aoki:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

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Program #/Poster #: P118.02

Topic: B.07. Synaptic Plasticity

Support: NIH Grant F30 DA052109

Title: Behavioral sensitivity to acute and chronic opioid exposure in neuroligin-3 knockout mice

Authors: *D. BRANDNER[1], C. RETZLAFF[1], P. G. MERMELSTEIN[1], P. E. ROTHWELL[2];
[2]Neurosci., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: The neuroligins are a family of postsynaptic cell-adhesion molecules that interact with presynaptic partners, the neurexins, to orchestrate the formation and functional properties of central synapses. Polymorphisms in these synaptic adhesion molecules have been shown to increase impulsivity and addiction-associated behaviors in humans. The mesolimbic pathway is a key neural substrate of addiction, encompassing dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Chronic exposure to drugs of abuse produces alterations in synapse structure and function in this pathway, accentuating the behavioral effects of these drugs. Neuroligin-3 (NL3) is an X-

linked neuroligin family member that has been shown to modify synaptic function in specific cell types within the VTA and the NAc, suggesting a possible role for this cell-adhesion molecule in mediating drug-induced plasticity. However, the mechanism by which NL3 modulates synaptic function remains incompletely understood, and a possible role for NL3 in mediating addiction-related behaviors by controlling synaptic adaptation in the mesolimbic dopamine pathway has not been explored. To characterize the effects of NL3 deletion on mesolimbic circuitry, we began by examining the psychomotor activating effects of morphine in constitutive NL3 KO animals. Owing to X-linkage of NL3, our analyses focused on male animals. Following acute morphine administration, these animals exhibited an increase in locomotor activity similar in magnitude to wild-type littermates. However, psychomotor sensitization was significantly reduced in NL3 KO animals following one week of morphine administered at 20 mg/kg daily. We conducted conditional knockout of neuroligin-3 in key neuronal populations throughout the mesolimbic dopamine pathway, including D1- and D2-dopamine receptor-expressing medium spiny neurons in the NAc as well as VTA dopamine neurons. Our findings show that knockout of NL3 from VTA dopamine neurons phenocopies the attenuated morphine sensitization seen in constitutive NL3 knockout animals. We are currently investigating the possibility that this altered behavioral response to morphine is related to opioid-induced synaptic adaptations that require neuroligin-3 for complete expression. We are also examining form and function of synaptic input onto VTA dopamine neurons. Understanding the effects of NL3 depletion on synaptic architecture may provide insight into mechanisms of psychomotor sensitization as well as pathologic alterations that influence human vulnerability to substance use disorders.

Disclosures: D. Brandner: None. **C. Retzlaff:** None. **P.G. Mermelstein:** None. **P.E. Rothwell:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P118.03

Topic: B.07. Synaptic Plasticity

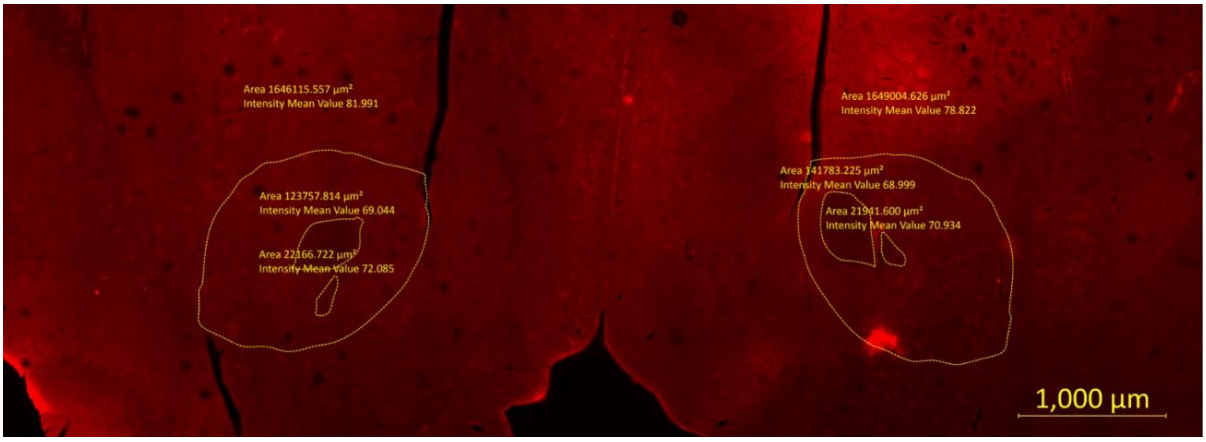
Support: DGAPA IN206521
UNAM

Title: Brain plastic changes induced by motivated behaviors in rats

Authors: Z. MIER-QUESADA[1], ***L. GAYTÁN-TOCAVÉN**[2], R. G. PAREDES[2], J. LOZA[1]; [1]INSTITUTO DE NEUROBIOLOGÍA, UNAM, Querétaro, Mexico; [2]Escuela Nacional de Estudios Superiores, Unidad Juriquilla, UNAM, Querétaro, Mexico

Abstract: Synaptic plasticity is the result of changes in the number and strength of synaptic connections due to the processing of different stimuli. Sexual experience can influence synaptic plasticity in the brain in many ways. We used the Partner Preference Task (PPT) and the Sexual Incentive Motivation (SIM) test to evaluate possible plastic changes in different brain areas with the synaptic vesicle marker synaptophysin (SYN). This project aimed to determine by immunofluorescence and stereology, the plastic changes induced by the acquisition of experience in the PPT and SIM in the amygdala (AMY),

hippocampus (HIP) ventromedial hypothalamus (VMH), and nucleus accumbens (ACC), structures related with motivation and sexual reward. 15 Wistar rats (300-350 gr) were used. They were divided into 3 groups: the control group (CG), PPT, and SIM group. After 10 weeks of the behavioral tests, the brains were extracted, 30 µm sections were obtained with confocal microscopy from -2.12 to -3.60 mm for (AMY, HPO, VMH), and from 0.48 to 1.7 for ACC. We average SYN intensity values of 4 coordinates (z = 3 µm each coordinate) in (AMY, HIP, VMH) and (z =10 µm each coordinate) in ACC to determine the volumetric value of each structure. Preliminary results showed a significant increase in SYN expression in the ACC in the PPT and SIM groups with respect to the CG. We also observed a significant increase in AMY and VMH in the SIM group vs the PPT group. Our preliminary data show an increase in SYP intensity in the SIM and PPT groups vs CG in the AMY, VMH and ACC without significant differences in the HIP. We suggest that behavioral experience causes plastic changes involving the expression of synaptic proteins such as synaptophysin, in structures that participate in circuits controlling motivated behaviors.



Disclosures: Z. Mier-Quesada: None. **L. Gaytán-Tocavén:** None. **R.G. Paredes:** None. **J. Loza:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

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Program #/Poster #: P118.04

Topic: B.07. Synaptic Plasticity

Support: Brain & Behavior Research Foundation NARSAD Young Investigator Grant 25488
University of Cincinnati Neurobiology Research Center Pilot Award
National Institutes of Health R21-MH120614

Title: Microglial BDNF regulates susceptibility to the cognitive and synaptic effects of stress

Authors: *S. WOODBURN[1], J. L. BOLLINGER[2], E. S. WOHLEB[3];
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Pharmacol. and Systems Physiol., [3]Dept. of Pharmacol. and Systems Physiol., Univ. of Cincinnati Col. of Med., Cincinnati, OH

Abstract: Chronic unpredictable stress (CUS) causes synapse loss in the prefrontal cortex (PFC), leading to working memory impairments and adaptations in stress coping. Previous work showed that deficient brain-derived neurotrophic factor (BDNF) signaling increases susceptibility to the behavioral and biological effects of CUS; however, these studies focused on neuronal sources of BDNF. Recent studies indicate that microglia are an important source of BDNF in physiological and pathological conditions. Consistent with this work, experiments from our lab showed that 14 days of CUS reduced *Bdnf* levels in PFC microglia. To further examine the role of microglial BDNF in stress susceptibility, we generated transgenic mice with a microglia-specific *Bdnf* depletion ($Cx3cr1^{Cre/+}:Bdnf^{fl/fl}$) and genotype controls ($Cx3cr1^{Cre/+}:Bdnf^{+/+}$). Mice were supplied with a tamoxifen diet for 3 weeks to drive Cre-induced gene recombination, then were left undisturbed for 14 days to allow peripheral monocytes to turnover, while *Bdnf*-depleted microglia remained. Mice were then exposed to 7 days of CUS or handled intermittently, followed by behavioral testing via forced swim test (FST) and temporal object recognition (TOR). Following this, synaptosomes were isolated from the PFC to assess synaptic protein expression. Interestingly, microglial BDNF depletion impaired TOR performance compared to genotype controls, which coincided with altered expression of proteins involved in glutamate signaling in PFC synaptosomes. These results indicate deficient microglial BDNF increases susceptibility to the neurobiological and behavioral effects of stress.

Disclosures: S. Woodburn: None. **J.L. Bollinger:** None. **E.S. Wohleb:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P118.05

Topic: B.07. Synaptic Plasticity

Support: NIH/NIA GR5270884

Title: Perisynaptic Schwann cells undergo a myriad of morphological changes yet remain at neuromuscular junctions during aging

Authors: *R. HASTINGS[1,2], A. O'YOUNG[1], J. PERES DA SILVA[1], G. VALDEZ[1,2];
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Abstract: Age-related changes in the pre-synaptic axon terminal and post-synaptic endplate of the neuromuscular junction (NMJ) have been well-documented. In contrast, little is known about the effect of aging on Perisynaptic Schwann cells (PSCs), which are essential for the function and stability of NMJs. In this study, we examined PSCs in young adult, middle-aged, and old mice. We visualized PSCs in transgenic mice expressing GFP in all Schwann cells and in wild type mice immunostained for S100B. Our data show that PSCs are more abundant at NMJs in the soleus and extensor digitorum longus (EDL)

muscles of aged mice. PSCs are increased at NMJs exhibiting age-related blebbing of the axon terminal or polyneuronal innervation. We provide data suggesting that PSCs may be increased because of migration of non-synaptic Schwann cells to aged NMJs. Additional analysis revealed that PSCs undergo a myriad of morphological alterations during aging in both the soleus and EDL muscles, including increased terminal sprouting and the formation of bridges between NMJs. These findings demonstrate that PSCs are similarly affected by aging in the soleus and EDL muscles, which have different functional demands and fiber type composition. To determine if PSCs undergo age-related changes regardless of location and susceptibility of a given muscle to aging, we examined PSCs in extraocular muscles (EOMs). Unlike the soleus and EDL muscles, EOMs and their NMJs remain largely unchanged in aged mice. Not surprisingly, the number and morphology of PSCs were also unchanged in aged compared to young EOMs. Altogether, these data will help unravel the intrinsic drivers of PSC aging as well as the contribution of these synaptic glia to NMJ and muscle aging.

Disclosures: R. Hastings: None. **A. O'Young:** None. **J. Peres da Silva:** None. **G. Valdez:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P118.06

Topic: B.07. Synaptic Plasticity

Support: Academia Sinica CDA AS-CDA-110-L05

Title: A progressive motor learning task for studying neural circuit remodeling in the primary motor cortex

Authors: P. ADHIKARI, S.-Y. CHUEH, P.-Y. WU, R.-N. WU, *Y.-W. WU;
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Abstract: The dynamic adaptations in the synaptic plasticity of the neuronal circuits in the brain enable us to process, learn, and retain a wide range of information. During motor skill learning, there is the rapid formation of new spines, and it is followed by the elimination of existing spines in pyramidal neurons of the primary motor cortex (M1). Combining *in vivo* two-photon imaging with forelimb motor learning tasks -- including lever pushing, food pellet reaching, and water droplet reaching -- has become a robust tool for studying learning-associated neural circuit remodeling. However, these tasks are either too easy or lack precise control of the progress of learning. Here, to explore the step-by-step circuit remodeling in learning multiple forelimb movements with increased difficulty, we have established a progressive learning paradigm. This progressive learning task is quantifiable, readily comparable, and also having a different spectrum of difficulty. We adopted a programmable joystick (Wagner et al. 2020), enabling pre-determining movement trajectories. Delving into mouse motor performance has provided an insight into the level of complexity of different trajectories. We observed reduced trial attempts and success rates with increasing linear distance and viscosity (artificial friction). In addition, mice performance for trajectories with turn is highly dependent on the turning angle, i.e., the performance of inward turning is significantly better than outward turning. We trained the mice to perform two task modules of progressive learning:

Module I: 4-mm forward, 8-mm forward, 4-mm forward + 4-mm outward turn, and Module II: 4-mm forward, 4-mm forward + 4 mm inward turn, 4-mm forward + 4 mm outward turn. We found that the learning time required for the subsequent tasks within each module is significantly faster than the first 4-mm forward task. After the training session, we monitored the apical dendrites of the sparse-labeled layer 2/3 and layer 5 pyramidal neurons in the M1 with 2-photon imaging through a chronically implanted cranial window. We could observe synaptic remodeling over different tasks within each module. In conclusion, the new insights gained from applying the progressive motor learning task will enable us to understand the underlying mechanism of circuit remodeling and its correlation with multi-task learning in the brain.

Disclosures: P. Adhikari: None. **S. Chueh:** None. **P. Wu:** None. **R. Wu:** None. **Y. Wu:** None.

Poster

P118. Structural Plasticity: Functional Outcomes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P118.07

Topic: B.07. Synaptic Plasticity

Support: NIH Grant

Title: Functional Inactivation of Hippocampus during memory consolidation of mixed choice task applied through the first learning trials is sufficient to suppress the use of Hippocampal strategy for the subsequent trials

Authors: *H. SEMWAL[1], W. PETTIBONE[1], A. SERGEEVA[3], K. UZHCA[4], G. R. POE[2], L. URPA[5], B. A. GROSS[2];
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Abstract: The hippocampal network plays a crucial role in the formation and encoding of novel environmental cues. The locus coeruleus (LC) is the source of noradrenergic innervation and projects throughout the forebrain and the hippocampus, influencing learning and memory. Normally, LC neurons go silent before a spindle in non-rapid eye movement sleep, and are actively inhibited from firing during rapid eye movement (REM) sleep. However, disorders such as PTSD are associated with increased NE during sleep, which suggests an increased presence of NE due to an overactive LC. Norepinephrine specifically influences hippocampal plasticity, including long term potentiation and depotentiation, which restructures memory networks during the learning process. Activation of the LC has been shown to interfere with sleep-dependent memory consolidation, and optogenetic stimulation of the LC during REM results in deficits in memory. We trained Long-Evans rats to search for rewards hidden in constant positions on a mixed-choice food reward task using an eight-box octagonal maze. To highlight the contribution of different memory systems, the maze was randomly rotated after each trial, and the rat's starting position was changed. We refer to rats who made no more than one error per lap as hippocampal learners. Rats who did not use a hippocampal strategy were still able to find food on every lap, albeit with two or more errors. Each group of rats was divided into four treatment groups that temporarily inhibited

hippocampal learning: (1) two hours of sleep deprivation, (2) isoflurane anesthesia, (3) intrahippocampal norepinephrine infusion, or (4) optogenetic stimulation of the LC during sleep. Each treatment suppressed hippocampal strategy, both during sessions following treatment and for the next six days of training. However, we show that the number of errors in the control groups was significantly lower than the hippocampal-suppressed groups. These findings suggest that the functional inactivation of the hippocampus temporarily impairs cognitive flexibility. To ensure that the treatment did not cause permanent damage to the hippocampus, treated animals were re-trained on the same task in a different environment and maze, and reached below one error per lap showed functional hippocampal strategy indicating treatment did not cause irreversible damage.

Disclosures: H. Semwal: None. **W. Pettibone:** None. **A. Sergeeva:** None. **K. Uzhca:** None. **G.R. Poe:** None. **L. Urpa:** None. **B.A. Gross:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P170.01

Topic: B.11. Glial Mechanisms

Support: ERC NEURO-PATTERNS
NIH Brain Initiative U19 NS107464
NIH Brain Initiative R01 NS109961
NIH Brain Initiative R01 NS108410

Title: Interplay between astrocytic and neuronal networks in the mouse hippocampus during virtual navigation

Authors: *S. ROMANZI[1,2,4], P. LAGOMARSINO[1,2,4], S. CURRELI[1,2], J. BONATO[2,3,5], S. PANZERI[2,3,6], T. FELLIN[1,2];
[1]Optical Approaches to Brain Function Lab., [2]Neural Coding Lab., Inst. Italiano di Tecnologia, Genova, Italy; [3]Neural Computation Lab., Inst. Italiano di Tecnologia, Rovereto, Italy; [4]Univ. of Genova, Genova, Italy; [5]Dept. of Pharm. and Biotech., Univ. of Bologna, Bologna, Italy; [6]Ctr. for Mol. Neurobio. (ZMNH), Dept. of Neural Information Processing, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Recent evidence shows that intracellular calcium dynamics of hippocampal astrocytes encode information about the animal's position and that information encoded in astrocytic signals is complementary to that encoded in the spike output of surrounding neurons. Given that changes in the intracellular concentration of calcium in astrocytes profoundly modulate the activity of nearby synapses and neurons, this recent evidence raises the possibility that calcium dynamics in hippocampal astrocytes may influence the neuronal representation of space. To test this hypothesis, we combined astrocyte-specific pharmacogenetic manipulation, two-photon functional imaging, and information theory analysis in the CA1 hippocampal region of head-fixed mice navigating in a virtual environment. Using adeno-associated viral injections, we first expressed the Gq-coupled hM3Dq receptor and the calcium indicator GCaMP6f selectively in CA1 astrocytes and controlled that activation of the hM3Dq receptor by

clozapine N-oxide (CNO) interfered with ongoing calcium dynamics into astrocytes *in vivo*. We then expressed the hM3Dq receptor in astrocytes and GCaMP6f in neurons and performed two-photon functional imaging of neuronal place cells before and after CNO application in mice navigating a virtual corridor. Analysis of spatial information content at the single-cell and at the network level under control conditions and upon CNO application is currently ongoing. The results of these experiments and analyses will provide important insights about the contribution of hippocampal astrocytes to the modulation of the neuronal representation of space.

Disclosures: S. Romanzi: None. **P. Lagomarsino:** None. **S. Curreli:** None. **J. Bonato:** None. **S. Panzeri:** None. **T. Fellin:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P170.02

Topic: B.11. Glial Mechanisms

Title: Calcium event-independent spontaneous ATP release in astrocytes in cortical slice

Authors: *Y. HATASHITA[1], Z. WU[2], Y. LI[2], T. INOUE[1];
[1]Life Sci. and Med. Biosci., Waseda Univ., Tokyo, Japan; [2]Sch. of Life Sciences, Peking Univ., Beijing, China

Abstract: Astrocytes are the most abundant glial cell type in the central nerves system, tiling the brain with their highly ramified structures. Recent studies revealed that calcium transients in astrocytes play crucial roles in synaptic modulation by releasing chemical substances, called gliotransmitters, including ATP, glutamate and D-serine. Although the spatiotemporal properties of calcium transients in astrocytes have been well investigated, the dynamics of gliotransmitters at subcellular resolution remain poorly understood due to the lack of appropriate techniques to visualize. A recently developed genetically encoded extracellular ATP sensor, $GRAB_{ATP}$ (G protein-coupled receptor activation-based ATP sensor), showed a high sensitivity in monitoring ATP release *in vitro* and *in vivo*, however, spatiotemporal correlation between ATP release and intracellular calcium activity in astrocytes has not been investigated. Using $GRAB_{ATP}$, we investigated spatiotemporal dynamics of ATP release simultaneously with intracellular calcium activity in astrocytes in hippocampal primary culture and cortical acute slices. In neuron-astrocyte coculture, tetrodotoxin (TTX) insensitive ATP release events were detected, while calcium activation by high K^+ or thrombin did not induce detectable ATP release. In acute slice experiment in which cortical astrocytes expressed $GRAB_{ATP}$ sparsely by means of *in utero* electroporation, ATP release events observed, which were TTX-insensitive and inhibited by astrocyte specific metabolic inhibitor, fluorocitrate, indicating that astrocytes in acute slice also spontaneously release ATP. Typical ATP release events in slice occupied approximately 50-200 μm^2 with durations of 10-60 seconds. Extracellular ATP concentration ranged roughly 0.5-5 μM, implying that the spontaneous ATP release from astrocytes may be capable of activation of purinergic receptors in nearby synapses. Simultaneous extracellular ATP and intracellular calcium imaging with $GRAB_{ATP}$ and genetically encoded calcium sensor, REX-GECO1 or Lck-REX-GECO1 in cortical slice, revealed that the two events

rarely co-occurred, thus most of the spontaneous ATP release in astrocytes were independent of intracellular calcium events. In conclusion, our findings suggest that astrocytes in acute slice release ATP independently of surrounding neuronal activity as well as *in vitro*, which may affect nearby synapses depending on the size and amplitude of released ATP. And, spontaneous calcium transients may not be responsible for this gliotransmission.

Disclosures: Y. Hatashita: None. **Z. Wu:** None. **Y. Li:** None. **T. Inoue:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P170.03

Topic: B.11. Glial Mechanisms

Support: Starting grant (Chair of Excellence) from the Foundation Ecole des Neuroscience de Paris (ENP)
European Marie Curie career integration grant
DIM Cerveau & Pensée - Région Ile-de-France grant
French ministerial PhD fellowship

Title: Role of astrocytic Ca^{2+} signaling in synaptic transmission, plasticity and memory: implications for neurodegenerative diseases

Authors: *E. MOUKARZEL, C. AGULHON;
Paris Univ. - CNRS - Integrative Neurosciences & Cognition Ctr., Paris, France

Abstract: Astrocytes are the most abundant glial cells in the central nervous system and are in close contact with synapses. In response to neurotransmitters, they increase their intracellular Ca^{2+} levels, leading to the release of neuroactive molecules. In addition, astrocytic Ca^{2+} signaling is respectively increased and decreased in Alzheimer's and Huntington's neurodegenerative diseases. Patients' memory is also altered in both diseases. Our main hypothesis is that chronic modulation of astrocytic Ca^{2+} signaling leads to altered release of glutamate or pro-inflammatory factors from astrocytes, and consequent deficits in synaptic transmission, long-term potentiation, and memory formation. We have tested this hypothesis *in vivo* using the mouse primary visual cortex as a model system, combined with electrophysiology, chemogenetics, genetic tools, immunohistochemistry, and behavior. We found that chronically increasing or inhibiting astrocytic Ca^{2+} leads respectively to a depression or potentiation of visual recognition memory formation. The mechanisms underlying such changes are currently under investigation.
Our study could have profound implications in the clinic, as it may lead to a better understanding of the astrocyte role in memory deficits and in the etiology of neurodegenerative diseases.

Disclosures: E. Moukarzel: None. **C. Agulhon:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

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Program #/Poster #: P170.04

Topic: B.11. Glial Mechanisms

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European Marie Curie career integration grant
DIM Cerveau & Pensée-Région Ile-de-France grant

Title: Satellite glial cells modulate proprioceptive neuron function

Authors: *C. AGULHON, Y. RABAH;
Integrative Neurosciences & Cognition Ctr. - CNRS, Paris Univ., Paris, France

Abstract: Proprioceptive neurons are crucial for coordinating the activity of motoneurons and skeletal muscles to achieve essential motor tasks, such as posture, locomotion, manoeuvring one's way around obstacles or reacting rapidly to external perturbations. They arise from muscle spindles and tendons, and synapse onto ventral horn motoneurons in order to deliver information about the length and contraction of muscles. Proprioceptor cell bodies reside within the dorsal root ganglia (DRGs) and are tightly enwrapped by a thin sheath of glial cells, called satellite glial cells (SGCs). SGCs control the homeostasis of sensory neurons through the clearance of extracellular glutamate and potassium. Additionally, they express a number of Gq protein coupled receptors (G_q GPCRs), which are activated by ATP, glutamate or acetylcholine, leading to SGC intracellular Ca^{2+} elevations. There is evidence that transmitters released from sensory neuron cell bodies activate receptors at the surface of SGCs. Both SGCs and somata of sensory neurons express a plethora of receptors, including G_q GPCRs, supporting the hypothesis that SGC-to-neuron communication also takes place in DRGs. However, only a few studies have investigated SGC-to-sensory neuron interactions and no study has specifically investigated SGC-to-proprioceptor interactions. We hypothesized that activation of SGC G_q GPCR-mediated Ca^{2+} signaling induces the release of neuroactive molecules from SGCs to modulate proprioceptor functions. Using 2-photon microscopy, chemogenetics, and novel genetic tools, we have shown that selective activation of DRG SGC G_q GPCR signaling induces P2R-mediated Ca^{2+} increases in proprioceptors. These data demonstrate that SGCs are able to modulate proprioceptor activity, which, to our knowledge, has not yet been reported. To test whether SGC G_q GPCR activation is sufficient to cause sensory-motor deficits, we are setting up an experimental approach to locally infuse CNO selectively in DRGs.

Disclosures: C. Agulhon: None. **Y. Rabah:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

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Program #/Poster #: P170.05

Topic: B.11. Glial Mechanisms

Support: ERC NEURO-PATTERNS
NIH Brain Initiative U19 NS107464
NIH Brain Initiative R01 NS109961
NIH Brain Initiative R01 NS108410

Title: Astrocytes and neurons encode complementary spatial information in mouse hippocampus during virtual navigation

Authors: *S. CURRELI[1,2], J. BONATO[2,3,4], S. ROMANZI[1,2,5], S. PANZERI[2,3,6], T. FELLIN[1,2]; [1]Optical Approaches to Brain Function Lab., [2]Neural Coding Lab., Inst. Italiano di Tecnologia, Genova, Italy; [3]Neural Computation Lab., Inst. Italiano di Tecnologia, Rovereto, Italy; [4]Dept. of Pharm. and Biotech., Univ. of Bologna, Bologna, Italy; [5]Univ. of Genova, Genova, Italy; [6]Dept. of Neural Information Processing, Ctr. for Mol. Neurobio. (ZMNH), Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: In the hippocampus, neural place cells encode spatial information through the modulation of their firing rate as a function of the animal's position, providing a cellular substrate for spatial cognition. Whether spatial information is encoded beyond neural circuits is currently unknown. Using simultaneous two-photon calcium imaging of astrocytes and neurons in the CA1 hippocampal area of mice navigating in a virtual environment, we demonstrate that astrocytic calcium signals are actively involved in the encoding of information about the animal's position in virtual space. Calcium events carrying spatial information occurred in topologically-restricted and topographically-organized regions of the astrocyte, including the cell body and the proximal processes. Astrocytes had larger spatial fields, which were centered in different positions compared to those of neurons. Moreover, astrocytes encoded spatial information which was complementary and synergistic to that carried by neurons, improving decoding performance when considering astrocytic signals in addition to neuronal signals. These results reveal a fundamental new level of organization for spatial information encoding in the hippocampus: local CA1 non-neural elements provide an additional reservoir of spatial information, which complements that encoded in the spike output of projecting CA1 neurons, expanding hippocampal network population-coding capacity.

Disclosures: S. Curreli: None. **J. Bonato:** None. **S. Romanzi:** None. **S. Panzeri:** None. **T. Fellin:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P170.06

Topic: B.11. Glial Mechanisms

Support: Chellgren Endowed Funding to Robin L. Cooper
University of Kentucky Neuroscience Research Priority Area Grant to Shelby McCubbin

Title: The effect of optogenetically activating glia on neuronal function

Authors: *S. MCCUBBIN, C. PANKAU, R. L. COOPER;
Dept. of Biol., Univ. of Kentucky, Lexington, KY

Abstract: Glia, or glial cells, are considered a vital component of the nervous system, serving as an electrical insulator and protective barrier from the interstitial (extracellular) media. Certain glial cells (i.e. astrocytes, microglia, and oligodendrocytes) within the CNS have been shown to directly affect neural functions, but these properties are challenging to study due to the difficulty in selectively activating particular glia. To overcome this hurdle, we used selectively expressed light-sensitive ion channels (i.e. channel rhodopsin, ChR2) in glia of larvae and adult *Drosophila.* Upon activation of ChR2, both adults and larvae showed a rapid contracture of body wall muscles with the animal remaining in contracture even after the light was turned off, deactivating the channel rhodopsin. Furthermore, recovery of function once in the dark was related to the duration of light exposure. During ChR2 activation, electrophysiological recordings of evoked excitatory junction potentials within body wall muscles of the larvae confirmed a train of motor nerve activity. Additionally, when segmental nerves were transected from the CNS and exposed to light, there was no noted difference in quantal or evoked responses. This suggests that either there is not a high expression of ChR2 in the glia around the distal regions of segmental nerves, or there's not enough expression to influence the segmental axons to detect in our paradigm. Activation of the glia within the CNS is sufficient to excite the motor neurons. Studies are underway to see how repetitive activation of glia can influence neural circuity and neural development in the Drosophila model.

Disclosures: S. McCubbin: None. **C. Pankau:** None. **R.L. Cooper:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

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Program #/Poster #: P170.07

Topic: B.11. Glial Mechanisms

Support: NIH Grant 1RF1AG059610-01

Title: Inhibitory effect of Apolipoprotein E (ApoE) on axonstimulating effect of astroglial exosomes

Authors: *S. JIN[1], R. JARVIS[1], V. PROMES[1], Y. YANG[2];
[1]Neurosci., Tufts university, Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Exosomes, a major type of Extracellular vesicles (EV), are originated from the endosomal compartment and are known to be released by most cell types, including neurons and glia cells in the CNS. These nanovesicles are typically 50-200 nm in size and carry specific proteins, RNAs and lipids. Exosomes have been shown to function as new type of messengers involved in neuron-glia communication and participate in various physiological and pathological functions. In our current study, by selectively isolating astroglial exosomes using size-exclusion chromatography (SEC), we defined a new astroglial exosome-dependent mechanism for promoting axon growth of primary cortical and spinal

(motor) neurons. RNA-seq analysis of gene expression changes in cortical neurons following astroglial exosome treatment showed a dramatic decrease in cholesterol synthesis pathways compare to control neurons. We then tested the hypothesis that astroglial exosomes carry lipids such as cholesterol that can be uptaken by neurons to facilitate neuronal axon growth. In contrast to our hypothesis, direct treatment of cortical neurons with cholesterol, high-, or low-density lipoproteins (HDL or LDL) have no stimulatory effects on axon growth. In the CNS, Apolipoprotein E (ApoE) is a major transporter of extracellular lipids and cholesterol by binding to its receptor LDLR to transfer lipid to recipient cells. Consistently, direct treatment of human ApoE or other Apolipoproteins (ApoB or ApoJ) also has no stimulatory effect on neuronal axon growth. Co-treatment of astroglial exosomes with RAP, a selective LDLR inhibitor, has no effect on astroglial exosome-mediated stimulation on axons. Surprisingly, Astroglial exosome-induced axon growth is completely inhibited when ApoE is added together with astroglial exosomes onto cortical neuronal cultures. This inhibitory effect appears to be specific to ApoE but not to other Apolipoproteins. In addition, all commonly known human ApoE isoforms ApoE 2, 3, and 4 are able to equally inhibit astroglial exosome-induced axon growth. Immunoblotting of ApoE also showed that more than 98% of astroglia secreted ApoE is expressed in exosome-free astrocyte conditioned medium (ACM). Consistently, mixture of exosome-free ACM is able to completely abolish the stimulatory effect of astroglial exosomes on neuronal axon growth. Taken together, our study uncovered a new inhibitory interaction between astroglia secreted ApoE and neuronal protective effect of astroglial exosomes, providing a new insight on astroglial modulation of neuronal functions in the CNS.
Key words: Astroglia, ApoE, astroglial exosomes, axon

Disclosures: S. Jin: None. **R. Jarvis:** None. **V. Promes:** None. **Y. Yang:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P170.08

Topic: B.11. Glial Mechanisms

Support: NEURON-JTC2018-024, ERA-PerMed2018-127

Title: Pyramidal cell myelination is region-dependent and predicted by local axonal morphology in mouse and human neocortex

Authors: *M. PASCUAL-GARCIA[1], S. HIJAZI[1], M. A. W. UNKEL[1], J. A. SLOTMAN[2], A. BOLLEBOOM[3,4], B. L. J. BOUWEN[3,4], A. B. HOUTSMULLER[2], C. M. F. DIRVEN[4], Z. GAO[3], S. A. KUSHNER[1];
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Abstract: Myelin enhances axonal conduction velocity and provides metabolic support to neurons. The myelination profile of pyramidal cells is highly diverse and depends on their electrical activity and long-range connectivity. However, there is still insufficient knowledge about the cellular determinants underlying the distribution of internodes along the axon of neocortical pyramidal cells. Our recent studies of fast-spiking interneurons have shown that local axonal morphology is highly predictive of segmental

myelination. Whether pyramidal cell myelination adheres to similar parameters or other mechanisms are involved, is yet to be determined. Here, using wild type and tuberous sclerosis complex 1 (*TSC1*) floxed mice, we investigated the relationship between pyramidal cell axonal morphology and myelination in layer II/III of mouse somatosensory and prefrontal cortices. We performed whole-cell patch-clamp recordings together with biocytin labelling and structured illumination microscopy (SIM). Next, we measured the axonal diameter and interbranch distance of myelinated and unmyelinated segments along layer II/III pyramidal cell axons. Using receiver-operating characteristic (ROC) analysis, we found that the joint combination of axonal calibre and segment length was strongly predictive of segmental myelination, and a better predictor than either parameter alone. The optimal predictive thresholds for axonal diameter and interbranch distance in the somatosensory cortex of wild-type mice were 237 nm and 19.7 µm, respectively (AUC 0.98). In the prefrontal cortex, we found that few pyramidal cells were myelinated at the same neurodevelopmental time point (postnatal weeks 8 - 12). Conversely, enlargement of pyramidal cells by local viral Cre recombinase-mediated cell-specific deletion of *TSC1* robustly increased axonal myelination in the prefrontal cortex. Lastly, we confirmed that these findings extend to human *ex vivo* neurosurgically resected tissue, in which the optimally predictive thresholds for pyramidal cell axonal diameter and interbranch length were 269 nm and 19.0 µm, respectively (AUC 0.91). Similar to neocortical fast-spiking interneurons, local axonal morphology of pyramidal cells appears to explain a substantial proportion of the variance underlying segmental myelination and might function as a causal biophysical constraint for oligodendrocytes to initiate axonal myelination.

Disclosures: M. Pascual-Garcia: None. **S. Hijazi:** None. **M.A.W. Unkel:** None. **J.A. Slotman:** None. **A. Bolleboom:** None. **B.L.J. Bouwen:** None. **A.B. Houtsmuller:** None. **C.M.F. Dirven:** None. **Z. Gao:** None. **S.A. Kushner:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

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Topic: B.11. Glial Mechanisms

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Indiana Wesleyan University Hodson Research Institute Award
Indiana Wesleyan University University Scholar Award

Title: ATP-mediated H+ efflux from cultured mammalian astrocytes: a role for monocarboxylate transport.

Authors: *M. KREITZER[1], ***M. KREITZER**[1], R. LEININGER[1], R. MERILLAT[1], R. P. MALCHOW[2]; [1]Indiana Wesleyan Univ., Marion, IN; [2]Dept. Biol. Sci. & Ophthalmology, Univ. of Illinois at Chicago Dept. of Biol. Sci., Chicago, IL

Abstract: Alterations in H+ levels can profoundly impact synaptic transmission by regulating neurotransmitter release, removal of neurotransmitter from synaptic cleft, and post-synaptic receptor

activation. We have previously reported that low micromolar levels of extracellular ATP induce a significant increase in extracellular H+ flux from Müller cells isolated from the retinae of tiger salamanders and other vertebrates, including human. The ATP-induced acidification in Müller cells is mediated by activation of purinergic receptors, leading to calcium release from internal stores and activation of sodium/hydrogen exchange (NHE). Cryopreserved mammalian astrocytes from the cortex and hippocampus of rat can also be provoked by exogenous ATP to release H+ via activation of a purinergic receptor, and H+ release from these cells also depends on release of intracellular calcium. Here we report further observations on H+ fluxes from cultured mammalian astrocytes using H+-sensitive self-referencing microelectrodes (see Tchernookova et al., 2018 and Choi et al., 2021). Our observations suggest that only a small fraction of ATP-induced increases in H+ flux from astrocytes may be mediated by activation of NHE, based on the ability of 2 mM amiloride to partially reduced the increase in H+ efflux. An additional large contribution of ATP-mediated extracellular acidification appears to be mediated by activation of monocarboxylate transporters (MCT), which are expected to co-transport H+ along with lactate (or other substrates) out of the cells. The monocarboxylate transporter inhibitor 4-cin (1 mM) significantly reduced 100 μM ATP-mediated increases in H+ efflux from both cortical and hippocampal astrocytes. Also, we detected extracellular akalinizations around astrocytes following extracellular application of 10 mM lactate, which would be expected to result in the inward movement of lactate and H+ into the cells. These observations lend support for a significant role of MCT transporters in mediating ATP-elicited changes in extracellular H+ from astrocytes. Given the very high sensitivity of synaptic transmission to extracellular H+, we hypothesize that ATP-mediated extrusion of H+ from astrocytes (and glia more broadly) may play a key role in regulating signaling at synapses within the nervous system.

Disclosures: M. Kreitzer: None. **R. Leininger:** None. **R. Merillat:** None. **R.P. Malchow:** None.

Poster

P170. Glia-Neuron Interactions in Physiology II

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Program #/Poster #: P170.10

Topic: B.11. Glial Mechanisms

Support: NIH R01 NS113565
ALSA 20-PDF-510

Title: Norrin modulates neuronal network communication and synaptic biology via a cortical astrocyte-subgroup signaling pathway

Authors: *E. G. THOMPSON, S. VIDENSKY, T. WESTERGARD, J. D. ROTHSTEIN;
Neurol., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Astrocytes are the most abundant cell type in the central nervous system (CNS) and are essential for brain function. As such, astrocytes play critical roles in ionic and glutamate balance, providing metabolic support to neurons, and regulating neuronal communication. In recent years there has been a newfound appreciation for the heterogeneity of astrocytic functions within sub-regions of the brain

and the emergence of astrocyte subtypes. Our group recently identified one such subpopulation of astrocytes in the cerebral cortex that can be distinguished based on the expression of alternative Wnt receptor ligand Norrin. While previously Norrin has been studied as a protein critical for vascular development in the retina and as a driver of the rare neurodevelopmental genetic disorder Norrie Disease (ND), the characterization of Norrin's effects within the cerebral cortex has been limited in breadth. We found that the selective expression of Norrin in astrocytes within layer II/III and V of the adult cerebral cortex influenced neural network communication and synaptic structure. Specifically, adult Norrin-null (Ndp-/-) animals had a significant decrease in synaptic length and density, that accompanied behavioral deficits. *In vitro* experiments also demonstrated that Norrin significantly increased firing frequency and neuron connectivity in primary cortical neuron cultures when evaluated with multi-electrode array (MEA) analysis. Moreover, we found that Norrin modulates the expression of various synaptic components *in vitro* and *in vivo*. We also generated two novel mouse models of ND that carry the human equivalent of the V43E and H41X *NDP* mutations for evaluation of cortical elements in ND. Initial characterization of these mice has revealed synaptic structure abnormalities and behavioral deficits that recapitulate the human disease. Collectively, these findings suggest that astrocyte-derived Norrin plays a significant modulatory and functional role within the cerebral cortex neuronal network.

Disclosures: E.G. Thompson: None. **S. Vidensky:** None. **T. Westergard:** None. **J.D. Rothstein:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P174.01

Topic: B.12. Demyelinating Disorders

Support: Midwestern University Faculty Startup Fund
Midwestern University One Health Stimulus Research Award

Title: Exploring the role of microglia during CNS demyelination in the DTA mouse model

Authors: S. SINGH[1], M. RIITANO[1], H. ZHANG[2], *M. TRAKA[1,2];
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Abstract: To investigate the demyelination and remyelination processes in the central nervous system (CNS), we have developed the *DTA* mouse model that specifically targets the ablation of oligodendrocytes by activating the expression of the diphtheria toxin A subunit (DT-A) in these cells through tamoxifen injections into young adult *PLP/CreER^T;ROSA26-eGFP-DTA* (*DTA*) mice (Traka et al., 2010). The tamoxifen-treated *DTA* mice develop severe neurological symptoms by 35 days post-induction (dpi) that correlate with widespread oligodendrocyte death and demyelination in the CNS. Remarkably, these animals fully recover from disease symptoms and they display extensive oligodendrocyte replenishment and widespread remyelination of the demyelinated areas by adult oligodedrocyte progenitor cells (OPCs) at approximately 70 dpi. Given the robust remyelination potential of the young adult tamoxifen-treated *DTA* mice, it is unclear why remyelination fails in CNS

demyelinating diseases such as multiple sclerosis (MS). Microglia are the resident macrophages of the CNS that have been shown to be beneficial for remyelination in various myelin mutants by clearing the inhibitory myelin debris and by secreting cytokines that promote the differentiation and maturation of OPCs. Nevertheless, microglia activation can also play a detrimental role in myelin repair. To better understand the role of microglia in CNS demyelinating diseases, we monitored disease progression and recovery in tamoxifen-treated *DTA* mice fed with PLX3397-chow or normal chow (controls), starting from 14 dpi and continuing till 35 dpi (n= 6 mice/group). PLX3397 is a small molecule CSF-1R inhibitor, that can cross the blood brain barrier and thus rapidly deplete microglia in mice fed with PLX3397-chow. Only male *DTA* mice were used in each group since females develop severe disease symptoms and they die by 21 dpi (Traka et al., 2010). Experiments and data analyses were blinded. Interestingly, our findings showed that microglia elimination in tamoxifen-treated *DTA* mice fed with PLX3397-chow slightly improved their recovery from disease symptoms as compared to control mice, indicating a potential negative role of microglia in CNS remyelination. Further studies on these mice are currently in progress.

Disclosures: S. Singh: None. **M. Riitano:** None. **H. Zhang:** None. **M. Traka:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Program #/Poster #: P174.02

Topic: B.12. Demyelinating Disorders

Support: National Institute Of Neurological Disorders And Stroke of the National Institutes of Health R21 NS098170
Kentucky Spinal Cord and Head Injury Research Trust 16-3A
NeuroCures Foundation, Inc.

Title: Astroglial CXCL12 regulates the demyelinating process and the response of oligodendrocyte progenitor cells

Authors: *T. CHU[1], W. ZENG[1], Y.-P. ZHANG[3], G. N. BARNES[2], C. B. SHIELDS[3], J. CAI[1];
[1]Pediatrics, [2]Neurol., Univ. of Louisville, Louisville, KY; [3]Norton Neurosci. Inst., Louisville, KY

Abstract: Multiple sclerosis (MS) is the most common demyelinating disorder with no cure to stop its progression. Oligodendrocyte progenitor cell (OPC) response and glial network communication determine the pathogenesis of MS. As a vital chemokine, CXCL12 is significantly increased in reactive astrocytes within MS plaques. Little is known about its roles in glial interaction and how it affects the demyelinating process. This study is to reveal its mechanism in astrocyte-OPC interaction, which may offer promising therapeutic targets to modulate lesion microenvironment and alleviate demyelination. To examine the spatiotemporal change of CXCL12 expression during the demyelination-remyelination process, focal demyelination was induced by microinjecting lysophosphatidylcholine into the dorsal funiculus of spinal cord in female C57BL/6J mice. CXCL12 expression was up-regulated at the demyelinating and initial-remyelinating stages, and returned back to the normal when remyelinated. CXCL12 was expressed primarily by astrocytes and by microglia/macrophages (M/M) at a relatively low

level, while its receptor CXCR4 was widely expressed in all glial cells. To reveal the roles of astroglial CXCL12, we created $GFAP^{creER}$;$CXCL12^{fl/fl}$ mice to selectively ablate CXCL12 from astrocytes after tamoxifen administration. CXCL12 was sharply diminished in $GFAP^{creER}$;$CXCL12^{fl/fl}$ mice during the demyelinating process, confirming that astrocyte is mainly responsible for CXCL12 synthesis. Demyelination was alleviated as accessed by the reduction in lesion area and the improvements in fine sensorimotor function and somatosensory evoked potential. Astroglial CXCL12 deletion also reduced the recruitment of OPCs. We therefore generated $Pdgfr\alpha^{creER}$;$CXCR4^{fl/fl}$ mice to specifically delete CXCR4 from OPCs. Consistently, OPC recruitment was greatly disrupted with fewer OPCs distributed along the lesion. These evidences indicate that astroglial CXCL12 is a major chemokine that recruits OPCs via CXCR4. Moreover, we created $GFAP^{creER}$;$CXCR4^{fl/fl}$ mice to explore astrocyte self-activation via CXCR4 based on the finding of reduced Brdu-labelled astrocytes after astroglial CXCL12 deletion. Demyelination was alleviated and astrocytic proliferation was limited when CXCR4 was ablated from astrocytes, suggesting a feedback loop in astrocyte activation that exacerbates myelin damage. These findings suggest that therapies designed to regulate CXCL12-driven responses of astrocyte and OPC, as well as their interactions, may ameliorate neurological impairments by alleviating demyelination and restraining astrogliosis.

Disclosures: T. Chu: None. **W. Zeng:** None. **Y. Zhang:** None. **G.N. Barnes:** None. **C.B. Shields:** None. **J. Cai:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P174.03

Topic: B.12. Demyelinating Disorders

Title: Selective oligodendrocyte ablation in the optic nerve induces deficits in nerve function and altered retinal connectivity

Authors: *A. BALRAJ, R. H. MILLER;
Anat. & Cell Biol., George Washington Univ., Washington, DC

Abstract: The survival of individual neurons within neural networks is dependent on successful signal propagation. In white matter tracts like the optic nerve, the myelin sheath provides critical insulation for axonal conduction and when disrupted, can result in the block or delay of neural signals. Because optic neuritis, characterized by the inflammation and demyelination of the optic nerve, results in persistent visual deficits and thinning of retinal layers, we hypothesize that demyelination disrupts normal axonal signaling in retinal ganglion cells (RGCs) and drives changes in upstream retinal network connectivity. In the MBP-iCP9 transgenic, the myelin basic protein (MBP) promoter drives expression of an inducible caspase 9 (iCP9) sequence and a DsRed reporter. Eye injection of the chemical inducer of dimerization (CID) results in the selective apoptosis of oligodendrocytes and subsequent demyelination with minimal inflammation. MBP-iCP9 mice were injected at P14 with either CID or vehicle (EtOH/PBS) for three consecutive days. Two weeks post-injection, oligodendrocyte ablation and retinal cell density were quantified by immunohistochemistry. Optic nerves were assessed using an ex vivo extracellular recording

method, where electrical stimulation induces simultaneous action potentials of RGC axons, generating a compound action potential (CAP) waveform. Axon populations with distinct conduction speeds were identified as peaks. Within-nerve controls used tetrodotoxin to eliminate the stimulus artifact. A significant loss of oligodendrocytes, identified as DsRed+ CC1+ cells (n>5, p=0.0433), was observed in CID-treated nerves when compared to controls (vehicle or non-injected nerves). The number of functional axons, measured as the CAP area, was lower in CID-treated mice (n>3). The slow-conducting axon populations present in control responses, were absent in CID-injected ones, however the fastest-conducting populations were maintained. Comparison of the corresponding retinas of CID-injected and control nerves demonstrated a significant loss of Brn3a+ cells in CID-treated mice (n>4, p=0.0243). The oligodendrocyte loss and demyelination in the MBP-iCP9 transgenic was sufficient to block normal axonal conduction in a subset of RGC axons and preferentially affected the slowest-conducting axons. Loss of alpha-retinal ganglion cells suggests that functionally-relevant demyelination can impact the survival of individual neurons and disrupt upstream network connectivity. Future studies to characterize affected retinal cell types will identify susceptibility to demyelination-induced damage and cell death.

Disclosures: A. Balraj: None. **R.H. Miller:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P174.04

Topic: B.12. Demyelinating Disorders

Support: R01NS095884

Title: Developing an in vitro model of Autosomal Dominant Leukodystrophy using patient-derived induced pluripotent stem cells

Authors: *T. DEFRANCESCO-ORANBURG[1], Q. S. PADIATH[2];
[1]Human Genet., [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Autosomal Dominant Leukodystrophy (ADLD) is an adult-onset demyelinating disease with no cure. Tandem duplications involving the *LMNB1* gene (ADLD-dup) and deletions upstream of *LMNB1* (ADLD-del) have been identified in ADLD patients. These mutations lead to overexpression of the ubiquitously expressed nuclear lamina protein, laminB1. Why the overexpression of a ubiquitously expressed protein such as laminB1 should cause a specific demyelination phenotype remains unknown. A mouse model in which *LMNB1* overexpression is driven specifically in oligodendrocytes, the myelinating cells of the central nervous system (CNS), shows a similar phenotype to ADLD patients, including vacuolar degeneration of the spinal cord. Using luxol fast blue, we have found that in these mice peripheral myelin is also affected, presumably due to *LMNB1* overexpression being driven by a promotor that is also expressed by Schwann cells, the myelinating cells of the peripheral nervous system. These data suggest that oligodendrocytes are not uniquely susceptible to the effects of laminB1 overexpression. Further, peripheral myelin is not affected in ADLD patients suggesting a disease mechanism that targets *LMNB1* overexpression to CNS cell types including oligodendrocytes. Since these CNS tissues cannot be

studied in living patients, we are utilizing induced pluripotent stem cells (iPSCs) from patients with the different classes of mutations. We have shown that the known *LMNB1* expression levels and genotypes at a single nucleotide polymorphism (SNP) in the region are maintained in these cells, thus they prove to be a valid and accurate *in vitro* model. We have shown that we can use CRISPR-Cas9 to correct the tandem duplication and restore *LMNB1* levels to normal. To assess cell specificity, we are differentiating these patient-derived iPSCs into neurons, astrocytes, and oligodendrocytes, and assessing *LMNB1* expression. This in vitro model will prove critical in identifying a cell specific mechanism that leads to disease and establish a platform in which to evaluate personalized medicine therapeutic options for these patients.

Disclosures: T. DeFrancesco-Oranburg: None. **Q.S. Padiath:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Program #/Poster #: P174.05

Topic: B.12. Demyelinating Disorders

Support: R01NS088627
R01NS110949
R01NS112144)

Title: Monocyte infiltration underlies sexual dimorphism in neuromyelitis optica pathogenesis

Authors: *T. CHEN, V. A. LENNON, L.-J. WU;
Mayo Clin., Rochester, MN

Abstract: Neuromyelitis Optica (NMO) is an inflammatory autoimmune demyelinating disease of the central nervous system. Women are more prone to develop NMO. However, the mechanism of sex difference in NMO is still unclear. We recently developed a new murine model which continuously infuses AQP4-IgG intrathecally and induces NMO liked pathology and motor impairment (Chen et al., JCI, 2020). Interestingly, we observed AQP4-IgG infusion causes more substantial functional impairment in female mice when compared with males. The pathological investigation indicated that AQP4 loss and astrocyte activity have no difference between male and female mice after AQP4-IgG injection, indicating similar AQP4 internalization and astrocyte reactivity in both sexes. However, $Iba1^{+}$ microglia/macrophages are much abundant in females than in male mice after AQP4-IgG infusion. Using CyTOF mass cytometry technology, we found that monocytes number dramatically increased in female AQP4-IgG recipients, not males. Consistently, monocyte depletion in female mice but not in males significantly reduced the motor impairment, indicated that AQP4-IgG induced monocyte infiltration is female-specific. Finally, in female mice with ovariectomy, AQP4-IgG infusion induced less monocyte infiltration and better motor function. In summary, our results revealed that monocyte infiltration underlies sex dimorphism in NMO pathogenesis and suggest monocyte a potential target for NMO therapeutic intervention.

Disclosures: T. Chen: None. **V.A. Lennon:** None. **L. Wu:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Program #/Poster #: P174.06

Topic: B.12. Demyelinating Disorders

Support: Fundación Ramón Areces (Ref. CIVP9A5928)
MICINN (PID2019-105218RB-I00)

Title: Clonal NG2-Cell Response and Proteomic Profile in Two Experimental Models of Multiple Sclerosis

Authors: *S. BARRIOLA[1], L. M. DELGADO-GARCÍA[2,1], N. SALVADOR[1], E. LÓPEZ MARTÍNEZ[1], A. C. OJALVO-SANZ[1], R. SÁNCHEZ-GONZÁLEZ[1], L. LÓPEZ-MASCARAQUE[1];
[1]Inst. Cajal, Madrid, Spain; [2]Lab. of Mol. Neurobio., Univ. Federal de São Paulo, São Paulo, Brazil

Abstract: Multiple sclerosis (MS) is an autoimmune and neurodegenerative disorder of the central nervous system (CNS). The variability in the pathophysiology of this disease makes difficult its study. Nevertheless, the use of different animal models gives a more holistic comprehension of this disease. Here we used both the experimental autoimmune encephalomyelitis (EAE) and toxin-induced demyelination by cuprizone (CPZ), to simulate the relapsing-remitting and the primary progressive MS courses respectively in human. NG2-glia, also known as oligodendrocyte precursor cells (OPC), are of great interest in demyelinating diseases due to their remyelination potential. Here we investigate their differential clonal response to CPZ and EAE brain lesions by combining the StarTrack, a genetic lineage-tracing tool, along with a single-cell morphometric cluster analysis. Data from the morphometric analysis allowed us to unravel different NG2-cells clusters categorized by morphological parameters related, not only to their ontogenic origin, but also to their changes due to the different demyelinating scenarios. In addition, to address the differential altered neural pathways, we compared the proteomic profile of EAE mice (during the disease peak), and CPZ mice (during the acute phase) in two different brain regions: somatosensorial cortex and spinal cord. Bioinformatics analysis revealed changes and protein regional differences between the EAE and CPZ models. In addition, the detailed morphometric analyses of NG2-glia clusters sheds light on the NG2-glia heterogeneity, relevant to deciphering the physiological role of these cells in response to MS.

Disclosures: S. Barriola: None. **L.M. Delgado-García:** None. **N. Salvador:** None. **E. López Martínez:** None. **A.C. Ojalvo-Sanz:** None. **R. Sánchez-González:** None. **L. López-Mascaraque:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Topic: B.12. Demyelinating Disorders

Support: NIH Grant 1R01NS107523-01

Title: Amino acid dependent metabolic reprogramming of microglia/macrophages regulates CNS remyelination

Authors: *M. BAYDYUK[1], J. HU[1], E. LI[1], H. WANG[1], S. H. WAKELIN[1], N. V. SHULTS[1], S. G. GYCHKA[2], J. K. HUANG[1];
[1]Biol., Georgetown Univ., Washington, DC; [2]Dept. of Pathological Anat., Bogomolets Natl. Med. Univ., Kyiv, Ukraine

Abstract: Successful remyelination in multiple sclerosis (MS) depends on resolution of pro-inflammatory microglia/macrophage activity in demyelinated lesions. In progressive forms of MS, inflammation and slow myelin degeneration persist leading to neurodegeneration and accumulating neurological disability. It remains unclear how proinflammatory microglia/macrophages prevent remyelination and whether strategies to reprogram activated microglia/macrophages to a pro-regenerative state would be beneficial to the repair process in MS. Here, using metabolomic analysis of lysolecithin-mediated focal demyelinated lesions in the mouse CNS, we show that amino acid levels were significantly increased following demyelination and returned to baseline during remyelination. The amino acid increase in demyelinated lesions was accompanied by the upregulation of Slc7a5, a neutral amino acid transporter, expressed in activated microglia/macrophages. Pharmacological inhibition of Slc7a5 activity or the conditional deletion of *Slc7a5* in microglia/macrophages dramatically decreased the expression of several pro-inflammatory markers including iNOS and Ly86 and phagocytic-related marker CD68 in lesions after demyelination. Moreover, blocking Slc7a5-mediated amino acid transport inhibited mTOR pathway in microglia/macrophages, resulting in significantly decreased appearance of amoeboid microglia/macrophages, while increasing the density of ramified, homeostatic microglia, marked by increased P2RY12 expression. Importantly, inhibiting Slc7a5 in microglia/macrophages led to increased density of mature oligodendrocytes and enhanced remyelination in focal lesion and cuprizone models of demyelination. Furthermore, we found that therapeutic administration of the Slc7a5 inhibitor in mice with experimental autoimmune encephalomyelitis (EAE) prevented the accumulation of clinical disability, reversed the course of the disease, and significantly improved motor function. Together, our results suggest that metabolic reprogramming of microglia/macrophages through Slc7a5-mediated mTOR activation regulates CNS inflammation in demyelinating lesions. Therefore, pharmacological inhibition of Slc7a5 may be a novel treatment option for preventing the expansion of chronic inflammatory lesions, allowing for endogenous myelin repair in progressive MS.

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Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

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Support: Hilldale Undergraduate/Faculty Research Fellowship
Nancy & Jean-Pierre Boespflug Foudation for Myopathic Research
SCRMC Postdoctoral Fellowship

Title: Gli2 regulates the recruitment of adult neural stem cells for remyelination via Slit2

Authors: *A. JOHNSON, D. RADECKI, E. CLAWSON, D. NIEVES-TORRES, J. SAMANTA; Univ. of Wisconsin, Madison, Madison, WI

Abstract: Enhancing repair of myelin is an important therapeutic goal in many neurological disorders characterized by demyelination. In the healthy adult brain, ventral neural stem cells (vNSCs) residing in the subventricular zone, marked by Gli1 expression, do not generate oligodendrocytes. However, in response to demyelination, their progeny are recruited to lesions where they differentiate into oligodendrocytes, and ablation of Gli1 further enhances remyelination. Genetic ablation of Gli1 in vNSCs also increased Gli2 expression, and combined loss of both transcription factors decreased the recruitment of their progeny in demyelinated lesions, suggesting that Gli2 plays an essential role in recruitment of Gli1 vNSCs to the demyelinating lesion. To understand the molecular mechanisms involved in recruitment of vNSC to the demyelinating lesion, we performed an RNAseq analysis to compare the genes expressed in vNSCs expressing Gli1 to those lacking Gli1 expression following demyelination. Through this analysis, we identified Slit2 as a positive regulator of recruitment of vNSCs since it was significantly upregulated in vNSCs in the absence of Gli1 expression. Consistently, expression of Slit2 was reduced in the subventricular zone following demyelination and genetic loss of Gli1 prevented this reduction. Furthermore, pharmacological inhibition of Gli2 in vNSCs in vitro resulted in downregulation of Slit2 expression. Slit2 is a ligand that interacts with Robo receptors on the cell surface to induce a signaling cascade leading to an upregulation of actin polymerization genes and increased cell migration. Thus, our data indicate that, loss of Gli1 induces Gli2 expression which in turn enhances the recruitment of vNSCs to the demyelinating lesion by upregulating Slit2. This could lead to development of therapeutic strategies for enhancing remyelination by regulating the recruitment of vNSCs.

Disclosures: A. Johnson: None. **D. Radecki:** None. **E. Clawson:** None. **D. Nieves-Torres:** None. **J. Samanta:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P174.09

Topic: B.12. Demyelinating Disorders

Support: MS Society of Canada (MSSOC) postdoctoral fellowship

Title: Ferroptosis, an iron-dependent form of cell death in chronic experimental autoimmune encephalomyelitis

Authors: *P. JHELUM, J. ZARRUK, S. DAVID;
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Abstract: A relatively new form of regulated, non-apoptotic cell death called “ferroptosis” was identified first in cancer and recently in various neurodegenerative diseases. Ferroptosis requires iron-mediated free radical generation that triggers lipid peroxidation in the absence of sufficient levels of the antioxidant glutathione. Oxidative stress and iron toxicity play a key role in the Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE), an animal model used to study MS. We, therefore, assessed if ferroptosis plays a role in EAE. Previously, we reported on the role of ferroptosis in cuprizone (CZ) -induced demyelination in mice. We found that CZ-induced oligodendrocyte (OL) cell death is seen as early as 2 days after the start of CZ diet, which was accompanied with the expression of several markers of ferroptosis. In addition, treatment with ferrostatin-1 (a ferroptosis inhibitor) prevents this loss of OL and demyelination. Currently, we assessed the mRNA expression of several ferroptosis markers in the spinal cord tissue of both relapsing-remitting (RR-EAE) and chronic EAE (CH-EAE) mice. We found that the expression of ACSL4, ACSF2, IREB2, TfR1, and NCOA4 is greater in CH-EAE compared to RR-EAE. Expression of NCAO4, a cargo receptor that shuttles ferritin to autophagosome for degradation (ferritinophagy) and releasing redox-active iron is also increased in CH-EAE. We also found an increase in lipid peroxidation (a hallmark of ferroptosis) as assessed by 4HNE at the peak and progressive stages of CH-EAE. Importantly, treatment with UAMC-3203 (inhibitor of ferroptosis) started at the peak of disease (grade3) improved clinical outcome and reduces lesion volume in CH-EAE. These results provide strong evidence that ferroptosis plays a role in CH-EAE.

Disclosures: P. Jhelum: None. **J. Zarruk:** None. **S. David:** None.

Poster

P174. Demyelinating Disorders: Molecular and Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P174.10

Topic: B.12. Demyelinating Disorders

Support: Charcot Marie Tooth Association
Muscular Dystrophy Association

Title: Axonal proteomic profiling in mouse models of X-linked Charcot Marie Tooth Disease

Authors: D. D. LOIZZO[1], *M. M. FREIDIN[2], E. LANCASTER[3], J. LI[3], S. S. SCHERER[3], C. K. ABRAMS[1];
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Abstract: X-linked Charcot Marie Tooth Disease (CMT1X) is associated with hundreds of mutations in *GJB1*, the gene encoding the gap junction forming protein connexin 32 (Cx32). Cx32 is a component of

the myelin sheath and localizes to the paranodes and Schmidt-Lanterman incisures of myelinating Schwann cells. Though Cx32 is expressed only in the Schwann cell in the peripheral nervous system, CMT1X is characterized by early and prominent axonopathy, and the mechanism by which disruption or loss of Cx32 leads to CMT1X neuropathy is poorly understood. Study of both the phenotype in patients with CMT1X and in animal models generated in our laboratory and by others, suggest that most if not all mutations in Cx32 lead to loss of function of Cx32. We used CRISPR/Cas-9 technology to generate targeted transgenic mice expressing the p.T55I or p.R75W mutations in *Gjb1*. These mutations lead to abnormal accumulation of Cx32 in the Golgi (p.R75W) or ER (p.T55I) and represent the observed abnormal subcellular distributions of Cx32 for at least half of the mutations known to cause CMT1X. Phenotypic profiling of these mice showed that they are authentic models of CMT1X. We then employed a label-free quantitative proteomic profiling of axons isolated from sciatic nerve of age-matched Cx32T55I- and Cx32R75W-CRISPR mutant mice along with wild-type (WT) and *Gjb1*-knockout littermates to identify potential cellular functions altered in axons from CMT1X models. Analysis of differentially regulated proteins revealed changes in proteins involved in RNA processing, axon regeneration, and other axonal cellular functions. Candidate proteins from the quantitative proteomic analysis are currently being studied for transcriptional differences in spinal cord, sciatic nerve, and dorsal root ganglia of WT and mutant mice. Our work illustrates that loss or mutation in Cx32 leads to axonal changes in protein expression, enhancing our understanding of underlying mechanisms of regulating the neuropathy associated with CMT1X, and should lead to improved ability to design potential therapeutics for patients.

Disclosures: D.D. Loizzo: None. **M.M. Freidin:** None. **E. Lancaster:** None. **J. Li:** None. **S.S. Scherer:** None. **C.K. Abrams:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.01

Topic: B.13. Neuro-Oncology

Support: This work was fundend by “Consejo Nacional de Salud y Cerveza de México, SA”
The student Rubén Figueroa Rosales receives a scholarship by CONACYT, No. 2021-000001-01NACF-10904, CVU = 1108781

Title: The cytotoxic effect of hops α-iso-acids-Rho in human glioma cell lines

Authors: *R. FIGUEROA-ROSALES[1,2], F. PERALTA-GONZALES[1], A. SALAZAR-RAMIRO[1], V. PEREZ DE LA CRUZ[3], B. PINEDA OLVERA[1];
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Abstract: Glioblastoma is the most frequent malignant tumor of the central nervous system (CNS) and the over-all survival has not increased significantly since the introduction of standard of care therapy at

the beginning of the Century. The search of new therapeutics with anti-carcinogenic effects is of vital importance to improve the quality of life of patients. Hops α-iso-acids are one of the principal bitter compound present in beer and it gives its signature taste. Prior studies had showed it promising bioactive potential and potent cytotoxic activity. In the present work we evaluate the possible induction of cytotoxicity by α-iso-acids-rho over human glioma cell lines U87, U373, LN18 and A172 by MTT reduction assay. Each assay was carried out in triplicate and three repetition of each experiment were performed. The IC_{50} at 72 hrs were calculated for U87 = 20.040 ± 1.990 µg/mL; U373 = 27.190 ± 3.565 µg/mL; LN18 = 7.598± 1.129 µg/mL; A172 = 23.560 ± 5.542 µg/mL. All statistical analysis were made using GraphPad Prism 8. Our result are similar to those reported in literature in other cancer cell lines and gives us the proof of concept where this bioactive compounds could be explore further as potent anticarcinogenics in the CNS.

Disclosures: R. Figueroa-Rosales: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was fundend by "Consejo Nacional de Salud y Cerveza de México, SA". **F. Peralta-Gonzales:** None. **A. Salazar-Ramiro:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was fundend by "Consejo Nacional de Salud y Cerveza de México, SA". **V. Perez De La Cruz:** None. **B. Pineda olvera:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was fundend by "Consejo Nacional de Salud y Cerveza de México, SA".

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.02

Topic: B.13. Neuro-Oncology

Title: Mitochondrial metabolic efficiency as a requirement for the proliferation of glioblastoma multiforme cells

Authors: H. BAE[1], A. M. MILLET[1], M. TSUJISHITA[1], G. GUL[1], N. MACHARD[1], G. NOSOVITSKAYA[1], T. S. TIERNEY[1], P. J. S. SMITH[2], *K. N. ALAVIAN[1];
[1]Dept. of Brain Sci., Imperial Col. London, London, United Kingdom; [2]Inst. for Life Sci., Univ. of Southampton, Southampton, United Kingdom

Abstract: Gliomas are among the most common and deadly brain tumors. Current therapeutic methods, including surgery, radiation, and chemotherapy, fail to yield a significant clinical outcome in the malignant types of this disease, including adult and pediatric glioblastoma multiforme (GBM). A prominent feature of cancer cells, including these aggressive tumors, is their high metabolic demand and their reprogramming of energy metabolism. De novo ATP production through mitochondrial oxidative

phosphorylation and production of the intermediates of the tricarboxylic acid cycle, required for anabolic growth, are both dependent on the generation of an electrochemical gradient of protons across the mitochondrial inner membrane and are modulated by the mitochondrial inner membrane ion leak currents. The evidence for the involvement of mitochondrial "efficiency" (as a requirement) for the growth of cancer cells has been lacking. Here we demonstrate a direct role for mitochondrial efficiency, modulated by the anti-apoptotic molecule, Bcl-XL, and the mitochondrial inner membrane leak currents in the proliferation of GBM cells. We also demonstrate the potential for the use of this mechanism as a druggable therapeutic target for GBM.

Disclosures: H. Bae: None. **A.M. Millet:** None. **M. Tsujishita:** None. **G. Gul:** None. **N. MacHard:** None. **G. Nosovitskaya:** None. **T.S. Tierney:** None. **P.J.S. Smith:** None. **K.N. Alavian:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.03

Topic: B.13. Neuro-Oncology

Title: Rfx1 is a potential target of hypoglycemic drugs to affect cell growth and migration in glioblastoma cells

Authors: *Z. ZUO[1], **W. SHAN**[2];
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Abstract: Regulatory factor X1 (RFX1), a transcription factor, is a member of the regulatory factor X family. Our previous studies have found that RFX1 play an important role in glioblastoma development. But about how RFX1 is regulated is still unknown. From NCBI Gene Expression Omnibus (GEO) Profiles, we found that three hypoglycemic drugs (pioglitazone, rosiglitazone and WY-14643) might regulate the expression of RFX1. In this study, we tested that RFX1 contributed to the effects of these three hypoglycemic drugs on the proliferation, survival, invasion and migration of glioblastoma cells. The human glioblastoma U251 and U87 cells were incubated with various concentrations of pioglitazone, rosiglitazone and WY-14643 for 72 hours in the presence or absence of siRNA for RFX1. They were then used for assays of cell growth, survival, invasion and migration. Western blotting analysis of RFX1 expression and matrix metallopeptidase 2 (MMP2) activity assay were performed. We found that the growth, survival, migration and invasion of glioblastoma cells were inhibited by the three hypoglycemic drugs. The expression of RFX1 were elevated after treatment of three drugs. MMP2 activity in the U251 and U87 cells was inhibited after treatment with these three drugs, the inhibitory function was blocked when co-cultured with siRNA of RFX1. And also, the hypoglycemic drugs' inhibitory effects on the growth and invasion of glioblastoma cells were eliminated by siRNA of RFX1. To validate the *in vitro* results, U87 cells were implanted into mouse brain and these mice were treated with 5 mg/kg pioglitazone for 8 days before used for immunofluorescence staining. Dual luciferase assay was performed and showed that the three hypoglycemic drugs boosted RFX1 promoter activity. Our results suggest that pioglitazone, rosiglitazone and WY-14643 inhibit the cancer cell behaviors of glioblastoma cells through

RFX1. MMP2 is a potential target of RFX1 to inhibit the migration of glioblastoma cells. RFX1 is a potential target for treating glioblastoma.

Disclosures: Z. Zuo: None. **W. Shan:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

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Program #/Poster #: P179.04

Topic: B.13. Neuro-Oncology

Support: NIH Grant 5R01CA227149-03
Virginia Tech Carilion School of Medicine Student Research Stipend

Title: Reactivation of p53 plays a dual role in controlling glutamate pathophysiology in glioblastoma

Authors: *A. MINER[1], R. A. UMANS[2], H. SONTHEIMER[3];
[1]Virginia Tech. Carilion Sch. of Med., Roanoke, VA; [2]Fralin Biomed. Res. Inst., Roanoke, VA; [3]Sch. of Med., Univ. of Virginia, Charlottesville, VA

Abstract: Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and has an extremely poor prognosis with a median overall survival of 15 months. The cysteine-glutamate exchanger (system x_c^-, SXC) is upregulated in many GBM tumors, and overactive SXC results in high levels of extracellular glutamate linked to excitotoxicity, seizures, and enhanced tumor survival and invasion. SXC expression has been found to correlate with p53 mutation status, raising the possibility that p53 has a non-canonical role as a transcriptional regulator of the SXC gene *SCL7A11* and may be a more effective therapeutic target than the transporter itself. p53 restorative agents have emerged as a promising treatment for many cancers but their specific mechanism and utility in GBM has yet to be extensively explored. To better understand the mechanism behind system x_c^- regulation, we treated established patient-derived glioma xenolines with known wt-p53, mut-p53, and null-53 genotypes with the p53 restorative agent PRIMA-1^{MET} at a 30µM concentration for 48 hours. Trypan blue assays were used to assess cell survival and expression of putative targets were assessed via western blot. Glutathione levels and ROS staining were used as functional measures of SXC and redox activity. Treatment with PRIMA-1^{MET} resulted in significant glioma cell death independent of p53 mutation status, with a higher sensitivity in wt-p53 and null-p53 cell. Analysis of post-treatment samples did not show significant changes in p21 or SXC protein levels regardless of p53 status. PRIMA-1^{MET} induced cell death was fully rescued by exogenous glutathione in all cells lines and mut-p53 cells were found to express higher levels of enzymes involved in glutathione metabolism in comparison to wt-p53 and null-p53 lines. Measurement of endogenous glutathione production was decreased after PRIMA-1^{MET} treatment *in vitro*, but analysis of *in vivo* flank tumor samples did not show any significant changes. The observed effect of PRIMA-1^{MET} on glioma cells independent of p53 status suggests the existence of a primarily off-target mechanism of action for p53-restorative agents in glioma. Glutathione studies support the existence of alternative direct PRIMA-1^{MET} redox targets with a potential ROS-resistant phenotype associated with p53 mutation. This novel off-target mechanism holds implications for applicability of the drug class to a wider range of glioma patients

and the potential to modulate tumorgenicity through direct and indirect impacts on redox dynamics and tumor metabolism.

Disclosures: A. Miner: None. **R.A. Umans:** None. **H. Sontheimer:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.05

Topic: B.13. Neuro-Oncology

Title: Glial Scar Causing Drug Resistance and Inhibiting Glioblastoma Growth in a 3D Human Glioblastoma Microenvironment

Authors: *Y. N. DIEP[1,2], H. Y. KO[3], W. LIM[4], S. PARK[4,5], M. YUN[3], H. CHO[1,2];
[1]Inst. of Quantum Biophysics, Dept. of Biophysics, Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Dept. of Intelligent Precision Healthcare Convergence, Suwon, Korea, Republic of; [3]Dept. of Nuclear Medicine, Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [4]Dept. of Biomed. Engineering, Sungkyunkwan Univ., Suwon, Korea, Republic of; [5]Sch. of Mechanical Engineering, Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Glial scar formation is an innate immune response confining injured regions in a central nervous system. In the scar formation in response to glioblastoma (GBM), microglia (MG) are found both inside and outside the GBM tumor mass, while astrocytes (AC) mainly encapsulate the tumor. There are reports about the promotion of immunosuppressive environment and tumor aggressiveness induced by reactive astrocytes and microglia in brains. However, their role during scar formation is still under investigation. Here, we construct an in vitro 3D human GBM microenvironment reconstituting the glial scar formation. GBM spheroids were preformed and then co-cultured with glial cells (AC+MG) in 3D Matrigel. We found that activated AC formed a glial scar around GBM with linear-shaped morphology. Chemokines from GBM spheroids, such as CCL2, GM-CSF, G-CSF, and MIF, induced preceding microglial recruitment, followed by astrocytic scar formation. A wide spectrum of cytokines associated with tumor progression, invasion, and angiogenesis were also measured, such as IL-6, IL-8, and CXCL1. Activation markers, including GFAP for AC and CD206 (M2) for MG, were upregulated in our GBM microenvironment. We also validated that the glial scar significantly restricted the cross-sectional area of GBM spheroids by 2.2 times compared to GBM spheroids without the scar. Moreover, the scar encapsulation acted as a physical barrier limiting drug penetration into GBM spheroids and leading to the drug resistance, shown by a no significant reduction in the cross-sectional area of GBM spheroids with scar even with TMZ treatment, while those without the scar were decreased in area by 1.4 times. Taken together, our 3D human GBM microenvironment has a potential for understanding the gliosis process and the GBM-glia crosstalk, facilitating drug discovery targeting aggressive GBM.

Disclosures: Y.N. Diep: None. **H.Y. Ko:** None. **W. Lim:** None. **S. Park:** None. **M. Yun:** None. **H. Cho:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.06

Topic: B.13. Neuro-Oncology

Title: Investigation and regulation of TREM1-positive microenvironment in glioblastoma.

Authors: *N. FILIPPOVA, D. NAMKOONG, E. HAYWARD, X. YANG, B. NABORS;
Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: The harmful contribution of the uncontrollable inflammatory systematic immune response to the development of glioblastoma heterogeneity and recurrence is recognized in recent years and is likely associated with tumor infiltrated immunosuppressive myeloid-derived cells with activated TREM1-dependent cell signaling pathways. Infiltration of TREM1- positive cells to the glioblastoma microenvironment has a negative impact on the patient's overall survival according to the R2: platform. TREM1 appearance in the glioma microenvironment, along with the infiltration of myeloid-derived cells, is grade-dependent and enhanced with tumor grade. The weight of the TREM1- positive cells increases from 21.3% in primary GBM to 36.8% in the recurrent GBM that implies the TREM1-positive population of cells in tumor recurrence. We utilized two immunocompetent mouse glioblastoma models based on the intracranial injection of established mouse glioblastoma GL261 cell line and mouse TRP cell line of transformed astrocytes (truncated SV40 T antigen, Kras G12D mutation, Pten deletion) and performed isolation and analysis of tumor infiltrated immune cells; C57Bl/6 mice without tumor implantation were utilized as control. Our results suggest that the main sources of the TREM1-positive cells in the glioblastoma microenvironment consist of monocytes, macrophages that emerged from monocytes recruited to the tumor bed, neutrophils, and at a low degree activated resident microglia and endothelial cells. 70-90% of de novo formed tumor/host cell hybrids detected in the glioblastoma microenvironment acquire TREM1 expression. Such overwhelming selection of the TREM1-positive hybrid cells in the glioblastoma microenvironment could be explained i) by selective activation and migration of TREM1-positive peripheral immune cells to the ischemic and inflammatory tumor microenvironment favorable for cell fusion, ii) by selective survival of fussed cells acquiring TREM1 expression due to TREM1-dependent activation of anti-apoptotic Bcl2-family proteins and mitofusin molecules that support mitochondria function at stress conditions, iii) by TREM1- dependent local magnification of inflammatory cytokine cascade triggering fusogen expression and causing rearrangement of cytoskeletal architecture essential for cell fusion. We utilized recently developed by our group BBB permeable HuR dimerization inhibitor and found that the HuR inhibition was associated with a significant reduction of TREM1- positive glioblastoma microenvironment, cell fusion, and glioblastoma progression.

Disclosures: N. Filippova: None. **D. Namkoong:** None. **E. Hayward:** None. **X. Yang:** None. **B. Nabors:** None.

Poster

P179. Neuro-Oncology: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P179.07

Topic: B.13. Neuro-Oncology

Support: NIH Grant P20 GM103629

Title: Cytomegalovirus-induced metabolic reprogramming of glioblastoma cells disrupts lactate homeostasis and enhances the potential for paracrine manipulation of the tumor microenvironment

Authors: *M. A. A. HARRISON[1], E. M. HOCHREINER[2], B. P. BENJAMIN[2], S. E. LAWLER[3,4], K. J. ZWEZDARYK[2];
[1]Tulane Univ. Grad. Neurosci. Program, New Orleans, LA; [2]Tulane Univ., New Orleans, LA; [3]Neurosurg., Brigham and Women's Hosp., Boston, MA; [4]Neurosurg., Harvard Med. Sch., Cambridge, MA

Abstract: Glioblastoma (GBM) is an aggressive central nervous system neoplasia with limited therapeutic options and very poor prognosis. Following initial reports of cytomegalovirus (CMV) transcripts and proteins in and around GBM tumors, the use of anti-viral drugs in conjunction with the standard of care was shown to significantly increase longevity for GBM patients. A mechanism for the role of CMV in tumor progression has yet to be fully elucidated. We hypothesized that CMV infection induces metabolic reprogramming of GBM or the surrounding microenvironment and that these alterations may account for enhanced tumor progression. We infected LN-18 GBM cells with CMV and employed a Seahorse Bioanalyzer to characterize metabolic function. We observed increases in mitochondrial respiration and glycolysis relative to uninfected controls. Changes were accompanied by increased levels of reactive oxygen species and lactate, respectively. Increased intra- and extra-cellular lactate concentrations led us to investigate enzymes and transporters central to lactate homeostasis. We found increased levels of monocarboxylate transporter 4, a lactate exporter, following CMV infection. Extracellular lactate is a potent paracrine signaling molecule which can promote tumor progression in myriad ways. To examine the paracrine effects of CMV infected GBM cells we conducted indirect co-culture experiments using stromal cells. Our results indicate that, independent of viral transmission, the secretome of infected cells altered expression of metabolic proteins and epigenetic markers in neighboring cells. These results suggest a potential role for CMV as an oncomodulator in the context of GBM and the tumor microenvironment.

Disclosures: M.A.A. Harrison: None. **E.M. Hochreiner:** None. **B.P. Benjamin:** None. **S.E. Lawler:** None. **K.J. Zwezdaryk:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Education, Singapore, MOE AcRF Tier 3 Award MOE2017-T3-1-002

Title: Impaired hippocampal spatial coding in aging and neurodegenerative disease

Authors: *Y. FANG, G. J. AUGUSTINE;
Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore

Abstract: Spatial memory is degraded both in normal aging and in neurodegenerative diseases, such as Alzheimer's disease (AD). Spatial memory is encoded in hippocampal circuits, both via the activity of place cells as well as in neuronal ensemble activity. Although it is known that place cell properties are altered during aging and in AD, the effects of these processes on neuron ensemble encoding are unclear. We therefore characterized hippocampal spatial coding in both aged and AD disease model mice by performing *in vivo* two-photon calcium imaging of the activity of CA1 neurons while mice travelled on a treadmill. Bayesian decoding methods determined how accurately neuron ensemble activity could predict mice position; the degree of decoding error was used to quantify spatial coding in CA1 neuron ensembles. The effect of aging on spatial coding was examined by comparing spatial coding in young (4-6 months) and aged (13-15 months) mice. Young mice exhibited good spatial coding performance: neuron ensemble activity accurately decoded mouse position on the treadmill. However, aged mice had larger position decoding errors, indicating a decline in spatial encoding. We next characterized spatial coding in young and aged AD model mice. These mice had three human AD-related mutations knocked-into their amyloid precursor protein gene (APP-TKI; Nature Neurosci. 17: 661). An aging-related decline in spatial coding performance was also observed in APP-TKI mice. Further, in comparison to wild-type control mice, APP-TKI mice tended to have larger position decoding errors, a smaller fraction of place cell neurons, and wider place fields. Thus, spatial coding appears to be disturbed in APP-TKI mice. In summary, our results indicate that hippocampal spatial coding declines during aging and that this process is accelerated in AD.

Disclosures: Y. Fang: None. **G.J. Augustine:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1MH114103
1R01NS088958-01
BrainHub Postdoctoral Fellowship

Title: Pathway-specific increase in CA3 to CA1 synapses is associated with early hippocampal hyperactivity in a mouse model of Alzheimer's disease

Authors: *A. RAY[1], I. LOGHINOV[1], S. M. BERNHARD[2], D. A. KULJIS[3], A. L. BARTH[1];
[1]Carnegie Mellon Univ., PITTSBURGH, PA; [2]Dept. of Neurosci., Washington Univ. Sch. of Med., St. Louis, MO; [3]Dept. of Biol., Sacred Heart Univ., Fairfield, CT

Abstract: Late-stage Alzheimer's disease (AD) is characterized by progressive and broad synaptic loss and cell death across neural circuits. Pre-symptomatic changes in neural connectivity and function have been understudied, in part because of the difficulty of tissue collection in prospective studies in humans. However, both human and animal studies indicate that neuronal hyperexcitability and hyperactivity in the hippocampus are common features of preclinical AD, suggesting that there may be early changes in circuit connectivity that are associated with the disease. Here we used molecular-genetic methods for synapse labeling targeted to CA1 pyramidal neurons to assess progressive alterations in synapse distribution in the transgenic APP/PS1 mouse model of AD. Stereotaxic injections of virus encoding the pan-synaptic labeling reagent (FAPpost) were targeted to the dorsal hippocampal CA1 region, and synapse distribution between wild-type and transgenic mice was compared at three different ages. Digital reconstruction of fluorescently-labeled pyramidal cells and dendrites were carried out for quantitative synaptic analysis across dendritic and somatic compartments. Surprisingly, we found that CA1 pyramidal neurons showed a site-specific increase in the number of synapses in the apical dendritic compartment attributed to inputs from CA3 neurons from 3 to 6 weeks of age. Synapse density in the apical tuft of CA1 pyramidal neurons was decreased at 6 weeks, suggesting progressive modification of the hippocampal-entorhinal circuit over time. Analysis of aged transgenic animals (13-16 months) showed a uniform loss of synapses across all compartments. Expression of the activity-dependent transcription factor c-fos was enhanced in both CA3 and CA1 at 3 and 6 weeks of age, suggesting hyperactivity of the hippocampal circuit during early development. These data indicate that increase in AD-associated amyloid-β load in the APP/PS1 transgenic line is sufficient to drive aberrant circuit activity and connectivity, and suggest that early detection of abnormal circuit function may facilitate interventional strategies to delay or prevent AD.

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Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.03

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: NIGMS T32 GM008541
NIH/NIA R21AG056947
NIH/NIA R21 AG061553

Title: Tgf344-ad rats display differing levels of gabra5 transcript in single neurons of the ca1 during disease progression

Authors: *J. GEORGE, A. TIPTON, D. FARB, S. RUSSEK, V. KUMARESAN, M. RATNER; Boston Univ., Boston, MA

Abstract: In the United States, 5.5 million individuals suffer with Alzheimer's Disease (AD). This neurodegenerative dementia is characterized by a decline in cognition and the eventual lethal disruption

of all brain functions. There is no cure for AD and current treatments can only temporarily improve symptoms. The pharmacological administration via oral gavage of the cognitive enhancer a5IA, a negative modulator of the γ-aminobutyric acid A receptor ($GABA_AR$) that contains the α5 subunit, increases sharp wave ripple oscillations in wild-type rats but not in the transgenic AD (TgF344-AD) rat. TgF344 was created by injecting rat pro-nuclei with two human AD-associated genes: Swedish mutant human APP (APPsw) and Δ exon 9 mutant human presenilin-1 (PS1ΔE9). We hypothesize that the loss of sharp wave ripple modulation by a5IA in the TgF344-AD rat reflects a molecular reorganization of trisynaptic hippocampal function, which may contribute to deficits in memory consolidation over time. Determining the underlying mechanism of circuit reorganization will provide insight on AD and lead to the development of cognitive enhancers for the successful treatment of this debilitating disease, increasing the length and quality of life. Towards this goal, we used a novel fluorescent *in situ* hybridization technique, RNAscope, to interrogate the spatial expression of *Gabra5* in dissected brains of TgF344-AD and littermate control wild-type rats (Ct), n=4, at two different ages, 9mo and 16mo, to determine if there is a change in transcript abundance in the hippocampus. Our results show that in the CA1 of 16mo TgF344-AD rats, the expression of *Gabra5* across all neurons is decreased compared to Ct and 9 mo animals. Interestingly, 16mo TgF344-AD rats display a decrease in the average number of *Gabra5* transcripts per cell. This decrease in the amount of *Gabra5* containing neurons occurs in the 16mo TgF344-AD rats and not 9mo and was not due to an overall decrease in the number of CA1 neurons which did not change between groups, indicating that the decrease in *Gabra5*$^+$ neurons in the aged TgF344-AD rats was due to a decreased *proportion* of *Gabra5*$^+$ neurons in the CA1 population. In contrast, 9mo TgF344-AD rats presented with an increase in *Gabra5* when compared to Ct, suggestive of a homeostatic response to the beginnings of circuit dysfunction that we will be exploring in our ongoing studies using immunohistochemistry and immunoprecipitation to determine $GABA_AR$ subunit composition in select neurons of the TgF344-AD hippocampal formation.

Disclosures: J. George: None. **A. Tipton:** None. **D. Farb:** None. **S. Russek:** None. **V. Kumaresan:** None. **M. Ratner:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Early impairment of hippocampal synaptic plasticity in the TgF344-AD rat model for Alzheimer's disease

Authors: *Y. SUN[1], J. GIGG[2], M. HARTE[1];
[1]Div. of Pharm. and Optometry, [2]Div. of Neurosci. & Exptl. Psychology, Univ. of Manchester, Manchester, United Kingdom

Abstract: Hippocampal hyper-excitability has been associated with cognitive decline in early Alzheimer’s disease (AD). The TgF344-AD transgenic rat expresses age-dependent beta-amyloid (Aß) aggregation, tauopathy and neuroinflammation, becoming a useful AD model to study pre-symptomatic

changes in synaptic strength. Here, we sought to determine whether hippocampal excitability changes also occur in this model. For the first part of this study, in vivo evoked field excitatory post-synaptic potentials (fEPSPs) were recorded in the hippocampal CA3 to CA1 projection of the 9-month-old TgF344-AD (TG) and wild-type (WT) rats (males; n=8), to determine the induction properties for short- and long-term synaptic plasticity. Accordingly, the TG rats demonstrated diminished paired-pulse facilitation (PPF), as well as weaker long-term potentiation (LTP) following high-frequency stimulation (HFS) compared to the WT. Interestingly, TG rats also showed larger CA1 fEPSPs with an upwardly-shifted input-output (I/O) curve. These results indicate a baseline increase of presynaptic transmitter release in the hippocampal CA3 to CA1 synapse at this age; this synaptic hyper-excitability then limits the scope for induced synaptic plasticity. To determine whether changes can be seen at an earlier stage of pathology in the model, the same protocol for evoked fEPSPs was applied on the TG model at the younger age of 6 months when soluble Aß oligomers can first be detected (Cohen et al., 2013). As a preliminary result, these TG rats also showed significantly lower LTP after HFS compared to the control (males; n(WT)=6, n(TG)=7), but the magnitude of responses was reduced gradually instead of reaching a steady plateau. In addition to the previous stimulating protocol, low-frequency stimulation (LFS) was applied after LTP to determine the capacity for downregulation of plasticity. Consequently, the response magnitude of the TG rats was markedly smaller compared to the WT, and fell to below the pre-HFS baseline. Further work is underway to analyse PPF and I/O to test for changes in short-term plasticity and baseline connectivity. Collectively, the current results suggest synaptic dysfunction in the hippocampal CA3 to CA1 projection of the TG model for AD. Next, Aß oligomers and other pathologies will be measured using the post-mortem tissue of TG rats and WT littermates at corresponding ages. Since the animals do not show abundance of Aß plaques at the age tested here (Cohen et al., 2013), these results could reveal a possible mechanism for the effect of soluble Aß oligomers that contributes to the memory impairment in AD diagnosis.

Disclosures: Y. Sun: None. **J. Gigg:** None. **M. Harte:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG064656
NIH Grant AG056060
NIH Grant AG067597

Title: Targeting histone 3 K4 trimethylation for treatment of cognitive and synaptic deficits in mouse models of Alzheimer’s Disease

Authors: *Q. CAO, W. WANG, J. B. WILLIAMS, F. YANG, Z. WANG, Z. YAN;
State Univ. of New York at Buffalo, Buffalo, NY

Abstract: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by significant memory impairment and cognitive decline. Epigenetic dysregulation of gene transcription plays a key role in mediating gene-environment interactions relevant to AD pathophysiology. Here we show that the permissive histone mark, histone 3 K4 trimethylation (H3K4me3) and its catalyzing enzymes, SET1/MLL family of methyltransferases, are significantly elevated in the prefrontal cortex (PFC) of human and mouse models of AD. Importantly, the cognitive deficits and impaired PFC synaptic transmission in mouse models of AD are substantially recovered by selective inhibition of SET1/MLL. H3K4me3 is associated with transcriptional activation, including gene targets we found to be enriched in neurodegenerative-related pathways. We also discovered that aberrant H3K4me3 elevation and its corresponding dysregulated genes are reversed by the SET1/MLL inhibitor WDR5-0103. Among the upregulated genes linked to increased H3K4me3, one identified top-ranking target, the protein kinase Sgk1, is reversed to normal levels after administration of WDR5-0103. Furthermore, we found that selectively inhibiting Sgk1 directly reduced hyperphosphorylated tau, restored synaptic function, and ameliorated cognitive deficits in an AD mouse model. These findings provide potential mechanistic insights that aberrant epigenetic modifications associated with gene dysregulation in Alzheimer's-related pathophysiology could be a promising strategy for therapeutic intervention.

Disclosures: Q. Cao: None. **W. Wang:** None. **J.B. Williams:** None. **F. Yang:** None. **Z. Wang:** None. **Z. Yan:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This work was supported by a grant from Tata Trusts.

Title: Synaptic new protein synthesis and Akt1/mTOR signaling pathway is dysregulated in hippocampus of Alzheimer's disease mouse model

Authors: *R. KOMMADDI[1], R. GOWAIKAR[2], K. SINGH[2], A. HASEENA P[1,3], V. RAVINDRANATH[1];
[1]Ctr. for Brain Res., [2]Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India; [3]Manipal Acad. of Higher Educ., Manipal, India

Abstract: Akt/mammalian target of rapamycin (mTOR) signaling pathway is one of the major signaling pathways and it is activated by BDNF that facilitates new protein synthesis at the synapse which lead to the formation of long-term memory in the hippocampus. Recently, we have shown that BDNF stimulated Akt1 mediated new protein synthesis is abolished in primary cortical neurons from APP_{Swe}/PS1ΔE9 (APP/PS1) mice compared with wild type (WT). However, the molecular mechanisms underlying the impairment of new protein synthesis at the synapse is still elusive. Our aim is to understand the molecular mechanisms early by assessing the phosphorylation of Akt1 and the mammalian target of rapamycin (mTOR) signaling cascade molecules and new protein synthesis in hippocampus of WT and APP/PS1

male mice. Intriguingly, pAkt1, pGSK3β, pmTOR, p70S6K, pS6 ribosomal protein, p4E-BP1 levels were significantly decreased in both post nuclear supernatant (PNS) and synaptosomal fractions isolated from hippocampus of one month old (presymptomatic) APP/PS1 male mice compared to WT male mice. Further, activity dependent protein synthesis at the synapse was impaired in synaptoneurosomes isolated from hippocampus of presymptomatic APP/PS1 mice, and this deficit was sustained at young adults (three months). However, no impairment was observed in basal protein synthesis at both ages in APP/PS1 male mice compared to WT male mice. Thus, we conclude that dysregulation of Akt1/ mTOR and its downstream signaling molecules in hippocampus contributes to synaptic dysfunction in Alzheimer's disease, observed as loss of activity dependent new protein synthesis at the synapse in hippocampus which is essential for synaptic plasticity and maintenance.

Disclosures: R. Kommaddi: None. **R. Gowaikar:** None. **K. Singh:** None. **A. Haseena P:** None. **V. Ravindranath:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer Society of Canada

Title: Presynaptic susceptibility to glutamate spillover in a mouse model of alzheimer disease

Authors: *K. J. BRYMER[1], J. R. BARNES[2], M. P. PARSONS[2];
[1]Biomed. Sci., Mem. Univ., St. John's, NL, Canada; [2]Biomed. Sci., Mem. Univ., St John's, NL, Canada

Abstract: Tight control over the spatiotemporal dynamics of extracellular glutamate is necessary to prevent the toxic effects associated with excess glutamate accumulation. This control is mediated by glutamate transporters located on astrocytes and neurons, with GLT-1 responsible for the majority of glutamate clearance. Previous literature has described an asymmetrical distribution of glutamate transporters in the hippocampus, with presynaptic sites having less glial coverage than postsynaptic sites of the synapse. We reasoned that such an asymmetry would make the presynapse prone to slowed glutamate clearance. To test this hypothesis, we developed a novel approach to quantify the unique glutamate clearance dynamics in presynaptic and postsynaptic microenvironments in the hippocampus of the C57 mouse through a combination of intensity-based glutamate sensing fluorescent reporter (iGluSnFR) and two-photon microscopy. Interestingly, presynaptic microenvironments in acute hippocampal slices were more susceptible to slowed glutamate clearance from a low concentration of DHK than postsynaptic microenvironments. Having established that this asymmetry in the form of glial coverage makes the presynapse vulnerable to slowed glutamate clearance, we next asked what the consequences of this asymmetry are in a brain disease with compromised glutamate uptake, such as Alzheimer disease (AD). We utilized the same iGluSnFr and 2-photon microscopy approach described above in male and female 3xTg and control mice. By 6 months, an age corresponding to the emergence of an AD-like phenotype in the 3xTg mouse, glutamate clearance in presynaptic microenvironments was

impaired while postsynaptic clearance was unimpaired. Remarkably, at 12 months, presynaptic glutamate clearance remained impaired while no evidence of a postsynaptic clearance deficit emerged despite advanced disease pathology. We confirmed that the glutamate clearance impairment in presynaptic microenvironments is mediated by GLT-1, as DHK application to acute hippocampal slices increases glutamate clearance time in presynaptic microenvironments but the magnitude of this increase is less than in WT mice. Moreover, GLT-1 overexpression via ceftriaxone speeds up glutamate clearance in presynaptic microenvironments. These results strongly suggest that glutamate transporters have different capabilities depending on the specific microenvironment within a given region, and that impaired glutamate clearance in presynaptic microenvironments may set the stage for synaptic pathology characteristic of AD.

Disclosures: K.J. Brymer: None. **J.R. Barnes:** None. **M.P. Parsons:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA grant to KD: RF1 AG067049

Title: PSD-95 palmitoylation in Alzheimer's model mice

Authors: K. MERRITT, A. PHAM, ***K. DORE**;
Neurosciences, UCSD, La Jolla, CA

Abstract: The first change in the brains of Alzheimer’s patients and the best biomarker of the disease is synaptic loss. Several studies have shown that PSD-95 (a major scaffolding protein at the synapse) is significantly depleted in brain tissue of Alzheimer’s patients as well as in neurons exposed to Aβ. Consistently, we recently discovered that elevated levels of PSD-95 can prevent synaptic weakening by Aβ (Dore et al, Cell Reports, 2021). The amount of synaptic PSD-95 is controlled by a process called ‘palmitoylation’ which mediate the insertion of PSD-95 in post-synaptic membranes. In the hippocampus of 6-month old APP/PS1 mice, we observed a 50% reduction in palmitoylated PSD-95 while total PSD-95 amounts were reduced by only 10%. This suggests that loss of PSD-95 palmitoylation would happen before reductions in total PSD-95 in this mouse model. Moreover, we characterized PSD-95 palmitoylation in male and female mice of different ages to assess the time course of this decrease and how it is affected by the presence of amyloid plaques. The specific enzyme responsible for PSD-95 depalmitoylation, ABHD17, which removes PSD-95 from synapses, was recently identified. We thus started to test the potential of a novel drug target, ABHD17, as a new therapeutic avenue against Alzheimer’s. Our preliminary *in vitro* and *in vivo* results, using a commercially available inhibitor of that enzyme (Palmostatin B), are very promising. *In vitro* experiments showed that this drug could rescue Aβ-induced synaptic depression and Aβ-mediated effects on dendritic spines. Notably, using immunohistochemistry, we saw that Palmostatin B injections in the intraperitoneal cavity rapidly rescued palmitoylated PSD-95 in a dose dependent manner in APP/PS1 mice, which indicates that this drug can

access brain synapses *in vivo*. We observed similar results using a biochemical approach to quantify PSD-95 palmitoylation (APEGS assay). Moreover, we now have new preliminary data showing that blocking PSD-95 depalmitoylation with Palmostatin B can rescue memory deficits in the Morris Water Maze test and also improve synaptic physiology deficits in APP/PS1 mice. Our data show that PSD-95 palmitoylation is significantly reduced in 6-month old APP/PS1 mice, which might indicate a previously unknown step in the pathophysiology of Alzheimer's disease. Furthermore, pharmacological blockade of PSD-95 depalmitoylating enzyme rescued palmitoylation levels in the hippocampus of APP/PS1 mice and also had promising effects on behavioral and synaptic physiology deficits. Consequently, PSD-95 depalmitoylating enzyme could be an exciting new drug target against Alzheimer's disease.

Disclosures: K. Merritt: None. **A. Pham:** None. **K. Dore:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.09

Topic: C.02. Alzheimer's Disease and Other Dementias

R01 AG055581
R01 AG056622
Alzheimer's Association grant NIRG-15-362799
BrightFocus Foundation grant A2017457S

Title: Suppression of AMPKα2 aggravates cognitive deficits in a mouse model of Alzheimer's disease

Authors: *H. JESTER[1], S. GOSRANI[2], H. R. ZIMMERMANN[3], X. ZHOU[1], T. MA[1];
[1]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston-Salem, NC; [2]Emory Univ., Atlanta, GA; [3]Northwestern Univ., Chicago, IL

Abstract: AMP-activated protein kinase (AMPK) is a cellular energy censor that plays a critical role in protein synthesis regulation, metabolism, autophagy, and mitochondrial biogenesis. Dysregulation of AMPK signaling has been implicated in the pathophysiology of Alzheimer's disease (AD). The catalytic α isoforms (α1 and α2) of AMPK are normally expressed in a homeostatic equilibrium but are differentially expressed in AD brains. Roles of AMPK isoforms in development of AD pathophysiology remain elusive. In this study, AMPKα2 and α1 were conditionally knocked down in excitatory forebrain neurons in the Tg19959 AD mouse model to create heterozygous AMPKα2/Tg19959 and AMPKα1/Tg19959 double mutants. At 3-5 months of age, before cognitive impairments become evident in AD model, the mice were subjected to the Novel Object Recognition (NOR) task and the Morris Water Maze (MWM) that measure hippocampus-dependent spatial learning and memory. In addition, immunohistochemistry, and transmission electron microscopy of the hippocampus were performed to determine alterations in plaque deposition, post-synaptic densities, and polyribosomes. The double mutant AMPKα2/Tg19959 mice showed significant memory impairments in both the MWM and NOR task compared to Tg19959, and α1/Tg19959 genotypes. The AMPKα2/Tg19959 double mutant mice also showed significant decreases in post-synaptic density size and in the number of polyribosomes. An

increase in amyloid plaque deposition was also observed. Taken together, these findings suggest that reduction of AMPKα2 may accelerate cognitive decline and AD pathogenesis. This finding could provide a future therapeutic target and/or diagnostic/prognostic biomarkers for AD.

Disclosures: H. Jester: None. **S. Gosrani:** None. **H.R. Zimmermann:** None. **X. Zhou:** None. **T. Ma:** None.

Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG064067

Title: In vivo imaging of dendritic excitatory-inhibitory synapse imbalance in mouse models of Alzheimer's disease

Authors: *S. NIRAULA[1], J. DODERER[1], S. INDULKAR[1], J. DENG[1], G. KEETER[1], K. BERRY[2], S. YAN[1], J. SUBRAMANIAN[1];
[1]Dept. of Pharmacol. & Toxicology, The Univ. of Kansas, Lawrence, KS; [2]Dept. of Pediatrics, Cincinnati Childern's Hosp. Med. Ctr., Cincinnati, OH

Abstract: The ratio of excitatory and inhibitory synapses is balanced (E/I balance) locally in the dendrites. Local dendritic E/I balance regulates dendritic depolarization and may influence neuronal plasticity and memory. Excitatory synapse loss is the strongest correlate for cognitive decline in Alzheimer’s disease (AD). It is unclear whether excitatory synapse loss triggers compensatory loss of inhibitory synapses to maintain E/I balance. Alternatively, excitatory synapse loss could be a compensation for a prior reduction in inhibitory synapses. Using multicolor two-photon imaging, we map the distribution and dynamics of excitatory and inhibitory synapses in the same neurons *in vivo* in a mouse model of AD (J20 mice). We show that neurons in the visual cortex of J20 mice display a spatially restricted reduction in dendritic E/I balance. Using a genetically encoded calcium sensor GCaMP6, we found that neuronal response plasticity associated with repeated experience of a grating stimulus is impaired in the visual cortex of J20 mice. Consequently, J20 mice are deficient in forming visual recognition memory of the grating stimulus. We test whether E/I imbalance in J20 mice is due to a deficiency in sensing changes to neuronal excitability and whether increasing E/I balance improves plasticity and memory despite lost synapses.

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Poster

P212. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: In Vivo Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P212.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01AG05063104
Alzheimer's Association Grant AARFD-16-44263

Title: Alzheimer's disease risk gene CD2AP modulates synaptic structure and plasticity

Authors: *M. PAVESKOVIC, S. OJELADE, B. PEKAREK, M. KOCHUKOV, B. ARENKIEL, J. SHULMAN;
Baylor Col. of Med., Houston, TX

Abstract: *CD2-Associated protein (CD2AP)* is associated with increased risk of late-onset Alzheimer's disease. We have previously shown that loss of *CD2AP*'s *Drosophila* homolog, *cindr*, exacerbates Tau toxicity and impairs synaptic maturation and function at the neuromuscular junction. However, little is understood about *CD2AP* at the central mammalian synapse. The present study demonstrates conservation of *CD2AP* function at the pre-synapse from fly to mouse, as well as characterizes *CD2AP*'s role in maintaining post-synaptic structure and function.
We examined short- and long-term plasticity using electrophysiologic measurements and synaptic structure and morphology using confocal imaging. Experiments were performed on homozygous *CD2AP* knockout mice and heterozygous *CD2AP* knockout mice to investigate potential haploinsufficient requirement. Mice constitutively expressing Cas9 endonuclease were used for brain-specific *CD2AP* knockout.
We found that homozygous and heterozygous *CD2AP* knockout mice exhibit increased paired-pulse facilitation, a form of short-term plasticity. This matches data from *Drosophila*, implying conservation from fly to mouse, and indicates decreased probability of presynaptic vesicle release with *CD2AP* loss. We found no change in long-term potentiation (LTP) at 4 to 6 weeks; however, our preliminary experiments demonstrate decreased LTP in aged heterozygous *CD2AP* knockouts. Ongoing experiments are investigating age as a factor in *CD2AP* function. Lastly, *CD2AP* knockout neurons exhibit increased dendritic branching and homozygous knockout mice have increased expression of postsynaptic density protein 95.
In sum, our analyses implicate *CD2AP* in modulation of synaptic plasticity and structure, suggest a conservation of CD2AP function from flies to mice, and support *CD2AP* haploinsufficiency. Going forward, we will investigate how *CD2AP* loss affects existing Alzheimer's pathogenesis in a tauopathy mouse model.

Disclosures: M. Paveskovic: None. **S. Ojelade:** None. **B. Pekarek:** None. **M. Kochukov:** None. **B. Arenkiel:** None. **J. Shulman:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant AARGD-18-566576
NIH Grant 1R56AG061878-01

Title: Synthetic and natural conformational variants of misfolded Aβ induce different pathological features in susceptible mice.

Authors: *R. MORALES[1], R. GOMEZ-GUTIERREZ[1], U. GOSH[2], K. DO[1], W.-M. YAU[2], C. DURAN-ANIOTZ[1], I. MORENO-GONZALEZ[1], N. GAMEZ[1], J. SCHULZ[1], C. KRAMM[1], R. TYCKO[2], C. SOTO[1];
[1]The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]NIH, Bethesda, MD

Abstract: Compelling evidence in humans and experimental rodents suggest that Alzheimer's disease (AD) -associated Aβ exists in a variety of conformational strains. Unfortunately, current research has not addressed the biological significance of Aβ strain variation in AD. This issue acquires additional relevance considering that mixtures of Aβ strains seems to exist in the brains of patients. Aβ strain variation may explain the pathological and clinical differences observed among people afflicted by AD. Here, we used brain-derived and synthetic Aβ strains to assess for potential differences in propagation and pathological manifestations. In a first set of experiments, two synthetic-$A\beta_{40}$ strains (2F and 3F) that have been thoroughly studied for their structural motifs, were biochemically characterized and injected in the brains of 50 days old Tg2576 mice. We assessed prion-like transmission of these materials by analyzing Aβ deposition 250 days later. A second set of experiments involved the administration of AD brain homogenates from individuals displaying diverse amyloid pathology. These human brain extracts were intra-cerebrally injected into 30 days old APP/PS1 mice that were sacrificed 150 days later. Pathological differences in both experiments were found at different levels, including the type and anatomical distribution of the aggregates, $A\beta_{40}/A\beta_{42}$ ratios, reactivity of amyloid deposits to dyes able to discriminate among misfolded protein conformations, among others. Importantly, differences in astro- and micro-glial activation were also observed. Our data support the concept and biological relevance of conformational strain variation in non-prion protein misfolding disorders. In addition, these results provide a good correlation between structural motifs and biological activity. Our findings may pave the way to identify the most deleterious particles responsible for AD and help in the design of conformation-specific strategies for diagnosis and treatment.

Disclosures: R. Morales: None. **R. Gomez-Gutierrez:** None. **U. Gosh:** None. **K. Do:** None. **W. Yau:** None. **C. Duran-Aniotz:** None. **I. Moreno-Gonzalez:** None. **N. Gamez:** None. **J. Schulz:** None. **C. Kramm:** None. **R. Tycko:** None. **C. Soto:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University of Leeds (UoL ABSL award)
Wellcome Trust (108466/Z/15/Z)
Academy of Medical Sciences Springboard Award

Title: In-tissue structure of Alzheimer's Disease pathology in the mammalian brain by cryo-electron tomography

Authors: *C. M. LEISTNER, R. A. W. FRANK;
Univ. of Leeds, Leeds, United Kingdom

Abstract: Senile plaques composed of amyloid-β (Aβ) are a major pathological hallmark of Alzheimer's disease (AD). Aβ fibrils prepared *in vitro* or purified from post-mortem tissue have been investigated extensively revealing their atomic structure. However, the native architecture of Aβ plaques and the organisation of Aβ fibrils within the brain itself is currently unknown.
Here, we developed a workflow to determine the *in situ* architecture of Aβ plaques using cryogenic correlative light and electron tomography (cryoCLET) in the brain of a knock-in mouse model of AD (1 year old male *App* NL-G-F, n=2). After injecting mice with Methoxy-X04, a fluorescent dye that labels Aβ plaques, fresh cortical tissue biopsies were vitrified by high pressure freezing. Next, tissue cryo-sections were collected on cryoEM grids and Methoxy-X04 stained plaques were mapped by correlative imaging to direct the collection of cryo-electron tomographic data.
3D reconstructions revealed the in-tissue molecular architecture of Aβ plaques. Aβ fibrils were organised within multiple distinct domains of varying densities, including a meshwork and parallel bundles. Interestingly, this correlative imaging approach revealed apparent conformational differences of Aβ fibrils in central versus peripheral regions of the plaque. Numerous other macromolecular features were observed within the plaque, including liquid-like droplets. Subcellular compartments interdigitated the pathology, within and between Aβ parallel bundles. These included membranes containing higher-order protein networks, C-shaped membranes, and membrane nanopodia. The boundary of Aβ plaques was characterised by cells in close proximity to Aβ fibrils that contained an abundance of mitochondria, endoplasmic reticulum, ribosomes and microtubules. Overall, these results reveal the molecular heterogeneity of Aβ plaques and the rich diversity of cellular constituents that define the amyloid pathology of AD.

Disclosures: C.M. Leistner: None. **R.A.W. Frank:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG050431
NIH Grant AG069229

Title: Hippocampus Specific Knock-Down of PPARα Aggravates Plaque Pathology in 5xFAD Mice

Authors: *M. MCKAY, S. RAHA, R. KUMAR, K. PAHAN;
Rush Univ. Grad. Col., Chicago, IL

Abstract: Peroxisome proliferator-activated receptor alpha (PPARα) is a transcription factor that regulates fatty acid metabolism. Although, metabolically active organs like the liver is rich in PPARα, we and others have demonstrated that PPARα is constitutively expressed in hippocampal neurons. To delineate the role of PPARα in the hippocampus in relation to Alzheimer's disease (AD), we generated 5xFAD mice lacking PPARα in the hippocampus (5xFAD$^{\Delta Hippo}$) via complex breeding among PPARα$^{Flox/Flox}$, calcium/calmodulin-dependent protein kinase II alpha (Camk2a)^{Cre} and 5xFAD mice. Although, phenotypically, 5xFAD$^{\Delta Hippo}$ mice looked similar to 5xFAD mice, we observed aggravated amyloid plaque pathology and enhanced glial activation in the hippocampus of 5xFAD$^{\Delta Hippo}$ mice as compared to 5xFAD mice. Accordingly, 5xFAD$^{\Delta Hippo}$ mice also exhibited decreased spatial learning and memory in comparison to 5xFAD mice. These results suggest that hippocampal PPARα plays an important role in the manifestation of AD-related pathologies and symptoms, and that activation of hippocampal PPARα may be beneficial for AD.

Disclosures: M. Mckay: None. **S. Raha:** None. **R. Kumar:** None. **K. Pahan:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS100704
NIH R01 AG067258

Title: Doxorubicin treatment did not affect AB plaque accumulation in a mouse model of APOE and amyloid.

Authors: *C. NG, M. F. LANFRANCO, G. W. REBECK;
Neurosci. Dept., Georgetown Univ., Washington, DC

Abstract: Cancer survivors often experience cancer-related cognitive impairment (CRCI), which is characterized by problems of attention, working memory, and other domains of cognition following chemotherapy. APOE4, the strongest genetic risk factor for Alzheimer's Disease (AD), is also a risk factor for CRCI. Apolipoprotein E (apoE) is involved in lipid metabolism, synapse regeneration, immune modulation, and clearance and degradation of amyloid β (Aβ) deposition; functions that vary across apoE isoforms. Here we tested whether doxorubicin, a chemotherapeutic drug commonly used for breast cancer treatment, increases AD-related neuropathogenesis in a mouse model expressing familial AD mutations (5XFAD) and the human APOE genotypes (EFAD). Six-month-old female E3FAD (control n=5, treated n=5) and E4FAD (control n=6, treated n=6) mice were treated with either doxorubicin (5 mg/kg) or DMSO vehicle twice, one week apart. Six weeks after the second injection, mice were euthanized, and brains were perfused and collected; one hemisphere was fixed for immunohistochemistry and the other was dissected into cortex, hippocampus, and cerebellum for biochemical assays. The fixed hemispheres

were sliced into 30 μm coronal sections. Immunostaining with 6E10 antibodies to analyze APP and Aβ accumulation in the cortex and hippocampus showed no differences in plaque accumulation after doxorubicin treatment in either APOE genotypes. As expected, we observed greater levels of plaques in regions of the E4FAD mouse brains compared to the E3FAD mouse brains. Sequential protein extraction with Tris-buffered saline (TBS), TBS with 1% Triton-X (TBSX), and formic acid (FA) was performed for measurements of Aβ42 in the hippocampus. No effects of doxorubicin treatment were seen for Aβ42 levels in TBS, TBSX, nor FA fractions. In addition, glial reactivity to the presence of Aβ accumulation was determined by co-staining with either GFAP, an astrocytic marker, or Iba1, a microglia marker, with Moab2 antibodies for the detection of Aβ plaques. These data show no effects of doxorubicin on select aspects of AD pathogenesis, specifically Aβ accumulation; other aspects are being analyzed in these EFAD mice.

Disclosures: C. Ng: None. **M.F. Lanfranco:** None. **G.W. Rebeck:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA RO1 AG06490
NIH/NINDS P01 NS074969
Alzheimer's Association SAGA

Title: Effect of sex hormones on the kinetics of amyloid-beta in an awake behaving mouse

Authors: *H. EDWARDS, C. YUEDE, J. CIRRITO;
Washington Univ. Sch. of Med., St Louis, MO

Abstract: Effect of sex hormones on the kinetics of amyloid-β in an awake behaving mouse
Hannah M. Edwards, Carla Yuede, John R Cirrito
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Alzheimer's disease (AD) is a neurodegenerative disease that is hallmarked by the accumulation of amyloid-beta (Aβ) and tau, followed by a progressive decline in cognitive acuity. Interestingly, AD affects women at a higher rate than men, even when controlling for differences in lifespan. Clinical trials utilizing hormone replacement therapy in older women have yielded conflicting results. To explain this difference, we looked at the direct effect of sex hormones on the temporal kinetics of brain interstitial fluid (ISF) Aβ using in vivo microdialysis. With probes implanted in the hippocampus of awake, behaving mice, we measured Aβ levels over a three-day period. Female animals were injected intraperitoneally with beta-estradiol. An increase in Aβ was seen after 12 hours. Animals were also dosed with norethindrone, a progesterone receptor agonist, using reverse microdialysis to focally target the hippocampus. Interestingly, a decrease in Aβ was seen almost immediately with Aβ levels returning to

baseline after administration of the drug was ceased. These novel results suggest a differential effect of the two most prevalent sex steroids in females, and work is ongoing to uncover the cause of this effect.

Disclosures: H. Edwards: None. **C. Yuede:** None. **J. Cirrito:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JP21dm0207073

Title: Isoform- and dose-dependent effects of apolipoprotein E in the deposition of Abeta in the brain of APP transgenic mice

Authors: *T. HASHIMOTO[1], A. KOKAWA[2], M. TANAKA[1], Y. OHNO[1], M. KASHIWAGI-HAKOZAKI[1], T. IWATSUBO[1];
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Abstract: Deposition and spreading of amyloid-β (Aβ) in the brain is an early and central event in the pathogenesis of Alzheimer's disease (AD). However, the molecular mechanisms underlying Aβ accumulation in the brain are not fully elucidated. Apolipoprotein E (apoE) is one of the lipid carriers in the brain and apoE is also known as Aβ binding protein. There are three common alleles of the human *APOE* gene, ε2, ε3, and ε4, encoding the apoE2, apoE3, and apoE4 isoforms, respectively. Among the three alleles of *APOE*, the ε4 allele is associated with a 6-folds increased risk for developing Alzheimer's disease compared with the most common ε3 allele. The density of Aβ deposition in the brains of *APOE*ε4carrier AD patients is significantly higher than that in *APOE*ε3 carrier, suggesting that apoE might impact the accumulation of Aβ in an isoform-dependent manner. In this study, we have generated APP tg mice expressing human apoE3 by crossing APP transgenic (tg) mice with human *APOE*ε3 knock-in (KI) mice. Gel filtration analysis showed that the level of lipidated apoE in the brains of APP tg/apoE3 KI mice was comparable with that in APP tg mice. *In vivo* microdialysis also revealed that the concentrations of Aβ42 in the brain interstitial fluid of APP tg/apoE3 KI and APP tg mice were at similar levels. By immunohistochemical analyses, APP tg/apoE3 KI mice exhibited a significantly lower Aβ burden in the brain compared with APP tg mice. These data suggest that human apoE3 suppresses the deposition of Aβ more strongly than mouse apoE. To test this hypothesis, we carried out an *in vivo* seeding experiment, which allows the induction of deposition and spreading of Aβ in the brain of APP tg mice by a single inoculation of Aβ seeds. Intra-hippocampal inoculation of TBS-soluble fraction from brains of Aβ-laden APP tg mice significantly induced the deposition of Aβ in the brains of APP tg mice. Notably, the seed-induced Aβ deposits in APP tg/apoE3 KI mice was less than that in APP tg mice. Furthermore, almost no Aβ deposits was observed in the brains of apoE-deficient APP tg mice in *in vivo* seeding experiments. Our findings implicate apoE in the deposition of Aβ by facilitating the seeding activity or spreading of Aβ seeds in the brain, suggesting that human apoE3 and murine apoE may have

different abilities to the facilitation of Aβ seeding. *In vivo* seeding experiments in the APP tg/apoE2 or apoE4 KI mice are underway to elucidate the isoform-dependent effects of apoE in the deposition of Aβ.

Disclosures: T. Hashimoto: None. **A. Kokawa:** None. **M. Tanaka:** None. **Y. Ohno:** None. **M. Kashiwagi-Hakozaki:** None. **T. Iwatsubo:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1-AG044342
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University of Minnesota Start-Up Funds
Institute of Translational Neuroscience Bridge Funds

Title: Knock-in versus transgenic insertion of mutant amyloid precursor protein leads to early differential spatial deposition of amyloid-β plaques in mouse models of Alzheimer's disease

Authors: *D. HART, R. PELZEL, S. LESNÉ;
Dept. of Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Animal models are commonly used to study the pathological mechanisms of Alzheimer's disease (AD). The overexpression, knock-out, and introduction of gain-of-function mutations allow for functional investigations of disease relevant proteins such as amyloid precursor protein (APP) and its metabolite amyloid-β (Aβ). Knowing the spatial development of pathology in different models is critical in understanding the potential and relevant translational ability of findings from these animals. To this end, we investigated the extent of Aβ deposition in the well-established transgenic APP J20 line and the newer knock-in App^{NL} and App^{NL-F} (n=6 of each genotype, including wild-type mice) at 9 months of age. All animals were maintained on the C57BL/6J background, and the cohort was made of both male and female mice. Sagittal sections throughout the left hemispheres from these animals were immunostained with 6E10, a commonly used marker for amyloid plaques. Aβ deposits were first registered at 10x and individually validated at higher 40x magnification. In the J20 line, we found cortical, hippocampal, and fiber tract Aβ plaques along with previously unreported subcortical deposition in the striatum. In comparison, knock-in App^{NL-F} mice displayed substantially more cortical deposition with no subcortical plaques. Consistent with previous reports, no Aβ plaques were found in the App^{NL} animals. The discrepancy of subcortical deposition between the J20 and App^{NL-F} lines mirrors that of human AD, whereby individuals with familial AD (fAD) develop subcortical Aβ plaques before hippocampal pathology, a phenotype not seen in sporadic AD (sAD). As such, J20 and App^{NL-F} mice may separately be useful models of fAD and sAD, respectively. Further studies will be needed to better understand the

functional role of these differences and their subsequent behavioral consequences, such as in spatial reference learning and memory and decision making.

Disclosures: D. Hart: None. **R. Pelzel:** None. **S. Lesné:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Discrete Spatiotemporal Trajectories of Aβ and Tau Pathologies in the Early Stages of Accumulation

Authors: *S. HOJJATI[1], D. DEVANAND[2], J. LUCHSINGER[2], Y. STERN[2], R. RAZLIGHI[1];
[1]Weill Cornell Med., New York, NY; [2]Columbia Univ. Irving Med. Ctr., New York, NY

Abstract: The aggregation of two misfolded proteins intracellular neurofibrillary tau tangles and extracellular amyloid-β (Aβ) plaques are the best-documented pathologies for Alzheimer's disease (AD). Spatiotemporal discrepancies between these two proteinopathies in initial stages of accumulation and their consequences for the brain structure and function are key unresolved challenges in understanding the pathogenesis of AD. In this study, we aimed to show that each pathology is associated with a unique alteration in brain structure (cortical thickness) and function (functional connectivity (FC) networks). Participants were selected from four separate research cohorts at Columbia University Irving Medical Center, and Weill Cornell Medicine. We identified 381 healthy controls with age of 50 years and older with three imaging modalities (T1-weighted structural, resting-state fMRI, 18F-MK-6240 positron emission tomography (PET), and 18F-florbetaben PET) acquired within 12 months. An in-house developed fully automatic quantification method has already been implemented and evaluated using histopathological data used for the quantification of PET scans. To trace the spatial and temporal characteristics of these two pathologies, first we categorized the participants to three groups based on their tau uptake in the regions involved in each Braak stage using the K-means clustering method. Then we performed vertex-wise linear regression models in each group to investigate the relationship between the two pathologies and cortical thickness as well as functional connectivity when age, gender and intracranial volume (ICV) are controlled. Results showed that the tau accumulations were independentely related to cortical atrophy in different brain regions (e.g. medial temporal lobe, posterior cingulate), whereas such relationship was missing for Ab accumulation. On the other hand, the Aβ accumulation were related to significant disruption in the functional connectivity of the Defualt mode network (DMN) as well as dorsal attention network (DAN), whereas tau had a weak association with DMN FC and almost no association with the DAN FC. These unique Aβ and/or tau related alterations in the structure and function of the brain suggests a discrete spatiotemporal trajectory in the early accumulation of the pathologies that are considered as hallmark of the AD. In other words, while later accumulation and coincide of the two pathologies seems to facilitate the brain alterations causing AD, the early accumulation seems to be initiated independently and follow unique trajectory. These findings suggest AD pathways that can be investigated in future studies.

Disclosures: S. Hojjati: None. **D. Devanand:** None. **J. Luchsinger:** None. **Y. Stern:** None. **R. Razlighi:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.09

Topic:

Support: Institutional Research Funds

Title: Melanopsin ganglion cell morphology in the 3xTg mouse model of Alzheimer's disease

Authors: *M. A. SMITH[1,3], S. DEWAN[4], C. M. DENGLER-CRISH[2], J. M. FERRELL[1]; [2]Pharmaceut. Sci., [1]Northeast Ohio Med. Univ., Rootstown, OH; [3]Akron Children's Hosp., Akron, OH; [4]Univ. of Akron, Akron, OH

Abstract: Circadian rhythm abnormalities are reported in AD patients very early in the course of the disease including abnormal timing and duration of the sleep cycle, the reduction of melatonin levels during the night, and alternating expression profile of clock genes. These deficits could arise from dysregulation within several brain sites, however, the retina has been postulated as one of the earliest neural structures affected in AD and melanopsin expressing retinal ganglion cells (mRGCs) are responsible for maintaining circadian rhythms, thus making the retina it an attractive target for investigating pathological mechanisms. In other neurodegenerations such as Parkinson's, Alzheimer's, and glaucoma loss of mRGCs, have been detected. While amyloid-β accumulation, mRGC loss, and gliosis in the retinas of mouse models of AD are evident, little is known about the progression of pathology in mRGC axons. Using a combination of immunohistochemistry, and high-resolution florescent microscopy, we examined the mRGC morphology in 4-7 month old 3xTg mice, a commonly used murine model of Alzheimer's disease. We found substantial decreases in in dendritic field complexity, dendritic area, and soma size in the retina of 3xTg mice. Importantly, mimicking the progression of other age related neurodegenerations, these changes occurred independent from a reduction in total RGC and mRGC somata density in the corresponding retinas. In conclusion, the 3xTg mouse exhibits early changes in mRGC morphology in the absence of cell body loss. The accessibility, isolation, and simplicity of the anterior visual system may provide a useful framework for studying the mechanisms of axonopathy in AD.

Disclosures: M.A. Smith: None. **S. Dewan:** None. **C.M. Dengler-Crish:** None. **J.M. Ferrell:** None.

Poster

P216. Dynamics, Kinetics, and Impacts of Amyloid Beta

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P216.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ohio Lions Eye Research Foundation

Title: Visual dysfunction in Alzheimer's disease: investigating the role of the parabigeminal nucleus

Authors: *G. FRAME, C. M. DENGLER-CRISH;
Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: The parabigeminal nucleus (PBGN) is an accessory visual structure that in rodents, communicates with the superior colliculus (SC) to mediate an escape response to overhead looming stimuli. While the PBGN seems to be important for defensive survival behavior in rodents, there is very little research on this nucleus in humans or how its structure/function may change with age or disease. However, what is known about this structure suggests it may be selectively damaged in Alzheimer's disease (AD). Clinical observations from AD patients report early, nuanced deficits in response to visual stimuli and movement perception, and accumulations of pathological AD proteins have been identified in the primary visual projection of both patients and experimental AD models (i.e. 3xtg mice) from retina > optic nerve > brain. In rodents, the primary projection target of the retina is the SC, with which the PBGN has strong, bidirectional connections. Additionally, the PBGN is predominantly a cholinergic nucleus—and these neurons are selectively vulnerable to the Alzheimer's disease process. Therefore, the overall goal of our research is to characterize PBGN structure, collicular connectivity, and function across age in both healthy mice (C57BL6) and disease (3xtg Alzheimer's mice) using a comprehensive set of neurohistochemical and behavioral-testing techniques. Here, we present data from our structural analyses comparing PBGN composition across age, sex, and disease state.

Disclosures: G. Frame: None. **C.M. Dengler-Crish:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.01

Topic: C.03. Parkinson's Disease

Support: POIR.01.01.01-00-0617/20-00 (National Centre for Research and Development, Poland)
statutory funds of the Maj Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland
Celon Pharma S.A.

Title: CPL500036 - a novel inhibitor of phosphodiesterase 10A - attenuates parkinsonian-like and L-DOPA induced dyskinetic effects in 6-OHDA lesioned rats

Authors: *M. MATLOKA[1], T. LENDA[2], K. OSSOWSKA[2], K. BERGHAUZEN-MACIEJEWSKA[2], D. BIAŁA[2], A. GAJOS-DRAUS[1], P. PANKIEWICZ[1], K. MULEWSKI[2], A. JANUSZ[1], D. SMUGA[1], M.

GORKA[1], J. PIECZYKOLAN[1], M. WIECZOREK[1], J. KONIECZNY[2];
[1]Celon Pharma S.A., Kazun Nowy, Poland; [2]Maj Inst. of Pharmacology, Polish Acad. of Sci., Krakow, Poland

Abstract: Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurotransmission. Dopamine replacement therapy, e.g. with levodopa (L-DOPA), remains the gold standard of therapy. Unfortunately, following years of exposure, L-DOPA causes motor complications such as L-DOPA-induced dyskinesias (LIDs). Phosphodiesterase 10A regulates cAMP/cGMP downstream signaling thus having a key role in the regulation of dopaminergic signaling in striatal pathways and seems to be of special interest as a potential therapeutic target in PD.
In the presented studies we examined the influence of CPL500036 (CPL036), a novel PDE10A inhibitor, on: 1) sensorimotor deficits and therapeutic effects of L-DOPA and 2) L-DOPA-induced dyskinesias in hemiparkinsonian rats.
Methods: Animals were unilaterally lesioned with 6-hydroxydopamine (6-OHDA). For antiparkinsonian assessment, CPL036 (0.1 and 0.3 mg/kg) was administered either acutely or chronically (2 weeks), alone or in combination with L-DOPA/benserazide (6 mg/kg/6 mg/kg) and sensorimotor deficits were examined in the stepping, cylinder, vibrissae and catalepsy tests. To assess antidyskinetic properties, dyskinesias were induced by L-DOPA/benserazide (6 mg/kg/6 mg/kg) (15 days). Dyskinetic animals were treated additionally with CPL036 (0.03, 0.1, 0.3mg/kg) for next 17 d. The severity of dyskinesia was assessed by Dyskinesia - Abnormal Involuntary Movements scale (AIMs). cAMP and cGMP level was assessed by HPLC method.
Results: Acute treatment with CPL036 reversed the lesion-induced impairments of contralateral forelimb use. Moreover, chronic treatment with CPL036 did not diminish the therapeutic effects produced by L-DOPA. Combined treatment with L-DOPA and CPL036 (0.03, 0.1 and 0.3 mg/kg) dose-dependently attenuated the L-DOPA-induced dyskinesia, and the beneficial effect of CPL036 increased with repeated doses. The level of cAMP and cGMP increased significantly for a dose of 0,3 mg/kg of CPL500-036 in dyskinetic animals.
Conclusion: CPL036 attenuated effectively L-DOPA induced dyskinesias in combination therapy with L-DOPA, without negative impact on the therapeutic antiparkinsonian efficacy of the latter drug, in a rat model of PD.

Disclosures: M. Matloka: A. Employment/Salary (full or part-time):; Celon Pharma S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A. **T. Lenda:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Celon Pharma S.A. **K. Ossowska:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Celon Pharma S.A.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Celon Pharma S.A. **K. Berghauzen-Maciejewska:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Celon Pharma S.A. **D. Biała:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Celon Pharma S.A.. **A. Gajos-Draus:** None. **P. Pankiewicz:** A. Employment/Salary (full or part-time):; Celon Pharma S.A.. **K. Mulewski:** None. **A. Janusz:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **D. Smuga:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **M. Gorka:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **J. Pieczykolan:** A. Employment/Salary (full or part-time):; Celon Pharma S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A. **M.**

Wieczorek: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A. **J. Konieczny:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Celon Pharma S.A.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Celon Pharma S.A..

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.02

Topic: C.03. Parkinson's Disease

Support: NIH grant AG048918

Title: Sex & brain region-based variation in paraoxonase-2 (PON2) expression in African green monkeys: Impact of pioglitazone treatment and implications for its use in Parkinson's disease

Authors: *S. JAMWAL, J. K. BLACKBURN, J. D. ELSWORTH;
Yale Univ. Sch. of Med., New Haven, CT

Abstract: The neuropathology of Parkinson's disease (PD) involves decreased mitochondrial performance and enhanced oxidative stress as a result of increased production of reactive oxygen species; however, none of the drugs used to treat PD targets these mechanisms. Previous studies have established that PON2 is a mitochondrial enzyme with potent antioxidant and anti-inflammatory properties and a promising target for drugs to impart protection to dopamine neurons and stem the progression of PD. This is supported by studies from our lab that identified a decline in PON2 expression with age in nonhuman primates (NHPs), which correlates with the sensitivity of dopamine neurons to oxidative stress induced by parkinsonian toxins. The value of activating PON2 as a strategy to halt PD progression would be enhanced if the enzyme was highly expressed in dopamine-rich regions and also displayed a sex bias in its distribution in NHP brain, as PD is 2-2.5 times more prevalent in males than females. First, we investigated the sex as well as region-based variation in PON2 expression in NHP brain, using St Kitts African green monkeys. We found a 2-2.5-fold greater PON2 expression in striatum compared with other brain regions and that females exhibit 2-3-fold higher expression compared with males. Second, we studied in vivo pharmacological stimulation of PON2, which has not been demonstrated before. Preclinical studies indicate that the PPARγ activator, pioglitazone, is neuroprotective in PD models by reducing oxidative stress and/or inflammation and clinical studies suggest it may reduce the risk of PD, however, its precise mechanism has not been elucidated. We hypothesized that pioglitazone's action depends on PON2 activation. Indeed, we found that sub-chronic pioglitazone treatment significantly augmented striatal expression of PON2 in mice. To determine the effect of pioglitazone on PON2 expression in a more translatable species, male African green monkeys were treated with oral pioglitazone (5 mg/kg/day) or vehicle for 1 or 3 weeks. Pioglitazone significantly increased PON2 expression in substantia nigra, striatum, dorsolateral prefrontal cortex and hippocampus, but after 3-weeks of treatment the effect on PON2 had subsided. Identifying the mechanisms responsible for the short-term

effect on PON2 is crucial for optimizing the use of pioglitazone and other PPARγ agonists in PD. This study establishes the existence of sex and region-based variation in PON2 protein expression in primate brain and provides a novel mechanism for pioglitazone-induced neuroprotection. We anticipate that these outcomes will contribute to the development of neuroprotective treatments for PD.

Disclosures: S. Jamwal: None. **J.K. Blackburn:** None. **J.D. Elsworth:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.03

Topic: C.03. Parkinson's Disease

Title: Regionally selective effects ofpirepematon catecholamine neurotransmissionupon local administration in cortical and subcortical brain areas

Authors: *S. WATERS[1], **D. ANDERSSON**[1], C. SONESSON[1], A. FAGERBERG[1], L. ROUSK[1], J. TEDROFF[1,2], N. WATERS[1], S. HJORTH[1,3];
[1]Integrative Res. Labs., Goeteborg, Sweden; [2]Dept of Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden; [3]Pharmacilitator AB (inc.), Vallda, Sweden

Abstract: Pirepemat (IRL752), is a new phenyl-pyrrolidine derivative with regio-selective effects on CNS transmission. It is currently in Phase II clinical development for the treatment of postural instability and prevention of falls in Parkinson's disease. Upon systemic administration, pirepemat produces dose-dependent increases in extracellular levels of dopamine, norepinephrine, and acetylcholine in cortical, but not subcortical areas, as measured by in vivo brain microdialysis. It is procognitive in preclinical assays, e.g. NOR and RL, and reverses tetrabenazine-induced hypoactivity but does not stimulate basal locomotor activity in normal animals. (JPET 2020 Sep;374(3):404-419). These in vivo effects have been attributed to antagonism at alpha2c-adrenoceptors, as well as 5HT7 receptors.
To further elucidate the pharmacological mode of action of pirepemat, we studied the effect of local administration of the compound in several brain regions: prefrontal cortex (PFC), hippocampus, striatum, nucleus accumbens (NAc), and locus coeruleus (LC). Using a dual microdialysis probe set-up, pirepemat 1-100 µM was applied by reverse-dialysis into the region of interest. Microdialysis samples were simultaneously collected in the same region, and in one additional region (ipsi- or contralaterally). The alpha2c adrenoceptor antagonist ORM12741 was tested in a similar fashion, however limited to application in the PFC and sampling in the PFC and the striatum. Systemic administration studies were performed for comparison.
Pirepemat produced marked increases in PFC catecholamines upon local administration, without concomitant effects in subcortical areas. Local application in the striatum or the NAc had no effect on catecholamine levels. Application in the LC produced a local concentration-dependent increase of NA, but no concomitant increase in catecholamines in the PFC, neither contra- nor ipsilaterally. The alpha2c adrenoceptor antagonist ORM12741 did not produce similar effects when administered locally, and elicited but a slight regio-selective increase in PFC catecholamines upon systemic administration (0.3 mg/kg, s.c.).

In conclusion, the local PFC effects of pirepemat parallel the effects seen after systemic administration; i.e., the effects are qualitatively similar. This suggests that local cortical mechanisms are the main drivers of the pharmacodynamic effects of the compound. An alpha2c adrenoceptor-selective antagonist failed to produce similar effects, suggesting that the overall in vivo effects of pirepemat may derive from interactions of the agent at several receptors and/or circuits impacting PFC catecholamine output.

Disclosures: S. Waters: A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories Sweden AB. **D. Andersson:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. **C. Sonesson:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories Sweden AB. **A. Fagerberg:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. **L. Rousk:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. **J. Tedroff:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories Sweden AB. **N. Waters:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories Sweden AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories Sweden AB. **S. Hjorth:** F. Consulting Fees (e.g., advisory boards); Integrative Research Laboratories Sweden AB.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.04

Topic: C.03. Parkinson's Disease

Title: Non-clinical pharmacology of YTX-7739, a clinical stage stearoyl-CoA desaturase inhibitor being developed for Parkinson's disease

Authors: *D. TARDIFF[1], M. LUCAS[1,2], I. WRONA[1,2], B. CHANG[1,3], C. CHUNG[1], B. LE BOURDONNEC[1,4], K. RHODES[1,5], R. SCANNEVIN[1,6];
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Abstract: Unbiased phenotypic screening and target deconvolution identified stearoyl-CoA desaturase (SCD) as a potential therapeutic target for Parkinson's and related neurodegenerative diseases. SCD inhibition ameliorated neuronal toxicity caused by aberrant α-synuclein, a lipid-binding protein implicated in Parkinson's disease. Inhibiting SCD depletes monounsaturated fatty acids, which may modulate α-synuclein conformations and membrane interactions. Herein, we have characterized the pharmacokinetic and pharmacodynamic properties of YTX-7739, a clinical-stage SCD inhibitor.

Administration of YTX-7739 to rats and cynomolgus monkeys for fifteen days caused a dose-dependent increase in YTX-7739 concentrations that were well-tolerated and associated with concentration-dependent reductions in the fatty acid desaturation index (FADI), the ratio of monounsaturated to saturated fatty acids. An approximate 50% maximal reduction in the carbon-16 desaturation index was observed in brain, with comparable responses in plasma, and skin. In rats, the plasma and skin FADI responses were mitigated by diet supplementation with SCD products. The brain, however, was more resistant to diet effects, as reductions in fatty acid desaturation persisted, consistent with local SCD inhibition and a more limited contribution of systemic fatty acids to brain lipids. Assessment of pharmacodynamic response onset and reversibility kinetics indicated that approximately seven days of dosing were required to achieve maximal responses, which persisted for at least two days after cessation of dosing. YTX-7739 thus achieved sufficient concentrations in brain to inhibit SCD and produce pharmacodynamic responses that were well-tolerated in rats and nonhuman primates. These results provide a framework for evaluating YTX-7739 pharmacology clinically as a disease-modifying therapy to treat synucleinopathies.

Disclosures: D. Tardiff: A. Employment/Salary (full or part-time):; Yumanity Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **M. Lucas:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **I. Wrona:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **B. Chang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **C. Chung:** A. Employment/Salary (full or part-time):; Yumanity Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **B. Le Bourdonnec:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **K. Rhodes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics. **R. Scannevin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yumanity Therapeutics.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.05

Topic: C.03. Parkinson's Disease

Support: SUNY Technology Accelerator Fund

Title: The Effects of Vilazodone, YL-0919 and Vortioxetine in L-DOPA treated hemiparkinsonian rats

Authors: S. SMITH[1], ***K. ELDER**[1], M. COYLE[1], A. CENTNER[1], S. COHEN[1], N. LIPARI[1], A. CRUZ-HARRIS[2], C. SHERMAN[3], C. BISHOP[1];

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Abstract: Parkinson's Disease (PD) is a debilitating, neurodegenerative disorder characterized by motor symptoms, including bradykinesia, tremor, stiffness, and postural instability, that result from significant nigrostriatal dopamine (DA) loss. The current gold standard treatment for PD involves replacement therapy via the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA); however, 90% of patients eventually experience choreic and dystonic side effects termed L-DOPA induced dyskinesia (LID). An experimentally supported driver of LID is neuroplasticity within the serotonin (5-HT) system leading to the unregulated release of L-DOPA-derived DA from 5-HT terminals into the motor circuits, including the striatum and substantia nigra. Previous work has implicated coincident 5-HT1A receptor agonism and 5-HT transporter (SERT) blockade as an effective therapeutic method for attenuating LID while maintaining L-DOPA efficacy. The present study examined 3 similar drugs, Vilazodone, YL-0919, and Vortioxetine, that act as 5-HT1A agonists and SERT blockers to test this approach. Adult female Sprague-Dawley rats received unilateral injection of 6-hydroxydopamine into the medial forebrain bundle -to lesion nigrostriatal DA neurons. Thereafter they received 2 weeks of daily L-DOPA treatment (6 mg/kg) until they developed stable abnormal involuntary movement (AIMs) akin to LID. Rats were also assessed for motor performance with the forepaw adjusting steps (FAS) test at baseline and on treatment. Results revealed that Vilazodone and Vortioxetine significantly reduced AIMs and maintained L-DOPA's beneficial prokinetic effects. In contrast, YL-0919 unexpectedly had no effect on LID but did not counteract L-DOPA efficacy. Overall, these findings support pharmacological targets within the 5-HT system that reduce LID. They also provide evidence for unique features of Vilazodone and Vortioxetine, both FDA-approved compounds, as potential adjunct therapeutics to optimize L-DOPA treatment for PD patients.

Disclosures: S. Smith: None. **K. Elder:** None. **M. Coyle:** None. **A. Centner:** None. **S. Cohen:** None. **N. Lipari:** None. **A. Cruz-Harris:** None. **C. Sherman:** None. **C. Bishop:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.06

Topic: C.03. Parkinson's Disease

Support: Department of Pharmaceuticals, Ministry of Chemical and Fertilizers, Government of India
NMHS grant (GBPI/NMHS-2017-18/HSF-02), Ministry of Environment Forest and Climate Change, Government of India

Title: Evodiamine Suppress Inflammatory Cascade and Potentiate Neuronal Survival in Parkinson's Disease allied Depressive-like Behavior: In-vitro and In-vivo Study

Authors: *M. KWATRA, V. NAIDU;
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Abstract: Preclinical and clinical data evidently suggested the devastating impact of stress on progressive and accelerating damaging effects on the nigrostriatal pathway in PD. However, the underpinning mechanism elaborating stress mediated-MPTP-induced redox dysregulation, SIRT1/AMPK, ASK1-related apoptosis signaling in cellular and mice models is not explained and validated to date. Moreover, we also studied the neuroprotective effect of EVD *in-vitro* and *in-vivo*. In first phase, we established and validated impact of prolonged restraint stress (168h; 7h/day, 1d-14d, 22d-28d; 3h/day, 15d-21d) on subacute MPTP doses (23.6 mg/kg, i.p. for 7 consecutive days, 15d-21d) injected in mice. We observed severe behavioral changes in the RS+MPTP group compared to RS and MPTP grouped mice for the enhanced reduction in brain vascularity, disrupted redox balance, highly activated apoptotic signaling in substantia nigra pars compacta (SNpc) region of mice brain. Secondly performed *in-vitro* studies for evaluating neuroprotective effects of EVD on LPS stimulated N9 microglial cells and MPP^+ induced neurotoxicity in N2a cells. Anti-inflammatory effect of EVD via repressing active NF-κB signaling while activating Nrf2 regulated Peroxiredoxin-5 (Prx-5) antioxidant axis in N9 cells. Moreover, EVD pretreatment suppresses inflammation and degenerated N2a cells by conditioned media of LPS stimulated N9 cells and further EVD caused inhibition of MPP^+ mediated neurotoxicity via its anti-apoptotic, antioxidant, and activation of neuronal survival (SIRT1/AMPK) mechanism in N2a cells. Lastly, we assessed the neuroprotective benefits of EVD (50 mg/kg and 100 mg/kg) against the RS+MPTP-induced neurobehavioral and neurochemical anomalies. Moreover, we also utilized 3H-1,2-Dithiole-3-thione (D3T); Nrf2 activator alone and in combination with EVD (100 mg/kg) to conclude its Nrf2 pathway activation. EVD, higher dose ameliorates blood flow to the brain on 28th day, increased the level of monoamines, lowered corticosterone level, mitigated the raised oxido-nitrosative stress, and restored the SOD, catalase, reduced NAD level in SNpc of mice. EVD potentially downregulated the NF-κB mediated inflammatory, apoptotic signaling mediators and activated SIRT1/AMPK/Nrf2 provoked anti-inflammatory signaling in SNpc of mice. Moreover, EVD also reversed the IBA-1, TH immunoreactivity, altered ultrastructural architectures to normal control in SNpc of mice. EVD with anti-inflammatory, anti-apoptotic, and neuroprotective properties may be used as adjunct therapy or nutraceuticals to clinically subside the motor and depressive-like behavior in Parkinson's disease.

Disclosures: M. Kwatra: None. **V. Naidu:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.07

Topic: C.03. Parkinson's Disease

Support: SUNY Technology Accelerator Fund

Title: Investigating the anti-dyskinetic effects of co-administered serotonin- and glutamate-acting compounds, Vilazodone and Amantadine, in hemiparkinsonian rats

Authors: S. COHEN[1], M. TERRY[1], M. COYLE[1], A. CENTNER[1], J. GLINSKI[1], S. SMITH[1], E. WHEELIS[1], C. BUDROW[1], F. P. MANFREDSSON[2], C. BISHOP[1];
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Abstract: Parkinson's disease is a progressive, neurodegenerative movement disorder caused by loss of nigrostriatal dopamine (DA) neurons. DA replacement therapy using L-3,4-dihydroxyphenylalanine (L-DOPA) improves motor functioning but often results in L-DOPA-induced dyskinesia (LID) typified by abnormal involuntary movements (AIMs). In states of DA depletion, striatal serotonin (5-HT) hyperinnervation and glutamate overactivity are implicated in LID. To capitalize on these co-mechanisms for LID reduction, this study investigated the anti-dyskinetic effects of FDA-approved Vilazodone (VZD), a 5-HT transport blocker and partial 5-HT1A agonist, and Amantadine (AMAT), an NMDA glutamate antagonist, using 6-hydroxydopamine lesioned hemiparkinsonian Sprague-Dawley rats in a series of experiments. First, dose-response curves for each drug against L-DOPA-induced AIMs were determined to identify threshold effective doses. Next, a second cohort of rats was tested with those threshold doses of VZD (1, 2.5 mg/kg, s.c.) and/or AMAT (40 mg/kg, s.c.) to examine their combined acute effects on LID. In a third cohort, AMAT and/or VZD were given daily with L-DOPA during the 14 day priming period to see whether these compounds could prevent LID development. In a final cohort, VZD and/or AMAT were chronically administered in rats with established LID for 2 weeks to examine their interventional properties. For all experiments, AIMs monitored dyskinesia severity and forepaw adjusting steps (FAS) recorded L-DOPA efficacy maintenance. Results revealed a significant decrease in AIMs and maintained FAS with acute, prophylactic and chronic VZD+L-DOPA compared to L-DOPA alone. AMAT+L-DOPA did not exert any significant effects on AIMs or FAS, but the combined administration of VZD and AMAT demonstrated intermediate effects relative to each drug across experiments. These results suggest co-administration of VZD and AMAT with L-DOPA does not synergistically reduce LID in hemiparkinsonian rats. Rather, our results suggest that AMAT may counter the anti-dyskinetic efficacy of VZD when co-administered. Importantly, even very low doses of VZD reduce the development and expression of LID while maintaining L-DOPA efficacy supporting its potential re-purposing as an already FDA-approved drug.

Disclosures: S. Cohen: None. **M. Terry:** None. **M. Coyle:** None. **A. Centner:** None. **J. Glinski:** None. **S. Smith:** None. **E. Wheelis:** None. **C. Budrow:** None. **F.P. Manfredsson:** None. **C. Bishop:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.08

Topic: C.03. Parkinson's Disease

Title: Usmarapride (SUVN-D4010): A 5-HT_4 receptor partial agonist alleviates haloperidol-induced Parkinson's disease associated cognitive dysfunction

Authors: V. GRANDHI, H. TALAKANTI, N. GANUGA, V. GOURA, J. TADIPARTI, R. MEDAPATI, R. ABRAHAM, S. GAGGINAPALLY, D. KANCHARLA, *P. JAYARAJAN, R.

NIROGI;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: Haloperidol is a classical antipsychotic drug known for its propensity to cause extrapyramidal symptoms and cognitive impairment, due to the blockade of striatal dopamine D_2 receptors. Drug-induced Parkinson's disease (PD) is indistinguishable from the pathological PD, as the symptoms are similar for both the conditions. PD patients experiences progressive cognitive decline over the years. Cognitive decline further deteriorates the health related quality of life (hQOL) in these patients. Although, rivastigmine is approved for PD related dementia by FDA, it has its own disadvantages, viz. dose limiting side effects, tremor at rest, and lack of efficacy over time etc. Hence, there is an unmet medical need to find effective yet, safe interventions. Usmarapride, a 5-HT_4 receptor partial agonist was evaluated for its potential to alleviate haloperidol-induced PD associated dementia. Haloperidol was supplemented in water feeder bottles at to induce PD associated dementia. Following one week of haloperidol supplementation, treatment with either usmarapride or rivastigmine was initiated. Rats were evaluated in the social recognition task (SRT). Familiarization and recognition trials were conducted with a trial delay of 30 min. Social investigation time spent by adult rat with either familiar or novel juvenile rat was assessed during recognition trial and compared among the juveniles. Discriminative index was calculated and compared among the groups. Chronic treatment with haloperidol produced PD dementia like state with social memory deficits in SRT task. However, preventive treatment with usmarapride alleviated haloperidol-induced PD dementia. Positive control, rivastigmine also significantly ameliorated PD related cognitive deficits. Significant increase in novel juvenile social investigation time or discriminative index was observed for the groups treated with usmarapride or rivastigmine, relative to familiar juvenile or vehicle control group, respectively. Usmarapride ameliorated PD related dementia in an animal model, thus it could be a future promising therapeutic strategy for PD associated dementia, thereby to improve the patients' hQOL.

Disclosures: V. Grandhi: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **H. Talakanti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Ganuga:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goura:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Tadiparti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gagginapally:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **D. Kancharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd..

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.09

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R43GM121117
MJFF Grant MJFF009602

Title: SB-0107, a Protein Kinase A II potentiator identified through machine learning, treats Parkinson's disease motor disability and levodopa-induced dyskinesia in rat and primate models

Authors: *A. BORDBAR[1], B. BLOEM[1], K. MERCHANT[2], D. M. WEINER[3], M. P. HILL[4], J. M. BROTCHIE[4], J. S. SCHNEIDER[4], T. H. JOHNSTON[4], I. FAMILI[1];
[1]Sinopia Biosci., San Diego, CA; [2]Transthera Consulting Co, Portland, OR; [3]Independent, San Diego, CA; [4]Atuka Inc., Toronto, ON, Canada

Abstract: Levodopa plus carbidopa (L/C) represents the most effective treatment for motor deficits of Parkinson's disease (PD). However, the efficacy of L/C diminishes with PD progression and L/C's chronic use often leads to the debilitating side effect termed levodopa-induced dyskinesia (LID). Thus, clinical management of PD requires a therapeutic regimen that can reduce motor symptoms without inducing dyskinesia. Using a machine learning approach trained on gene expression data from striatonigral neurons of 6-OHDA lesioned mice exposed to various levels of L-DOPA, we identified two genomic signatures associated with levodopa's motoric efficacy and dyskinesia liability. Computational analysis of *in vitro* transcriptomic profiling data of ~20,000 small molecules resulted in selection of SB-0107 as a candidate for follow-up as the compound induced a gene expression pattern similar to that associated with LC's motoric efficacy while reversing the pattern associated with LID. SB-0107 selectively potentiates protein kinase A II, a kinase downstream of dopamine receptors. Thus, we characterized SB-0107's effects in highly translatable rat and primate models of PD disability and LID. In 6-OHDA lesioned rats, the combination of SB-0107 and sub-therapeutic doses of L-DOPA resulted in anti-parkinsonian effects that are equivalent to or greater than high doses of L-DOPA alone, while not inducing LID-like behavior after repeated dosing. Further, SB-0107 significantly reduced expression of several genes associated with LID *in vivo*. In the MPTP-lesioned macaques, SB-0107 showed a dual benefit; it significantly enhanced L/C's effects on PD disability, while also significantly decreasing LID by ~50%. Additional studies with the chronic low dose MPTP macaque model of PD cognition indicated that SB-0107 significantly improved performance in cognitive tasks at certain doses. The unique mechanism of action and preclinical results warrant further development of SB-0107 for PD.

Disclosures: A. Bordbar: A. Employment/Salary (full or part-time):; Sinopia Biosciences. **B. Bloem:** A. Employment/Salary (full or part-time):; Sinopia Biosciences. **K. Merchant:** F. Consulting Fees (e.g., advisory boards); Sinopia Biosciences. **D.M. Weiner:** F. Consulting Fees (e.g., advisory boards); Sinopia Biosciences. **M.P. Hill:** None. **J.M. Brotchie:** None. **J.S. Schneider:** None. **T.H. Johnston:** None. **I. Famili:** A. Employment/Salary (full or part-time):; Sinopia Biosciences.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.10

Topic: C.03. Parkinson's Disease

Title: Brain-penetrant structurally targeted allosteric regulators for glucocerebrosidase (GCase) show promising in vivo pharmacological activity in animal models of Parkinsons disease

Authors: *B. GUZMAN[1], N. PEREZ[2], A. GARCIA-COLLAZO[2], *E. CUBERO[2], X. BARRIL[2], S. MORALES[2], A. RUANO[2], A. DELGADO[2], T. ROSA[1], M. BELLOTTO[1], R. MAJ[1];
[1]Gain Therapeut., Lugano, Switzerland; [2]Gain Therapeut., Barcelona, Spain

Abstract: *Abstract Body Max 2300 character*
Brain-penetrant structurally targeted allosteric regulators for glucocerebrosidase (GCase) show promising *in vivo* pharmacological activity in animal models of Parkinson's diseaseB. Guzman[1], N. Pérez[1], A. M. García-Collazo[1], E. Cubero[1], X. Barril[1], S. Morales[1], A. Ruano[1], A. Delgado[1], T. Rosa[1], M. Bellotto[1], R. Maj[1*1*] *Gain Therapeutics, Lugano (Switzerland) and Barcelona (Spain).*
ObjectiveDeficiency of glucocerebrosidase (GCase) activity due to mutations in the corresponding *GBA1* gene leads to toxic accumulation of sphingolipids and, in some cases, α-synuclein pathology. Due to the latter, GCase has recently attracted increasing attention given its potential role in Parkinson's disease (PD) pathophysiology: evidence shows that misfolding and loss of GCase activity causes pathologic accumulation of α-synuclein while GCase overexpression in brain reduces pathology and memory deficits in synucleinopathy mouse models. GCase activity is also diminished in cases of idiopathic PD without *GBA1* mutations and correlates with earlier disease onset and worse cognitive and non-motor symptoms. These findings suggest that decreased GCase activity may contribute to pathogenesis in many forms of PD and that enhancing the activity of both mutant and wild-type GCase may represent a potential therapeutic strategy.
MethodsGain Therapeutics has applied its innovative proprietary drug discovery platform, Site-directed Enzyme Enhancement Therapy (SEE-Tx™), to the development of small-molecule structurally targeted allosteric regulators (STAR[s]) that can stabilize misfolded GCase by binding to a site different from its active site, ultimately avoiding its degradation while facilitating its maturation and trafficking to the lysosomes.
ResultsOur orally bioavailable and brain penetrant lead STAR[s] have shown promising effects in different *in vitro* and *in vivo* models of PD. Here we report recent *in vivo* evidence of their beneficial effects towards rescuing GCase activity and protein levels in a dose-dependent manner as well as ameliorating α-syn pathology and behavioral phenotypes in rotenone and other pharmacologically induced animal models.
ConclusionAltogether, the allosteric regulators identified with the proprietary SEE-Tx™ drug discovery platform support the restoration of key biological activities found to be impaired in *GBA1*-related Parkinson's disease, thus warranting further development towards the clinic.

Disclosures: B. Guzman: None. **N. Perez:** None. **A. Garcia-Collazo:** None. **E. Cubero:** None. **X. Barril:** None. **S. Morales:** None. **A. Ruano:** None. **A. Delgado:** None. **T. Rosa:** None. **M. Bellotto:** None. **R. Maj:** None.

Poster

P267. Therapeutic Strategies: Preclinical Animal Models: Small Molecule Therapeutics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P267.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Department of Defense

Title: Montelukast Therapy Improves Brain Function with Modulation of Neuroinflammation in a Model of Chronic Gulf War Illness

Authors: *S. ATTALURI, B. SHUAI, M. KODALI, L. MADHU, J. GONZALEZ, X. RAO, A. SHETTY;
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Abstract: Gulf War Illness (GWI) is a multi-symptom illness afflicting ~30% of veterans who served in the first Gulf War. Epidemiological studies suggested that exposure to a combination of chemicals such as the nerve gas prophylactic drug, pyridostigmine bromide (PB), and pesticides during the war caused GWI. Indeed, concurrent exposure to low doses of chemicals used in the GW and mild stress for 28 days in rats leads to symptoms akin to those observed in veterans with GWI. GWI is associated with persistent cognitive and mood impairments, associated with chronic neuroinflammation, and decreased neurogenesis in the hippocampus. We investigated the efficacy of Montelukast (MLK), an FDA-approved drug for asthma with robust anti-inflammatory properties through the inhibition of cysteinyl leukotriene signaling, for improving brain function and modulating neuropathological changes in animals exposed to GWI-related chemicals and stress (GWI rats). We first exposed young rats to low doses of GWI-related chemicals such as the nerve gas prophylactic drug pyridostigmine bromide (PB), mosquito repellant DEET, insecticide permethrin (PM), and moderate stress for 28 days. Four months later, GWI rats received vehicle or MLK at 5, 10, 15, or 20 mg/kg (5 days/week) for eight weeks. A significant cognitive and mood dysfunction was observed in GWI rats receiving the vehicle when interrogated with behavioral tests such as the object-in-place test (OIPT), pattern separation test (PST), and the sucrose preference test (SPT). However, GWI rats receiving different doses of MLK exhibited improved cognitive and mood function, which was evident from their ability for spatial recognition memory in an OIPT, pattern separation in a PST, and no anhedonia in an SPT. Analysis of brain tissues revealed decreased neuroinflammation in GWI rats receiving MLK, evidenced by the reduced number of activated microglia. Additional biochemical studies assessing neuroinflammation and cysteinyl leukotriene signaling are currently in progress. The results suggest that MLK treatment has promise for improving brain function by modulating neuroinflammation.

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Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.01

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR FDN-143210
UBC Four Year Fellowship
Canadian Open Neuroscience Platform Scholarship

Title: In vivo striatal activity during motor skill learning and spontaneous behaviour in Huntington's Disease mice

Authors: *E. T. KOCH[1], J. CHENG[1], M. D. SEPERS[3], L. A. RAYMOND[2];
[2]Dept Psychiatry and Ctr. for Brain Hlth., [1]Univ. of British Columbia, Vancouver, BC, Canada; [3]Dept. of Psychiatry, UBC, Vancouver, BC, Canada

Abstract: Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, cognitive and psychiatric deficits. The dorsal striatum is the major site of neurodegeneration in HD, particularly the D2-expressing spiny projection neurons (D2-SPNs) early on, and the D1-expressing SPNs (D1-SPNs) late in the disease. Studies have shown aberrant cortico-striatal signalling in HD mice, including changes to the evoked and spontaneous activity of D1- and D2-SPNs, aberrant glutamatergic and dopaminergic signalling, and deficits in cortico-striatal plasticity. Although there has been extensive research on changes to cortico-striatal signalling *in vitro*, there has been relatively little research on how these changes correlate with behaviour *in vivo*. We combined the accelerating rotarod and open field tasks with calcium imaging using fiber photometry in the striatum of HD mouse models (YAC128 and Q175). This includes imaging of overall striatal activity with GCAMP7f, as well as population specific imaging of D1-SPNs and D2-SPNs simultaneously, using green and red calcium sensors (GCAMP and RCAMP). When imaging GCAMP7f expressed in all striatal neurons, we found that both WT and YAC128 HD mice showed increased striatal activity over baseline when they performed on the rotarod, and this activity reduced over days of training. In both genotypes, there was an inverse correlation between striatal GCAMP7f activity and latency to fall off the rotarod. In our 2-3 month age group, YAC128 mice showed no deficit in latency to fall from the rotarod, however, the correlation between striatal activity and behaviour on the rotarod and in the open field in these mice was significantly weaker. This indicates that striatal signalling is altered in YAC128 mice even at early stages before obvious behavioural deficits are present. We also have used the deep learning networks DeepLabCut and B-SOID to analyze behavioural patterns and kinematics, and correlated these behavioural measures with striatal calcium activity. We discovered changes to paw kinematics during rotarod in YAC128 mice, even in the 2-3 month age group when mice had no differences in latency to fall. This work begins to bridge the gap between our understanding of changes to signalling in the direct and indirect pathways determined from in vitro studies and the behavioural deficits observed in vivo.

Disclosures: E.T. Koch: None. **J. Cheng:** None. **M.D. Sepers:** None. **L.A. Raymond:** None.

Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

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Program #/Poster #: P276.02

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant R21OD025320
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NIH Grant R01NS119255

Title: Corticostriatal changes associated with the human-specific FOXP2 variant dampen striatal degeneration in Huntington's disease zQ175 knock-in mice

Authors: A. E. MOLERO[1], ***Y. M. ALTUN**[1], G. S. DEVAKANMALAI[1], M. F. MEHLER[2];
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Abstract: Cumulative investigations have identified a novel class of diverse hominid-specific genes and gene variants with key rostral lateralized neural developmental functions. Given their roles in enhancing neurogenesis, neural circuit formation and complexity, these genes not only optimize brain form and function, but may also differentially modify the progression of neurodegenerative disorders. Such is the case of a human-specific gene variant in the forkhead box P2 gene, h*FOXP2*, which induces a human-like enlargement of dendritic arbors of cell types that comprise cortico-striatal circuitry, one of the primary targets of Huntington's disease (HD). To examine the effects on HD-associated striatal degeneration and motor deficits of h*FOXP2*-dependent corticostriatal 'humanization', we launched an exploratory study in which we introduced h*FOXP2* in HD knock-in mice (the zQ175 model). Nissl-stained sections of 12-month old zQ175 specimens showed anticipated reductions in the number of striatal cells. By contrast, hFoxp2;zQ175 mice did not show significant striatal cell loss (80.3±21.4 vs 103.9±17.4, for hFoxp2;zQ175 and wild-type mice, respectively, Mann Whitney test exact $p = 0.2$). In line with histological preparations, electron microscopy studies revealed that the proportion of striatal cells with degenerative morphology was significantly reduced in hFoxp2;zQ175 compared to wild-type mice (19.3%, 95%CI = 16.4-22.6, vs 56.8, 95%CI = 51.1-62.3, Fisher's exact test $p < 0.0001$). Conversely, the introduction of the h*FOXP2* gene did not modify motor deficits in HD mice, as motor performance was comparable between 6- and 12-month old hFoxp2;zQ175 and zQ175 mice. These observations suggest that the human-specific *FOXP2* variant is a modifier of striatal degenerative changes but not of motor deficits in HD mice. Overall, these findings identify the *FOXP2* gene network as a target for therapeutic interventions aimed at remediating or even reversing neurodegeneration in HD.

Disclosures: A.E. Molero: None. **Y.M. Altun:** None. **G.S. Devakanmalai:** None. **M.F. Mehler:** None.

Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.03

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR Grant FDN 143210
Huntington Society of Canada Grant

Title: Chronic upregulation of endocannabinoid signalling in vivo with JZL184 normalizes impaired striatal synaptic plasticity and motor learning in YAC128 Huntington disease mice.

Authors: *M. D. SEPERS[1], C. WOODARD[1], M. N. HILL[2], L. RAYMOND[1];
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Abstract: Huntington disease (HD) is a dominantly inherited neurodegenerative disorder characterized by extensive degeneration of the striatum, a key structure of the basal ganglia involved in motor function and reinforcement learning. Prior to the onset of neurodegeneration, studies in animal models of HD have found significant dysfunction at a synaptic and circuit level including alterations in the expression and signaling of the CB1 cannabinoid receptor, a key component of the endocannabinoid system. Recent work from our lab has suggested that endocannabinoid-mediated long-term depression (LTD) at cortico-striatal synapses is impaired in YAC128 HD mice. As plasticity at corticostriatal synapses is thought to be critical for motor learning, it's possible that disruption of this plasticity contributes to the early symptoms of HD. In *ex vivo* brain slices from YAC128 mice, we found that LTD induced by high-frequency stimulation (HFS) could be rescued by application of JZL184, a drug that blocks degradation of the endocannabinoid 2-arachidonyl glycerol (2-AG), thereby increasing the activation of cannabinoid receptors. To determine whether *in vivo* treatment with JZL184 was able to rescue impaired synaptic plasticity and reverse behavioural phenotypes, we treated 5-month-old YAC128 mice with JZL184 daily for several weeks and performed behavioural and electrophysiology experiments. Two weeks of JZL184 treatment was sufficient to normalize motor coordination deficits in YAC128 mice on the rotarod test but did not rescue 'depressive' behaviour on the forced swim test. Interestingly, in brain slices collected from both treated and untreated WT mice, striatal HFS resulted in long-term potentiation (LTP) rather than LTD. While no significant HFS-induced plasticity was observed in control YAC128 mice, treated YAC128 mice showed comparable LTP to WT animals, indicating that chronic JZL184 treatment was able to rescue impaired synaptic plasticity in these mice. These results provide evidence that targeting impairments in endocannabinoid signaling may be an effective strategy for recovering neuroplasticity and treating the early motor symptoms of HD.

Disclosures: M.D. Sepers: None. **C. Woodard:** None. **M.N. Hill:** None. **L. Raymond:** None.

Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.04

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Pharmacologic inhibition of the classical complement pathway enhances neuronal function and HD R6/2 mouse survival

Authors: *A. TASSONI, V. MATHUR, J. VEREEN, E. CAHIR-MCFARLAND, S. SANKARANARAYANAN, T. YEDNOCK, Y. ANDREWS-ZWILLING;
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Abstract: BACKGROUND: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of CAG repeats in the *Huntingtin (HTT)* gene. Increased expression of early classical complement components, including C1q, C4 and C3, have been observed in striatal tissue from HD patients, and C1q has been implicated in synapse elimination and neuronal damage in HD mouse models.**AIM**: To examine complement expression, neuronal damage and the potential therapeutic benefit of classical complement inhibition in an HD animal model. **METHODS**: We used the R6/2 transgenic

mouse model of HD expressing a ~ 120 CAG expansion, and measured classical complement components in the plasma and cerebral spinal fluid (CSF) of transgenic vs. wild type mice. We also measured the levels of Neurofilament Light Chain (NfL) as a biomarker of neuronal damage. To test the role of the classical complement pathway in neuronal damage, we pharmacologically blocked C1q activity with an inhibitory antibody (ANX-M1), administered via intraperitoneal injection, and assessed NfL, behavioral function and animal survival. **RESULTS**: We found increased plasma levels of C1q and multiple complement components. NfL was increased in both the plasma as well as the CSF of R6/2 mice and there was a significant positive correlation between CSF NfL levels and plasma C1q, suggesting a potential role of the classical complement cascade in neuronal damage. Treatment of animals with anti-C1q fully blocked C1q in the plasma and normalized levels of complement components. Consistent with a role for the classical cascade in neuronal damage, anti-C1q treatment significantly reduced CSF levels of NfL, improved motor behavior in the open field assay, and increased R6/2 mouse survival.CONCLUSIONS: The results of this study suggest that inhibiting C1q protects against neuronal damage in mice with expanded CAG repeats in the HTT gene and that C1q is a potential pharmacological target in HD. A Phase 2 study of ANX005 anti-C1q therapy in HD patients is ongoing (clinical trials.gov NCT04514367).

Disclosures: A. Tassoni: None. **V. Mathur:** None. **E. Cahir-McFarland:** None. **S. Sankaranarayanan:** None. **T. Yednock:** None. **Y. Andrews-Zwilling:** None.

Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.05

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: RIG, BITS-Pilani, Hyderabad
Additional RIG, BITS-Pilani, Hyderabad

Title: Vitamin D3 attenuates oxidative stress and rescues motor dysfunction, neuromuscular impairment and spatial memory deficits observed in 3-nitropropionic acid induced mouse model of Huntington’s disease

Authors: *S. VENKATA MANJARI[1], P. KOMAL[2], S. MAITY[2], S. YU KU[3];
[2]Dept. of Biol. Sci., [1]Birla Inst. of Technol. and Sci. - Pilan, Hyderabad, Telangana, India; [3]The Hong Kong Polytechnic Univ., Kowloon, Hong Kong, Hong Kong

Abstract: Vitamin D3 attenuates oxidative stress and rescues motor dysfunction, neuromuscular impairment and spatial memory deficits observed in 3-nitropropionic acid induced mouse model of Huntington’s disease Manjari SKV[1], Shuvadeep Maity[1], Sonata Yu Ku[2] and Pragya Komal[1*2]Associate professor, The Hong Kong Polytechnic University, Hong Kong, kowloon Hong Kong [1]Department of Biological Sciences, Birla Institute of Technology and Sciences – Pilani, Hyderabad, Telangana, India – 500078; **** Corresponding author-pragya@hyderabad.bits-pilani.ac.in Background:*** Vitamin D3 is a neurosteroid known to have neuroprotective function across a range of mental disorders like Alzheimer’s

disease, Parkinson's disease, dementia and schizophrenia. However, limited evidence shows its beneficial effect in Huntington's disease (HD). In the present study, we aim to explore the neuroprotective effects of Vitamin D3 (VD) supplementation in 3-nitropropionic acid (3-NP) induced mouse model of HD. ***Methodology:*** For present study C57BL/6 male mice (3-4 months of age; n=8-15 animals per group) were divided into four different groups namely; **Group I**: Vehicle treated with sterile saline, **Group II**: animals were induced intraperitoneal (i.p) with 75mg/kg of 3-NP in three consecutive doses as described previously by Fernagut *et al*. **Group III**: animals injected i.p with only 500IU/kg of VD for 15 days and **Group IV**: 500IU/kg (12.5 μg/kg) of VD was given for 15 days through i.p to post 3-NP (75mg/kg) injected animals. Behavioral tests like locomotor activity, gait analysis, rotarod analysis, and morris water maze were carried out for a total period of 30 days. After 30 days, animals were decapitated and striatal tissues were isolated to check the mRNA expression of neurotrophins (nerve growth factor (NGF), brain derived neurotrophic factor (BDNF)) and antioxidative enzymes (superoxide dismutase (SOD), glutathione peroxidase (Gpx) and catalase (Cat)).***Results:*** Our behavior and mRNA results reflect that post VD treatment to 3-NP animals **(Group IV)** significantly rescued spatial memory deficits, locomotion dysfunction and neuromuscular coordination when compared with 3-NP induced HD mice **(Group II)**.***Conclusion:*** Overall, our current study infers that VD may rescue striatal neuron degeneration in HD and changes in the expression of antioxidative enzymes corroborate with the antioxidative property of VD.

Disclosures: S. Venkata Manjari: None. **P. Komal:** None. **S. Maity:** None. **S. Yu Ku:** None.

Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.06

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Grant CF-2019-51488

Title: Toll-like receptor 4 is involved in the phenotypic manifestations observed on the R6/1 mouse model for Huntington´s disease.

Authors: *P. E. MARTÍNEZ-GOPAR[1,2], C. GONZALEZ-ESPINOSA[2], F. PEREZ-SEVERIANO[1]; [1]Neurofarmacología Mol. y Nanotecnología, Inst. Nacional de Neurología y Neurocirugía, Mexico, Mexico; [2]Farmacobiología, Ctr. de Investigaciones y Estudios Avanzados del IPN, México, Mexico

Abstract: Toll-like receptors (TLRs) are pattern recognition receptors that can respond to internal damage-associated molecular patterns (DAMPs). Activation of TLRs stimulates a complex signaling cascade and triggers inflammatory responses. Different TLRs are expressed in glial cells and neurons and its overactivation leads to the production of pro-inflammatory molecules, neuroinflammation, and neural tissue damage associated with many neurodegenerative diseases such as Huntington´s disease (HD). HD courses with loss of GABAergic neurons in basal ganglia, oxidative damage, and neuroinflammatory processes. Disruptions in the TLR-4 signaling pathway have been reported in both, immunological cells of HD patients and in mice models . The transgenic R6/1 mouse expresses the first exon of human mutant

Huntingtin (mHtt), which causes. R6/1 mice shows a motor deficit at 18 - 20 weeks of age. The objective of this work was to study the participation of TLR-4 in the phenotype expressed in the R6/1 mice. For this purpose, we crossed B6CBA-Tg(HDexon1)61Gpb/1J mice (R6/1) and B6.B10scN-TLR4lps-del mice (TLR4-deficient), and we evaluated motor coordination, weight loss, and expression of feet-clasping weekly from 15 to 25 weeks of age. The body weight of R6/1 mice with normal TLR4 levels (TLR4+/+) and heterozygous TLR4 (TLR4+/−) did not show any difference. However, a delay in motor coordination and a significant lower rank of feet clasping were observed in R6/1 mice heterozygous for TLR4. Previously we had observed that TLR-4-deficient mice showed less neurological and oxidative damage in the neurochemical model of HD, and in this work, we show evidence that indicates that TLR-4 receptor participates in phenotypic motor alterations in the R6/1 model of HD. Taking these results together, we suggest that TLR-4 receptor could be a therapeutic target for the treatment of some deleterious reactions observed in HD. Supported by Conacyt (Grant CF-2019-51488).

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Poster

P276. Huntington's Disease: Circuit Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P276.07

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CAPES
CNPq

Title: Effects of environmental enrichment on modulation of behavioral and hippocampal neuroplasticity in the yac128 mouse model of huntington's disease

Authors: *E. PLÁCIDO[1], C. P. N. CASTRO[1], P. G. WELTER[1], M. FARINA[1], J. GIL-MOHAPEL[2], A. L. S. RODRIGUES[1], A. F. DE BEM[1], P. S. BROCARDO[1];
[1]Federal Univ. of Santa Catarina, Florianópolis, Brazil; [2]Univ. of Victoria, Victoria, BC, Canada

Abstract: Huntington's disease (HD) is a genetic neurodegenerative disease characterized by motor, psychiatric, and cognitive deficits. Emerging evidence has suggested that some of the emotional and cognitive deficits associated with this disease may be related to hippocampal dysfunction. To investigate this hypothesis we used the YAC128 mouse model of HD. We performed a temporal characterization of behavioral dysfunction in early and late symptomatic animals. Moreover, we investigate the effects on behavioral and neuroplasticity of environmental enrichment (EE) exposure in early symptomatic animals. The aim of this study was to perform a temporal characterization of behavioral alterations and determine if EE exposure for 60 days in early symptomatic animals has positive effects on HD symptoms and hippocampal neuroplasticity in YAC128 mice.
Wild-type (WT) and YAC128 mice (n=8-14) were behaviorally evaluated at early (3-4 months) and late (11-13 months) symptomatic stages of disease progression. The animals underwent to Open Field Test, Tail Suspension Test (TST), and T-maze Swimming Test (TMST). To analyze the effects of EE exposure on behavioral modulation and hippocampal neuroplasticity, a cohort of early symptomatic animals was

exposed to EE (2-4 months). After behavioral testing, brain sections were used to immunohistochemistry for cell proliferation (Ki-67 and PCNA) and neuron differentiation (DCX) in the hippocampus (HC). The total number of immunoreactive cells was counted. The tests were analyzed using a two-way analysis of variance and chi-square test. CEUA approved this project under n. 4502210318.
Early (3-4 months) and late (11-13 months) symptomatic YAC128 mice exhibited depressive-like behavior as demonstrated by increased immobility time in the TST. In addition, YAC128 mice presented cognitive deficits in the TMST during the late symptomatic stage. Exposure to EE in the early symptomatic animals reverted the depressive-like behavior in the YAC128 mice and improved their performance on the TMST. Moreover, EE increased HC-Ki-67 positive cells ($p < 0.05$) in the WT mice and decreased ($p < 0.05$) in the YAC128 mice. There were no differences in the number of HC-PCNA positive cells among groups. Also, EE increased HC-DCX positive cells) in WT and YAC128 mice ($p < 0.01$).
Our results show a temporal characterization of behavioral deficits and hippocampal neuroplasticity alterations in the YAC128 transgenic mice. In particular, the present study has further characterized the positive effects of EE on HD symptoms and modulating hippocampal neurogenesis in WT mice and YAC128 mice. EE may play a potential therapeutic role in the treatment of HD symptoms.

Disclosures: E. Plácido: None. **C.P.N. Castro:** None. **P.G. Welter:** None. **M. Farina:** None. **J. Gil-Mohapel:** None. **A.L.S. Rodrigues:** None. **A.F. de Bem:** None. **P.S. Brocardo:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant MH106392
DA013137
NS100624
P51 OD011104

Title: Post-acute SARS-CoV-2 infection in non-human primate olfactory system and pyriformcortex/amygdala

Authors: *R. BOOZE[1], H. LI[1], C. MACTUTUS[1], K. MCLAURIN[1], P. DATTA[2], J. RAPPAPORT[2]; [1]Univ. South Carolina, Columbia, SC; [2]tulane national primate research center, Covington, LA

Abstract: Adverse neurological and psychiatric outcomes (i.e., post-acute sequelae of SARS-CoV-2 infection (PASC)) persist in adults clinically recovered from SARS-CoV-2. However, viral invasion and persistence in the brain following full clinical recovery has not been elucidated. We examined the distribution of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), and transmembrane serine protease 2 (TMPRSS2) in clinically recovered SARS-CoV-2 infected (2019-nCoV/USA-WA1/2020) primates (8) and controls (4) using RNAscope technology. The olfactory epithelium and pyriform cortex/amygdala exhibited abundant SARS-CoV-2, ACE2, and TMPRSS2 mRNA. SARS-CoV-2

expression in the olfactory epithelium was limited to non-neuronal cells, including sustentacular cells, basal stem cells, and Bowman's gland cells. Strong co-localization between platelet-derived growth factor receptor β and SARS-CoV-2 mRNA supports pericytes as the predominant cell type to harbor the virus in the pyriform cortex/amygdala. Persistence of SARS-CoV-2 mRNA in the pyriform cortex/amygdala was independent of acute clinical symptoms, and included detection of anti-sense (minus) strand in addition to sense strand mRNA. Results support a potential mechanism underlying PASC including long-term neurovascular disruption in specific brain regions.

Disclosures: R. Booze: None. **H. li:** None. **C. Mactutus:** None. **K. McLaurin:** None. **P. datta:** None. **J. Rappaport:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neurological Manifestations and Covid-19

Authors: *A. THAPLIYAL[1], **A. SRIRANJANI**[1,2], K. PANT[1], M. THAPLIYAL[2];
[1]Graphic Era Univ., Dehradun, India; [2]Zoology, Government PG Col. Maldevta, Raipur, Dehradun, Dehradun, India

Abstract: As the serious intense respiratory condition Covid 2 (SARS-CoV-2) pestilence spreads, it is turning out to be progressively clear that Covid infection 2019 (COVID-19) isn't restricted to the respiratory framework, and that different organs can be influenced. Specifically, infection related neurological manifestations are being accounted for increasingly more often in the literature. We focused our study on the relationship between COVID-19 and neurological disorders. Our analysis suggests that in terms of per-clinical examination, SARS-CoV-2 could be responsible for a large number of neurological manifestations, and sum up the biochemical pathways that could underlie each neurological manifestation. However, the COVID-19 pandemic fundamentally influences pneumonia and cardior-renal functions, numerous medical practitioners and healthcare professionals noted the detailed neurological inclusion of SARS-CoV-2 in combination with either with either per-existing metabolic abnormalities, medical conditions, infections or even chronic to acute inflammatory episodes of the nervous system. Understanding the systems that lead to neurological manifestations in patients with COVID-19 and how these manifestations correlate with clinical results will be instrumental in directing the ideal utilization of targeted therapeutic techniques Normal 0 false false false EN-IN X-NONE HI /* Style Definitions */ table.MsoNormalTable {mso-style-name:"Table Normal"; mso-tstyle-rowband-size:0; mso-tstyle-colband-size:0; mso-style-noshow:yes; mso-style-priority:99; mso-style-parent:""; mso-padding-alt:0in 5.4pt 0in 5.4pt; mso-para-margin-top:0in; mso-para-margin-right:0in; mso-para-margin-bottom:8.0pt; mso-para-margin-left:0in; line-height:107%; mso-pagination:widow-orphan; font-size:11.0pt; font-family:"Calibri",sans-serif; mso-ascii-font-family:Calibri; mso-ascii-theme-font:minor-latin; mso-hansi-font-family:Calibri; mso-hansi-theme-font:minor-latin; mso-ansi-language:EN-IN; mso-bidi-language:AR-SA;} <![endif]-->

Disclosures: A. Thapliyal: None. **A. Sriranjani:** None. **K. Pant:** None. **M. Thapliyal:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Training Grant 5T32NS061788-14
State of Alabama General Funds

Title: Imaging before and after COVID-19: increased brain temperature and spectroscopic markers of brain injury in regions neighboring the olfactory neural-mucosa interface.

Authors: *A. SHARMA[1], J. P. SZAFLARSKI[2];
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Abstract: BACKGROUND. Fatigue, depression, and other post-COVID-19 (C19) symptoms of "brain fog" disproportionately impact patients who had mild infection. These symptoms may stem from neuroinflammation that outlasts active C19 infection. Most neuroimaging studies to date have investigated neurological manifestations in patients with severe C19 manifestations and in post-mortem brains. Prior work has also centered on analyzing structural brain scans, though tools such as volumetric magnetic resonance spectroscopic imaging and thermometry (MRSI-t) may offer a more comprehensive view. This study combined pre- and post-C19 MRSI-t data from the same participants to map virus-induced changes in brain temperature and metabolite markers of CNS injury. **METHODS**. Participants (N=3; 24 to 26 years old) with history of mild C19 and self-reported "brain fog" were scanned at three times each at 3T: two times before infection (t_1/t_2 12 weeks apart) and at 12 weeks post-C19 (t_3). The Metabolite Imaging and Data Analysis System software package was used for spatial reconstruction and spectral processing of MRSI-t data. This included frequency alignment, B_0 inhomogeneity correction, lipid suppression, lipid suppression, spectral fitting, normalization, and integration with water reference data. Voxelwise brain temperature was calculated using the following equation: $T_{CRE} = -102.61(\Delta_{H20\text{-}CRE}) + 206.1°C$. Regions with high gliosis and/or white matter injury were localized by deriving the myo-inositol/creatine (mI/CRE) and choline/CRE (CHO/CRE) ratios, respectively. **RESULTS**. All 3 participants demonstrated post-C19 T_{CRE} increases (p=0.0001), with regional variations in magnitude (p<0.0001). Mean global T_{CRE}=37.49°C at t_1, 37.48°C at t_2, and 37.69°C at t_3. Significant post-C19 increases in mI/CRE were found in the cerebellum and left (L) hippocampus. T_{CRE} and mI/CRE were both increased post-C19 in the L postcentral gyrus. Significant post-C19 T_{CRE} increases were found in the R hippocampus, fusiform, and putamen. Despite small variations in voxelwise T_{CRE}, T_{CRE} was uniformly higher in the orbitofrontal, temporal, and entorhinal cortices. **CONCLUSIONS**. Elevated T_{CRE} and mI/CRE levels were localized to regions neighboring or connected to the olfactory mucosa. This is consistent with current hypotheses regarding viral entry and progression of neuroinflammation. The incorporation of more multimodal imaging data to existing datasets would be valuable, especially for delineating microstructural changes that underlie increased T_{CRE} and mI/CRE in these regions.

Disclosures: A. Sharma: None. **J.P. Szaflarski:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Nrp1 and furin as putative mediators of sars-cov-2 entry in human brain cells

Authors: *A. KUMAR[1], V. PAREEK[2], S. KUMAR[3], R. K. NARAYAN[1], C. KUMARI[4];
[1]Dept. of Anat., All India Inst. of Med. Sciences-Patna, Patna, India; [2]Ctr. for Cognitive and Brain Sci., Indian Inst. of Technol., Gandhinagar, India; [3]Ctr. for Proteomics and Drug Discovery, Amity Inst. of Biotech., Mumbai, India; [4]Dept. of Anat., Postgraduate Inst. of Med. Educ. and Res., Chandigarh, India

Abstract: Introduction: COVID-19 has prominent neurological manifestations including psychiatric symptoms, indicating significant synaptic pathology. Surprisingly, existing evidence suggests negligible expression of the key SARS-CoV-2 host cell entry receptor—ACE2 in human brain, which complicates understanding of the etiomechanism of the psychiatric neuropathology in COVID-19. Along with ACE2, the cellular expressions of host proteases such as TMPRSS2 and furin, which cleave the viral spike protein are considered essential for SARS-CoV-2 infection. Recent studies suggested that an alternative host cell entry receptor, NRP1, can mediate entry of furin cleaved SARS-CoV-2 spike proteins into the host cells. However, the role of NRP1 and furin in mediating SARS-CoV-2 entry in human brain cells has been least explored and remains a lacuna in the literature. **Methods:** We performed an *in silico* analysis of the transcriptomic and proteomic expressions of SARS-CoV-2 host cell entry receptors and associated tissue proteases in human brain tissue using publicly available databases. **Results:** ACE2 and TMPRSS2 were found undetectable in both transcriptomic and proteomic analyses, whereas NRP1 and furin were found detectable with low regional specificity across the human brain. Significant protein expressions of NRP1 and furin were detectable in neuronal cell, neuropil, and glial cells of the brain tissue. NRP1 showed significantly higher expression in hippocampal formation. **Conclusion:** Based on the expression analysis, SARS-CoV-2 entry in human brain cells is likely to be mediated through NRP1 and furin. The significant expression in neuronal cells, and a higher expression in hippocampal formation, suggests NRP1 may have a role in the etiomechanism of synaptic pathologies and psychiatric manifestations in COVID-19. Further studies are warranted to validate our findings.

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Poster

P322. Routes of Infection and Impacts of SARS Cov2

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Program #/Poster #: P322.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada
Baycrest Foundation
Sunnybrook Foundation

Title: Resting state electroencephalography (rsEEG) in individuals recovering from COVID-19 after self-isolation: a longitudinal observational study

Authors: E. ROUDAIA[1], S. J. GRAHAM[2,3], A. HASHEMI[4], H. GROSBEIN[1], F. A. VAHEED[1,4], A. GILBOA[1], J. J. CHEN[1,3], B. J. MACINTOSH[2], X. JI[2], M. GOUBRAN[2], S. E. BLACK[2,1], J. A. CHAD[3,1], I. CHENG[2,3], R. FOWLER[2], F. GAO[2], C. HEYN[2], A. JEGATHEESAN[2], B. LAM[2], M. MASELLIS[2], J. S. RABIN[2,3], A. B. SEKULER[1,3,4];
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Abstract: SARS-CoV-2 coronavirus disease 2019 (COVID-19) impacts many biological systems, including the brain. Individuals report symptoms of fatigue, brain fog, sensory and cognitive deficits, and psychiatric complaints, which can linger for months post- infection. The potential neural effects of COVID-19 led to the April 2020 creation of NEUROCOVID-19, investigating chronic brain effects associated with COVID-19. NEUROCOVID-19 comprises a comprehensive evaluation including multiparametric MRI, EEG, sensory and cognitive tests, and neuropsychiatric assessments of individuals with different clinical courses of the disease. Here we report preliminary EEG results from individuals who tested positive for COVID-19 (COV+) and self-isolated at home, and controls who self-isolated with flu-like symptoms but tested negative for COVID-19 (COV-). Resting-state EEG (rsEEG) was collected at an initial visit (~118 days post infection) from 41 COV+ participants (mean age: 41, range: 1 -61, 41% female), and 14 COV- participants (mean age: 42.7, range: 26-70; 57% female); to date, 24 COV+ participants and 11 COV- have returned for a second assessment 3-months later. EEG data were collected during five minutes with eyes closed and eyes open using a portable EEG headband (Muse, InteraXon) containing two frontal (F) and two temporoparietal (TP) channels. After artifact rejection and removal of eye blinks, data were divided into 2 second epochs and average spectral power was extracted in the delta (2-4Hz), theta (4-7Hz), alpha (7-14Hz), and beta (14-30Hz) bands. Left and right F and TP electrodes were averaged, and group differences were examined in linear-mixed-effects models for each condition and visit, controlling for age and sex. At initial visit, spectral power was lower overall during eyes closed for COV+ vs COV- at TP channels ($p = 0.04$), with reliable differences in the theta ($p=0.02$) and alpha ($p=0.04$) bands, and a trend in delta ($p=0.06$); COV+ also showed reduced theta at F channels ($p=0.03$). During eyes open, COV+ showed reduced beta power in TP channels ($p=0.04$) and a trend for alpha ($p=0.06$); as well as reduced alpha ($p=0.05$) and theta ($p=0.01$) power, and a trend for delta ($p=0.08$) in F channels. No reliable group differences were observed at the 3-month follow up in the current sample, although follow-up assessments are ongoing so we have reduced power at this point in time. Our results show COVID-19 can have a protracted impact on brain function, over at least 4 months, with some potential resolution over 7 months. Future work will examine within-subjects analyses and relationships between EEG and sensory, cognitive, neuropsychiatric, MRI, and self-report symptom measures.

Disclosures: E. Roudaia: None. **S.J. Graham:** None. **A. Hashemi:** None. **H. Grosbein:** None. **F.A. Vaheed:** None. **A. Gilboa:** None. **J.J. Chen:** None. **B.J. MacIntosh:** None. **X. Ji:** None. **M. Goubran:**

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Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Virginia Tech center for emerging zoonotic and arthropod-borne pathogens seed grant

Title: Sensory and autonomic ganglia of the peripheral nervous system are permissive to infection with SARS-CoV-2 and may provide an avenue of neural invasion in K18-hACE2 mice

Authors: *J. D. JOYCE[1], G. A. MOORE[3], E. HENRY[1], A. S. BERTKE[2];
[1]Translational Biology, Medicine, and Hlth., [2]Virginia Tech., Blacksburg, VA; [3]Biomed. and Vet. Sci., Virginia Maryland Col. of Vet. Med., Blacksburg, VA

Abstract: Symptoms of nervous system involvement are increasingly associated with infection with SARS-CoV-2, the causative agent of pandemic COVID-19. These symptoms span both the central nervous system (dizziness, headache, impaired consciousness) and the peripheral nervous system (impaired taste/smell/vision, neuralgia, paresthesia). Recent studies have focused on central nervous system invasion via neuronal transport through the olfactory bulb or hematogenous entry through infection of endothelial or epithelial cells in the blood-brain or blood-cerebrospinal fluid barriers, respectively, with subsequent spillover into the parenchyma. To date, the potential for infection of and invasion through the peripheral nervous system has yet to be investigated. We intranasally infected transgenic mice (K18-hACE2 mice) expressing angiotensin-converting enzyme 2 (ACE2) which is used by the virus for cellular binding and entry, and their wild-type counterparts with SARS-CoV-2 isolate USA-WA1/2020 and monitored them for six days post infection. Peripheral nervous system sensory ganglia (dorsal root ganglia, trigeminal ganglia) and autonomic ganglia (superior cervical ganglia) along with individual brain regions (olfactory bulb, cortex, hippocampus, brainstem, cerebellum), whole brain hemispheres, and spinal cord samples were collected three- and six-days post infection to assess for neural invasion. Viral RNA was detected via RT-qPCR, viral antigen via immunofluorescence, and infectious virus via plaque assay. We detected viral genome and viral antigen in the sensory (trigeminal and dorsal root) and autonomic (superior cervical) ganglia of K18-hACE2 mice and their wild-type counterparts. These results show that sensory and autonomic ganglia of the peripheral nervous system are permissive to invasion via SARS-CoV-2. Additionally, we also report the spatiotemporal replication dynamics of the virus, using genome copy number and infectious virus titer, within specific brain regions in K18-hACE2 mice, which has yet to date been assessed. Taken together, our data indicate that sensory and autonomic ganglia of the peripheral nervous system are permissive to infection with SARS-CoV-2, and suggest that they may provide alternative routes of central nervous system invasion, which may contribute to nervous system associated sequelae.

Disclosures: J.D. Joyce: None. **G.A. Moore:** None. **E. Henry:** None. **A.S. Bertke:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MH096625
NS105584

Title: Sars-cov-2 induces formation of tunneling nanotubes to facilitate dissemination of viruses and viral factors.

Authors: *D. AJASIN[1], E. EUGENIN[2];
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Abstract: SARS-CoV-2 induces formation of tunneling nanotubes to facilitate dissemination of viruses and viral factors.
David Ajasin[1] and Eliseo Eugenin[1].[1]University of Texas Medical Branch (UTMB), Department of Neuroscience, Cell Biology and Anatomy, University of Texas Medical Branch, Galveston, TX, USA.
The emergence of SARS-CoV-2 and the resulting COVID-19 disease has significantly impeded human activities worldwide. While recent development of efficacious vaccines and vaccination has reduced the spread and severity of the disease, the mechanism of viral spread within cells is just being examined. Here, we show new data that indicates SARS-CoV-2 and its protein can spread to other cells *via* cell to cell-mediated mechanism after initial receptor-mediated viral entry. We observed that viral components, and maybe the virus, can be transmitted through tunneling nanotubes (TNT), thereby avoiding extracellular immune factors such as neutralizing antibodies and other extracellular immune components. TNT is a long cytoplasmatic bridge that accomplishes long-range directed communication between cells. The proposed function for TNT is a cell-to-cell transfer of large cellular structures. TNT may serve as an additional way for Coronaviruses to spread infection between connected human microglia/macrophages, in addition to the classical receptor-mediated extracellular infection route. In agreement with this, we detected that SARS-CoV-2 spreads at a significantly higher rate when compared to HIV and other human Coronaviruses.
We hypothesize that Coronaviruses, including SARS-CoV-2 and 229E, use TNTs as a mechanism for spreading to accelerate lung and CNS disease. Thus, further investigation is necessary to identify the specific mechanism by which SARS-CoV-2 and other coronaviruses induce the formation of TNTs and utilize these processes. Also, identifying the mechanism of TNT induction can aid in the design of new therapies to reduce the viral spread of SARS-CoV-2 and other new Coronaviruses that might emerge in the future. Our study will examine the cellular, molecular and viral factors and mechanisms that induce the formation of TNTs and the mechanisms of virus trafficking across TNT. Funding: We would like to thank National NeuroAIDS Tissue Consortium (NNTC) and CHARTER for providing all human

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Disclosures: D. Ajasin: None. **E. Eugenin:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AA025964

Title: Meta-analysis of the mechanisms underlying alcohol elevation of amyloid precursor protein expression upon SARS-CoV-2 infection

Authors: S. ALABED[1,2], W. HUANG[1,2], H. ZHOU[2], R. CAMACHO[2], S. ALI[1], *S. CHANG[1,2];
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Abstract: Meta-analysis of the mechanisms underlying alcohol elevation of amyloid precursor protein expression upon SARS-CoV-2 infectionSedra Alabed*, Wenfei Huang*, Heping Zhou, Ryan Camacho, Syed Ali and Sulie L. Chang
SARS-CoV-2 infection is responsible for COVID-19 in over 120 million people. Alcohol consumption has significantly increased during COVID-19 pandemic. Despite the sparse drinking records of COVID-19 patients, our in-silico network meta-analysis studies found that that IL-1β, IL-6, JUN, NR3C1 (GR), TNF, IFNG, STAT, NFKB, HIF1A. PPARG and PPARG-RXT may play an important role in mediating alcohol augmentation of SARS-CoV-2-induced systemic inflammation and COVID-19 pathologies. Neuroinflammation signaling pathway may be involved in alcohol modulation of amyloid precursor protein (APP) production, and that TNF, IFNG, STAT1, IL-1β, IL6, and STAT3 may act as upstream regulators to increase APP production during developed COVID-19 via. With these premises, we hypothesized that exposure to ethanol (EtOH) enhances buildup of APP expression induced by SARS-CoV-2 infection. Meta-analysis using QIAGEN IPA was conducted. Applying both IPA networking and Molecule Activation Predictor (MAP) tools on each of the 11 common inflammatory mediators between alcohol and COVID-19, we found that IL-1β, IL-6, JUN, NR3C1 (GR), TNF and IFNG would activate, PPARG and PPARG-RXT would inhibit, while STAT, NFKB and HIF1A would have no effect on APP expression. However, the overall effects of concurrent activation of these 11 genes would result in strong activation of APP expression holistically. IPA Core Analysis of these 11 genes revealed a series of canonical pathways, of which the Neuroinflammation signaling and IL-10 signaling pathways were among the top 5. Subsequently, we used the MAP tool to simulate increased ethanol exposure on expression of the 11 genes, which jointly led to further activation of APP expression. By showing EtOH augmentation on APP expression upon SARS-CoV-2 infection, our studies call attention on long-term complications of alcohol and COVID-19 on Alzheimer disease and other possible neurodegenerative complications (*equal contribution).

Disclosures: S. Alabed: None. **W. Huang:** None. **H. Zhou:** None. **R. Camacho:** None. **S. Ali:** None. **S. Chang:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: LSUHS SARS-COV-2 award
NIGMS 1P20GM134974-01A1

Title: A Novel Human ACE2 BAC Transgenic Mouse Model Reveals Multiple Neuropathogenic Routes of SARS-COV-2 to Inflict Neurological and Neurocognitive Sequelae

Authors: K. KEYS, *H. ZHANG, X. TIAN, H. LI, A. YUROCHECKO, X. LU;
Louisiana State Univ. Hlth., Shreveport, LA

Abstract: Given the increasing global-spread of SARS-CoV-2, many questions remain regarding the clinical outcomes of COVID-19, including the possibility of the development of neurological disorders. Evidence of the severity and persistence of neurologic manifestations of SARS-CoV-2 infection have been recognized and is increasing. Virus infection has been speculated as the trigger of neurodegenerative diseases such as Parkinson's disease. In order to provide causal evidence and to study neurological and neurocognitive sequelae from SARS-CoV-2 infection and COVID-19 in vivo, we developed a humanized transgenic mouse model with full-length human ACE2 regulatory regions. We determined the transgene copy number and confirmed human ACE2 mRNA expression in the cortex, striatum, midbrain, cerebellum, and olfactory bulb, lung, spleen, intestine, heart, and muscle. A recombinant pseudotyped vesicular stomatitis virus (rVSV) containing rSARS-CoV-2 Spike protein with GFP or mCherry was propagated in the Vero cell line to trace the neuronal entry routes. To reveal the possible routes of SARS-CoV-2 Infection to impact CNS, we performed intranasal inoculation or intravenous systemic administration of the pseudotyped virus in the transgenic mice. We observed fluorescence protein expression in multiple organs, including CNS. Our results suggest that SARS-CoV-2 may impact CNS through direct ross the blood-brain barrier, hijacking monocytes, or invoking cytokines to elicit persistent neuroinflammation. We describe for the first time the presence along axons of viral particles, suggesting axonal transport to distant brain regions is a valid propagation strategy. The constant presence of the virus in the neurons and axons and the concomitant inflammation are destined to cause long-term or chronic sequelae related to the development or aggravation of chronic neurological diseases. Thus, our study established a small animal model with full-length human ACE2 regulatory regions that faithfully recapitulated structure, tissue distribution, and gene regulation of human ACE2 that is more valuable than most of the existent non-full-length human ACE2 mouse models for studying pathogenesis, clinical complications, and developing countermeasures for SARS-CoV-2 infection. Exploiting knowledge on the routes of SARS-CoV-2 to inflict neurological and neurocognitive sequelae will enhance our ability to address the long-term clinical neurologic outcome of viral infection, as it will shed light on underlying mechanisms of neuropathogenesis and uncover potential druggable molecular virus-host interfaces.

Disclosures: K. Keys: None. **H. Zhang:** None. **X. Tian:** None. **H. Li:** None. **A. Yurochecko:** None. **X. Lu:** None.

Poster

P322. Routes of Infection and Impacts of SARS Cov2

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P322.10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 NS04817
R01 DA044552
R01 DA044552-03S1
DA033966
NS060632
MH122241

Title: Sars-cov-2 spike protein alters firing activity of medial prefrontal cortex pyramidal neurons in a concentration-dependent manner

Authors: *S. L. CASSODAY[1], L. CHEN[2], V. NGUYEN[4], A. DONNER[4], M. G. DEMARCO[4], L. AL-HARTHI[3], X.-T. HU[2];
[1]Rush Univ. Grad. Col., Chicago, IL; [2]Microbial Pathogens and Immunity, [3]Dept. Immunology/Microbiology, Rush Univ. Med. Ctr., Chicago, IL; [4]Rush Univ., Chicago, IL

Abstract: The Coronavirus disease 2019 (COVID-19) global pandemic caused by infection of the severe acute respiratory disease coronavirus 2 (SARS-CoV-2) not only results in respiratory complications, but also commonly induces long-lasting neurological and neuropsychiatric deficits, including but not limited to headache, ageusia/anosmia, seizure and delirium. Many of these neurological/neuropsychiatric manifestations can be related or attributed to hyperexcitability and neurotoxicity in key brain regions that regulate neurocognition, such as the prefrontal cortex (PFC; and others that are anatomically and functionally connected to PFC). However, the direct impact of SARS-CoV-2 on functional activity of living neurons in such key brain regions is unknown; and has not been studied. Moreover, the COVID-19 pandemic has also impacted the US urban arears where the HIV-Associated Neurocognitive Disorders (HAND, a.k.a. neuroHIV) and Substance Use Disorders (SUD) are prominent. Abnormal neuronal hyperexcitability in the PFC, which is associated with neurotoxicity and cognitive dysfunction, also occur in people living with HIV/AIDS (PLWH), especially those diagnosed with HAND, and SUD (including cocaine use disorders, CUD); both cause neurotoxicity in the PFC. But it is unknown whether, how, and to what extent SARS-CoV-2 worsens neuroHIV or SUD-induced neuronal dysfunction and ultimately the brain dysfunction, and vice versa, in the synergistic epidemic (syndemic) of COVID-19, neuroAIDS and CUD. Such knowledge gap prohibits us to advance our understanding for the impact of COVID-19 on neuroAIDS and CUD, and to define the mechanism underlying long-tern neurocognitive consequences in the syndemic of COVID-19/HAND/CUD. To fill this gap, we assessed the effects of SARS-CoV-2 Spike protein (S1 and S2; 5nM, 10nM, and 20nM in bath) on pyramidal neurons in rat brain slices containing the medial PFC (mPFC) using patch-clamping. Responses of mPFC pyramidal neurons to S1/S2 were

evaluated. We found that S1 initially facilitated firing of mPFC neurons at lower concentration (5nM) but suppressed it at higher levels (10-20nM; n=4-5/ea). Combined S1/S2 also caused a similar inhibition of firing. Larger sample size is needed to confirm these findings. Next, we will determine how and to what extent SARS-CoV-2 exacerbate mPFC neuronal dysfunction in the context of neuroHIV and/or CUD (modeled by cocaine self-administration) using HIV-1 transgenic (Tg) vs. non-Tg rats. Together, our novel findings suggest that SARS-CoV-2 induces abnormal hyperexcitability in mPFC pyramidal neurons, which may contribute to the neurocognitive deficits in COVID-19 patients.

Disclosures: S.L. Cassoday: None. **L. Chen:** None. **V. Nguyen:** None. **A. Donner:** None. **M.G. DeMarco:** None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.01

Topic: C.08. Ischemia

Support: Internal Tel Aviv University Grant

Title: Mild carotid stenosis creates gradual,progressive,lifelong brain and eye damage:An experimental laboratory rat model

Authors: *A. S. SOLOMON[1], A. TZAMERET[1], Y. PIONTKEWITZ[2], A. NITZAN[1], N. RUDOLER[1], M. BRUZEL[1], S. PRI-CHEN[1];
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Abstract: <META NAME="author" CONTENT="אריה">**Abstract**
Purpose:In humans, carotid stenosis of 70% and above might be the cause of clinical symptoms such as transient ischemic attack and stroke. No clinical or animal studies have evaluated mild carotid stenosis ,and few examined unilateral occlusion Asymptomatic Carotid Stenosis. **Methods :** Here,Westar rats underwent bilateral or unilateral carotid occlusion of 28%-45%.Long term effects were evaluated 9-11 months later. We conducted cognitive evaluation using spatial learning in a water maze and exploration behavior in an open field.Morphology of the brain was examined by MRI using diffusion -tensor imaging (DTI) and immunohistochemistry staining of vthe brain and eyes,**Results**: Cognitive deficit was found in spatial memory and explorartion behavior in both occluded groups,brain and eyes histology presented severe damagein the bilateral group,compared to the unilateral one.DTI revealed an increase in mean diffisivity(MD) in the ventral thalamus,and decrease in fractional anisotropy in optic nerve and optic tract in bilateral occluded rats.Unilateral occluded rats showed only an increase in MD in the ventral pons.In those areas,a significant change in astrocytes , microglia,and number of apoptotic ,cells were found.**Conclusion:** We found that mild carotid stenosis, bilateral and even in unilatera locclusion,creates behavioral abnormalities presented by brain and eye histopathology. The results support our hypothesis that gradual formation of mild carotid stenosis along the life course leads to progressive damage that may create different degenerative diseases at a later age.

Disclosures: A.S. Solomon: None. **A. Tzameret:** A. Employment/Salary (full or part-time):; Tel Aviv University. **Y. Piontkewitz:** A. Employment/Salary (full or part-time):; Tel Aviv University. **A. Nitzan:** A. Employment/Salary (full or part-time):; Tel Aviv University. **N. Rudoler:** A. Employment/Salary (full or part-time):; Tel Aviv University. **M. Bruzel:** A. Employment/Salary (full or part-time):; Tel Aviv University. **S. Pri-Chen:** A. Employment/Salary (full or part-time):; Sheba.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.02

Topic: C.08. Ischemia

Title: Confined plasma leak from capillary by laser irradiation in mouse brain

Authors: *H. KUBOTERA[1], O. KUTOMI[2], S. TAKEDA[2], H. IKESHIMA-KATAOKA[1], T. INOUE[1]; [1]Waseda Univ., Tokyo, Japan; [2]Yamanashi Univ., Yamanashi, Japan

Abstract: In the central nervous system, molecular transport to the brain parenchyma is restricted by blood-brain barrier (BBB). The integrity of BBB is supported by endothelial cells, pericytes and astrocytes. Under physiological conditions, endothelial cells play a key role as a physical barrier of BBB by tight junction through expressing specific proteins, and their expression is regulated by pericytes and astrocytes. However, whether alternative physical barriers exist in the case of endothelial disruption under pathological conditions is not known. In this study, we observed very restricted leakage of blood plasma in mouse brain *in vivo*, after laser irradiation by imaging with Evans Blue or FITC-conjugated dextran (4 kDa) as plasma tracers. It was not coagulant, as fluorescence of Alexa 488-conjugated fibrinogen was undetectable in the extravascular plasma leakage. To investigate cellular mechanisms which prevented the extravascular plasma from diffusion, endothelial cells, pericytes and astrocytes were labeled with tomato lectin, NeuroTrace 500/525 and Sulforhodamine 101 (SR101), respectively. Transgenic mouse line expressing EGFP under the control of Iba1 promotor was used to examine the involvement of microglia. Endothelial cells, microglia or pericytes did not appear to serve as physical constraints to have leakage confined. However, astrocytic endfeet circumscribed the leakage in some cases, which was observed by an electron microscopy. These results suggest that astrocytic end-feet may serve as a physical barrier to restrict the diffusion of extravascular plasma into cerebral parenchyma, where endothelial barricade are disturbed. This would be a kind of fail-safe system of BBB in pathological conditions such as stroke.

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Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.03

Topic: C.08. Ischemia

Title: Sabra rats as a novel model of cerebral small vessel disease with white matter hyperintensities and peripheral oxidative stress

Authors: *R. GUY[1,4], R. VOLKMAN[1,4], E. WILCZYNSKI[2], C. YAGIL[5,6], Y. YAGIL[5], M. FINDLER[7], E. AURIEL[8], U. NEVO[2,3], D. OFFEN[1,4,3];
[1]Human Genet. and Biochem., [2]Biomed. Engin., [3]Sagol Sch. of Neurosci., Tel Aviv Univ., Tel Aviv, Israel; [4]Felsenstein Med. Res. Ctr., Petha Tikva, Israel; [5]Israeli Rat Genome Ctr., Barzilai Univ. Med. Ctr., Ashkelon, Israel; [6]Hlth. Sci., Ben-Gurion Univ. of the Negev, Beer-Sheba, Israel; [7]Neurol., Rabin Med. Ctr., Petah-Tikva, Israel; [8]Neurol., Rabin Med. Ctr., Petha Tikva, Israel

Abstract: Cerebral small vessel disease (CSVD) is the second most common cause of stroke and a major contributor to dementia. CSVD manifests in a variety of pathological mechanisms including cerebral microbleeds, intracerebral hemorrhages (ICH), lacunar infarcts, white matter hyperintensities (WMH) and enlarged perivascular spaces. Chronic hypertensive models have been found to reproduce most key features of the disease. Nevertheless, no animal models have been identified to reflect all different aspects of the human disease. Here, we describe a novel model for CSVD using salt-sensitive 'Sabra' hypertension-prone rats (SBH/y), which display chronic hypertension and enhanced peripheral oxidative stress. SBH/y rats were either administered deoxycorticosteroid acetate (DOCA) (referred to as SBH/y-DOCA rats) or sham operated and provided with 1% NaCl in drinking water. Rats underwent neurological assessment and behavioral testing, followed by *ex-vivo* MRI, biochemical and histological analyses. SBH/y-DOCA rats show neurological decline and cognitive impairment, and present multiple cerebrovascular pathologies associated with CSVD such as ICH, lacunes, enlarged perivascular spaces, blood vessel stenosis, BBB permeability and inflammation. Remarkably, SBH/y-DOCA rats show severe white matter pathology as well as WMH, which are rarely reported in commonly used models. Our model may serve as a novel platform for further understanding the mechanisms underlying CSVD and for discovery of novel therapies for this disease.

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Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

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Program #/Poster #: P332.04

Topic: C.09.Stroke

Support: NIH Grant P30GM103400
University of New Mexico BBHI 2017-1006

Title: Endogenous zinc protoporphyrin formation critically contributes to hemorrhagic stroke-induced brain damage

Authors: *R. PAN, S. YU, H. ZHANG, G. TIMMINS, J. WEAVER, Y. YANG, X. ZHOU, K. LIU;
Univ. of New Mexico, Albuquerque, NM

Abstract: ABSTRACT Hemorrhagic stroke is a leading cause of death. The causes of intracerebral hemorrhage (ICH)-induced brain damage are thought to include lysis of red blood cells, hemin release and iron overload. These mechanisms, however, have not proven very amenable to therapeutic intervention, and so other mechanistic targets are being sought. Here we report that accumulation of endogenously formed zinc protoporphyrin (ZnPP) also critically contributes to ICH-induced brain damage. ICH caused a significant accumulation of ZnPP in brain tissue surrounding hematoma, as evidenced by fluorescence microscopy of ZnPP, and further confirmed by fluorescence spectroscopy and supercritical fluid chromatography-mass spectrometry. ZnPP formation was dependent upon both ICH-induced hypoxia and an increase in free zinc accumulation. Notably, inhibiting ferrochelatase, which catalyzes insertion of zinc into protoporphyrin, greatly decreased ICH-induced endogenous ZnPP generation. Moreover, a significant decrease in brain damage was observed upon ferrochelatase inhibition, suggesting that endogenous ZnPP contributes to the damage in ICH. Our findings reveal a novel mechanism of ICH-induced brain damage through ferrochelatase-mediated formation of ZnPP in ICH tissue. Since ferrochelatase can be readily inhibited by small molecules, such as protein kinase inhibitors, this may provide a promising new and druggable target for ICH therapy.

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Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.05

Topic: C.09.Stroke

Support: University of Hong Kong, Faculty of Medicine

Title: Role of ageing in intracerebral haemahorrhage outcome

Authors: *T. LAM, G.-K. LEUNG;
Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: [Background] Intracerebral haemorrhage (ICH) has a heavy disease burden globally. ICH represents 15% of the strokes, and it has a high mortality (50%) and poor recovery. From clinical data, old age is associated with higher mortality and poorer recovery after ICH. To pave way for clinical trials targetting ageing-specific pathophysiological pathways, this study aims to explore the role of ageing in ICH. **[Method]** C57BL/6N mouse is used to model intracerebral haemorrhage. To investigate the role of ageing, C57BL/6N mouse of 8 weeks old and that of 50 weeks old are used. To induce ICH in mouse, type IV collagenase is injected intrastriatally, 0.2 cm lateral to and 0.02 cm rostral to bregma. To evaluate the severity of ICH, modified neurological severity score is calculated for each mouse. Rotarod test is used to evaluate the mouse's motor deficit. Corner turn test and cylinder test are used to evaluate loco-motor asymmetry, as well as spontaneous forelimb usage.

Histology is used to fix the mouse brain and measure haematoma size. MRI is used to follow haematoma size in a living mouse continuously over time.
To evaluate the immune response, cytokine assays are used. Oxidative stress is measured by radical oxidative species measuring assay. **[Results]** In this study, we discover that aged mice have higher mortality, poorer functional outcome, and slower recovery. Histology reviewed that aged mice have larger haematoma size in brain and slower haematoma clearance. In aged mice, higher pro-inflammatory cytokines are reported. **[Conclusion]** Our findings suggest that ageing is associated with an attenuated immune response in the brain. This includes prolonged neuroinflammation and increased inflammatory cytokines. As this is an ongoing study, further efforts will be placed on in vitro immune cell response. Immune cells from aged and young mice will be compared.

Disclosures: T. Lam: None. **G. Leung:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.06

Topic: C.09.Stroke

Support: NIH Grant R01NS078026
NIH Grant R01NS102583
NIH Grant R01NS105894
AHA Grant 19CDA34660065

Title: Cx3cr1 Deletion Promotes Neuroinflammation in Experimental Intracerebral Hemorrhage Female Mouse Model

Authors: *T. ZHU[1], R. C. KOEHLER[2], X. LAN[3];
[1]Dept. of Anesthesiol. and Critical Care Med., Johns Hopkins Med. Institutions, Baltimore, MD; [2]Dept Anesthesiol Critical Care Med., Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins Med., Baltimore, MD

Abstract: Objective: Fractalkine receptors (Cx3cr1) and its sole ligand Fractalkine (Cx3cl1) mediate inflammatory responses between neurons and microglia during neurologic disorders. Recent studies on Cx3cr1-gene knockout (KO) mice illustrated a controversial role in acute brain injuries of male mice. Herein, we studied the functions and mechanisms in female intracerebral hemorrhage (ICH) mice to explore the role of Cx3cr1 after ICH. Methods: We used ICH-subjected $Cx3cr1^{gfp/gfp}$ (Cx3cr1 KO) and wild-type (WT) female mice to investigate the role of Cx3cr1 in post-ICH recovery. The ICH models were established via collagen injection, which lysed the mice's brain blood vessels in the striatum. Post-ICH neurologic deficit behavioral tests, including the 24-point scoring system and the wire-handling task, assessed the animals' ability to control body and limb movements. Subsequent immunostaining of the extracted brain tissues (3 days post ICH) was performed to study the microglia and astrocyte activation, and Fast blue staining was applied to determine the lesion volume on day 3 post-ICH. Results: The behavior tests showed slight improvements of motor function in $Cx3cr1^{gfp/gfp}$ female mice, but no

significant differences were detected. Immunostaining of the CD68, CD68/Iba1 and GFAP illuminance around the lesion area demonstrated significant increases in the number of activated microglia and the activation level of astrocytes in Cx3cr1$^{gfp/gfp}$ mice compared to WT. There were no significant differences in the lesion volumes between the two groups. Conclusion: Cx3cr1 deficiency facilitates the up regulation of astrocyte and microglia activation in ICH female mice, which might contribute to neuroinflammation in the acute phase of ICH in females. The mechanisms of Cx3cr1 regulating glial activation in females and the gender differences of Cx3cr1 modulating ICH outcomes need to be further studied in the future.

Disclosures: T. Zhu: None. **R.C. Koehler:** None. **X. Lan:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.07

Topic: C.09.Stroke

Support: Center for Clinical and Translational Science (CCTS) Research Grant

Title: Proteomic Differences in Intracranial and Systemic Blood of Smokers and Patients with Hypercholesterolemia Undergoing Endovascular Treatment (EVT) for Emergent Large Vessel Occlusion (ELVO)

Authors: *D. HOUSE[1], K. PENNYPACKER[2], J. FRASER[3];
[2]Neurosci., [3]Neurosurg., [1]Univ. of Kentucky, Lexington, KY

Abstract: Background: Smoking and hypercholesterolemia are risk factors for ischemic stroke (IS) development. Blood cholesterol levels and smoking status have also been associated with differing outcomes following EVT. Therefore, we propose that patients from these populations differ compared to patients without these exposures, specifically in proteomic expression at time of IS. **Objective:** Examine intracranial and systemic arterial blood, collected via Blood and Clot Thrombectomy Registry and Collaboration (BACTRAC) protocol, to determine how smoking, hypercholesterolemia, and age affect proteomic expression sampled at time of IS. **Methods:** Systemic and intracranial arterial blood from 61 IS subjects underwent a proximity extension assay to detect proteomic expression of 182 proteins. Smoking status, clinical hypercholesterolemia diagnosis, and age were used in categorizing each subject. Statistical analysis was employed to evaluate proteomic differences within demographic subsets. **Results:** 61 subjects were included in our analysis, of which 36 (59%) were female. 16 (26%) were previous smokers and excluded from our analysis, 16 (26%) were smokers, mean age 63.06, while 29 (48%) were non-smokers, mean age 69.81. 14 (23%), mean age 71.29, had a clinical diagnosis of hypercholesterolemia, while 47 (77%), mean age 66.79, did not. Significant differences were observed when examining proteomic expression in intracranial or systemic arterial blood, with 106 proteomic markers varying between at least one group, 48 between smokers and non-smokers, 51 between cholesterol groups, and 46 varying in expression with age. Proteins found to be significant have established mechanisms in inflammation, neurotrophic mechanisms, and blood brain barrier function. **Conclusions:** Smoking status, blood cholesterol levels, and age are associated with varying protein expression in both systemic and

intracranial arterial blood at time of IS. We are examining the functions and relationships of these proteins. Further evaluation of this data could result in personalized biomarker identification, revealing novel information about IS development, IS severity, or clinical outcome prediction.

Disclosures: D. House: None. **K. Pennypacker:** None. **J. Fraser:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.08

Topic: C.09.Stroke

Title: Vitamin D deficiency is associated with worse mortality and behavioural outcome after experimental intracerebral hemorrhage

Authors: *A. CHAN, G. K. K. LEUNG;
Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Background.
Vitamin D deficiency (VDD) is a globally common endocrinological finding that has been increasingly implicated in exacerbating various common pathologies such as ischemic stroke and myocardial infarction. Intracerebral hemorrhage (ICH) remains the most common subtype of haemorrhagic stroke worldwide, with high mortality and rarely full functional recovery. While VDD is proposed to cause blood-brain barrier (BBB) weakening, the consequence of its deficiency in ICH is unclear. Owing to its involvement in other vascular diseases, we hypothesized that a pre-existing VDD state may worsen outcome in ICH. **Methodology.** ICH was induced via stereotaxic injection of collagenase type IV into the right striatal region of C57BL/6N mice. VDD was induced via special diet for 3 weeks pre-stroke, while normal group was fed regular chow. Deficiency was validated by serum 25-hydroxyvitaminD_3ELISA. Mortality was assessed up to seven days post-stroke. Functional outcome post-stroke was assessed by a battery of neurological tests. T2*-weighted MRI was acquired with 7T MRI scanner post-surgery to visualize intracranial lesions. **Results.** VDD mice showed significantly greater mortality compared to normal mice within 24 hours post-surgery. Surviving VDD mice demonstrated significantly worse functional outcome compared to normal mice. T2*-weighted MR imaging showed a significantly larger lesion size in VDD mice compared to normal mice. **Conclusions.** VDD mice exhibited worse mortality and functional recovery on almost all outcome measurements evaluated as compared to normal mice. Results on MRI indicate an increased initial lesion size to be the likely cause of increased mortality in VDD mice. This pilot study serves to inform future mechanistic studies on VDD and BBB integrity. More attention should be directed to VDD as an exacerbating factor in ICH.

Disclosures: A. Chan: None. **G.K.K. Leung:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.09

Topic: C.08. Ischemia

Support: Diversity Supplement NS046072-S1
NIH RO1 NS046072

Title: Sexually Dimorphic Amygdala Dysfunction in a Mouse Model of Cardiac Arrest Cardiopulmonary Resuscitation

Authors: *J. VIGIL[1], N. CHALMERS[2], E. TIEMEIER[2], P. HERSON[3], N. QUILLINAN[2];
[1]Univ. of Colorado, Anschutz Med. Neurosci. Grad. Training Program, Aurora, CO; [2]Anesthesiol., Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; [3]Neurosurg., Ohio State Sch. of Med., Columbus, OH

Abstract: Advances in modern medicine have greatly increased chances of survival following traumatic events such as cardiac arrest, stroke, or heart attack. With more people able to recover from these ischemic insults, it is becoming apparent that survivors experience long-term effects, particularly, as it relates to brain function. Our lab has previously identified memory dysfunction in a mouse model of cardiac arrest/cardiopulmonary resuscitation (CACPR) and has attributed this dysfunction to hippocampal damage and impaired hippocampal plasticity. However, no study has attempted to identify amygdala dysfunction post CACPR, despite clinical and animal model evidence of emotional dysfunctions, such as anxiety and PTSD, following global ischemia. Therefore, it is important to identify the effect that CACPR has on the amygdala, to further understand the effects of the ischemic event on the patient, and to perhaps find ways to improve quality of life. I hypothesize CACPR results in deficits in amygdala- dependent learning tasks and circuit specific deficits of long-term potentiation (LTP), the cellular mechanism of learning and memory. Experimental CA was induced in adult (8-12 week) C57BL6 mice for eight minutes via injection of potassium chloride and subsequently resuscitated by injection of epinephrine and mild chest compressions. Seven days post CA, an amygdala-dependent, delay fear conditioning paradigm was used to assess the extent to which amygdala dependent learning and memory is disrupted and field excitatory post-synaptic potential recordings were performed in the basolateral amygdala. Thus far, we have revealed a sexually dimorphic deficit in amygdala dependent fear learning and memory. Both male and female mice display a previously reported contextual fear deficit (Male: 78.6% sham freezing vs. 51.2% CACPR freezing; Female 73.8% sham freezing vs. 40.6% CACPR freezing), however, only male mice display a diminished freezing response to cued fear (56.4% sham freezing vs. 31% in CACPR). Similarly, plasticity involving cortical inputs to the basolateral amygdala is also disrupted in a sexually dimorphic manner, with only males displaying diminished LTP relative to sham controls (202% of BL in controls vs. 99% of BL in CACPR). Interestingly intra-amygdala recordings revealed no disruption of LTP in this circuit. These results support the role of the amygdala in cognitive-affective impairments after CA and provide new insights into the role that biological sex plays in mediating brain dysfunction following CA. In the future, we will continue to unravel the mechanisms by which this sexually dimorphic impairment occurs and identify therapeutic targets.

Disclosures: J. Vigil: None. **N. Chalmers:** None. **E. Tiemeier:** None. **P. Herson:** None. **N. Quillinan:** None.

Poster

P332. Hemorrhagic Stroke: Models and Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P332.10

Topic: C.09.Stroke

Title: Connectome Reorganization in Aneurysmal Subarachnoid Hemorrhage: A Graph Analysis

Authors: S. E. NELSON[1], **C. WEINER**[2], A. SIGMON[2], J. HUA[3], H. I. SAIR[3], J. I. SUAREZ[4], *R. D. STEVENS[4];
[1]Neurol., Mount Sinai Hlth. Care Syst., New York City, NY; [3]Radiology, [4]Anesthesiol. and Critical Care Med., [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Background and Purpose: Aneurysmal subarachnoid hemorrhage (aSAH) is a distributed type of brain injury which may disrupt the connectome. In this exploratory study, we hypothesized that connectivity changes would occur in canonical brain networks in the acute phase of aSAH, and be associated with outcome at 6 months.Methods: Patients with aSAH were enrolled in a single-center prospective cohort. Study subjects underwent diffusion tensor imaging (DTI) as part of a multimodal MRI scan. A weighted undirected structural connectome was created from each DTI volume using 176 regions of interest (ROIs) defined by the Johns Hopkins Eve atlas. ROIs were sorted into four networks: Default Mode Network, Executive Control Network, Salience Network, and Whole Brain. Each ROI was characterized using three graph theoretic features: Node Strength (NS), Betweenness Centrality (BC), and Node Degree (ND). Clinical and DTI graph theoretic features were used separately and in combination to train Random Forest (RF) and Logistic Regression classifiers for the prediction of functional outcome at hospital discharge and at six months after discharge, measured using the dichotomized modified Rankin Score (mRS), with favorable outcome mRS 0-2 and unfavorable outcome mRS 3-6. Model performance was determined by the Area Under the Receiver Operator Characteristic Curve (AUROC) and the Area Under the Precision Recall Curve (AUPRC). Results: In total, 56 aSAH patients underwent DTI a median (IQR) of 7 (8.5) days after admission. The best performing model (RF) combined clinical variables with NS and BC from the Whole Brain and had a mean AUROC of 0.88 ± 0.00 and AUPRC of 0.95 ± 0.00 over 500 trials for the prediction of outcome at hospital discharge. The combined model performed better than the clinical model alone (AUROC 0.81 ± 0.01, AUPRC 0.91 ± 0.00), with p-value = 0.03. NS ranked higher than BC. The predicted labels from the RF model were added as a feature: estimated discharge mRS. A second RF model was built, identical to the first but with this one added feature. This model had a mean AUROC of 0.95 ± 0.00 and an AUPRC of 0.96 ± 0.00 over 500 trials for the prediction of outcome at 6 months. Conclusions: Results indicate significant reorganization of the connectome early after aSAH, which may be linked to future changes. Performance of clinical prognostic models was increased significantly by the inclusion of DTI-derived graph connectivity metrics.

Disclosures: S.E. Nelson: None. **C. Weiner:** None. **A. Sigmon:** None. **J. Hua:** None. **H.I. Sair:** None. **J.I. Suarez:** None. **R.D. Stevens:** None.

Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P355.01

Topic: C.10. Brain Injury and Trauma

Support: U.S. Department of Defense through Congressionally Directed Spinal Cord Injury Research Project (SC160213)
USU-UCSF Partnership, Brain Injury and Disease Prevention, Treatment and Research

Title: Evaluation of 4-aminopyridine as an acute therapy for white matter injury after experimental traumatic brain injury

Authors: *K. L. RADOMSKI[1], X. ZI[1], M. D. NOBLE[2], F. LISCHKA[1], R. C. ARMSTRONG[1];
[1]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Univ. of Rochester, Rochester, NY

Abstract: Currently, there are no effective treatments to prevent axon damage and myelin loss resulting from traumatic brain injury (TBI). Axon damage is a major pathology in all forms of closed head TBI. Demyelinated axons are vulnerable to further damage, aberrant potassium currents, slowed or failed action potential conduction, and impaired information processing in neuronal networks. 4-aminopyridine (4-AP), an inhibitor of voltage-gated potassium (Kv) channels, is FDA-approved to treat chronic stage walking disability in patients with multiple sclerosis. We tested the hypothesis that acute 4-AP treatment, as compared to vehicle control, may protect viable axons and myelin after TBI in male and female mice. Starting 1 day after TBI or sham procedures, mice were treated intraperitoneally with a clinically relevant low therapeutic dose of 4-AP (0.5 mg/kg) twice a day through day 7. Quantification of serum drug levels confirmed 4-AP dosage met the human clinical target range (20-100 ng/ml). Transmission electron microscopy was used to quantify axon damage and myelin loss in the corpus callosum (CC) under the impact site. After TBI in C57BL/6 mice, 4-AP treatment significantly reduced axon damage and demyelination. In addition, 4-AP treatment significantly reduced axon damage after TBI in Thy1-YFP reporter mice with fluorescently labeled CC axons that exhibit YFP-filled swellings as a sensitive indicator of axon damage by confocal microscopy. Furthermore, in vehicle treated Thy1-YFP mice, TBI disrupted CC axon node of Ranvier molecular organization where myelin attaches at Caspr-labeled paranodes and Kv1.2 channels are localized in juxtaparanodes. 4-AP significantly reduced formation of abnormal heminodes and asymmetrical paranodes, and improved Kv1.2 channel localization. Ex vivo electrophysiology was conducted to directly assay CC axon function at 7 days post-TBI. TBI slowed conduction velocity and reduced the compound axon potential amplitude of the myelinated axon population. However, these conduction deficits were not improved with 4-AP treatment. These results demonstrate significant 4-AP benefit on axon and myelin neuropathology and molecular organization while recovery of axon function may require a longer 4-AP treatment period or involve additional mechanisms. This analysis at 7 days post-TBI clearly demonstrates benefit from 4-AP therapy at an acute stage post-injury. Further analyses are warranted to further evaluate and optimize 4-AP effects to sustain axonal viability and promote myelin plasticity as a therapeutic strategy to enhance functional recovery and mitigate post-traumatic neurodegeneration.

Disclosures: K.L. Radomski: None. **X. Zi:** None. **M.D. Noble:** None. **F. Lischka:** None. **R.C. Armstrong:** None.

Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P355.02

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS114723
NIH Grant 5P20GM103444-07

Title: Rolipram loaded PgP nanocarrier reduced secondary inflammation marker after murine brain injury

Authors: C. E. JONES[1,2], C. D. PERNICI[1,3], J. S. LEE[2], *T. A. MURRAY[1];
[1]Biomed. Engin., Louisiana Tech. Univ., Ruston, LA; [2]Bioengineering, Clemson Univ., Clemson, SC;
[3]Col. of Pharm., Univ. of Utah, Salt Lake City, UT

Abstract: Traumatic brain injury (TBI) causes an evolving secondary injury resulting in worsening neurological impairments in patients. Injury-induced activation of phosphodiesterase IV causes excessive degradation of cAMP. This impairs second messenger signaling which affects cell metabolism, survival, and memory. Rolipram (Rm), a phosphodiesterase IV inhibitor, loaded on the amphiphilic nanocarrier poly(lactide-co-glycolide)-graft-polyethenimine (PgP) effectively reduced neuronal damage in spinal cord injury. In this study, PgP loaded with Rm (Rm-PgP) was evaluated for its potential as a controlled delivery agent and targeted therapy for TBI. To visualize the PgP, a red hydrophobic dye, DiR, was loaded in PgP (DiR-PgP) and injected it into the frontal cortex in live, adult C57BL/6 mice. We counterstained the vasculature with FITC-dextran to serve as a fiduciary marker for imaging. Using multiphoton microscopy through a cranial window we observed that DiR-PgP spread through the parenchyma and around blood vessels and that it remained for at least 3 days post injection. Next, we performed intraventricular injections in the same strain of mice using PgP complexed with a plasmid encoding β-galactosidase (PgP/pβ-gal). Sections were harvested and IHC staining performed against β-gal which revealed transfection of periventricular and cortical cells. To determine if PgP passes across the blood brain barrier (BBB), we delivered PgP/pβ-gal using clinically relevant intravenous (IV) and a less invasive intranasal (IN) methods of administration. At 3 days post administration, brain tissue was harvested, fixed, and sectioned. We observed β-gal-stained cells in brain sections from both IV and IN delivery. After confirming that PgP passes through the BBB, we treated mice with Rm-PgP within 1 hour of midline fluid percussion injury using the least invasive IN mode of delivery. Mice were sacrificed at 7 days post-injury, and IHC was performed on sagittal brain sections which revealed that Rm-PgP-treated mice had significantly less astroglial activation ($p=0.028$) in the external capsule than vehicle-treated mice. Thus, we have taken the first step in validating Rm-PgP as a potential therapy to reduce secondary inflammation after traumatic brain injury. Funding was provided by NINDS grant NS114723 to TAM and partly supported by NIH/NINDS 5R01 NS111037-02 to JSL. The authors declare no competing interests.

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Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P355.03

Topic: C.10. Brain Injury and Trauma

Support: DoD award# W81XWH-19-1-0522

Title: Nano-pulsed laser therapy prevents working memory dysfunction in rats subjected to blast-induced neurotrauma.

Authors: *N. GUPTA[1], K. JOHNSON[1], S. SELL[2], I. PETROV[1], Y. PETROV[1], D. DEWITT[1], D. PROUGH[1], M. MICCI[1];
[1]Univ. of Texas Med. Br., League City, TX; [2]Anesthesiol., Univ. of Texas, Med. Br., Galveston, TX

Abstract: Traumatic brain injury is a chronic disease process which is initiated by a head trauma and persists over time leading to debilitating and potentially life changing brain damage. A potential TBI therapeutic may arise from photobiomodulation; the non-invasive and non-heat generating use of light for therapeutic advantage. We have previously reported that Nano-Pulsed Laser Therapy (NPLT), which combines near-infrared light (which is neuroprotective but has limited penetration in the human brain) and optoacoustically generated low intensity ultrasound waves (which travel throughout the entire brain), significantly reduce neuronal death and microglial activation in a rat model of focal bTBI. More recently we have found that naïve rats treated transcranially with NPLT show a significantly greater expression of brain derived neurotrophic factor (BDNF) in the hippocampus as compared to untreated animals. Based on these data, we set up to test the exploratory hypothesis that NPLT could be an effective preventative treatment for combat soldiers at high risk of bTBI. Male adult Sprague-Dawley (N=12) rats were randomized to receive NPLT or sham treatment and further randomized to receive bTBI or sham injury 24 hours after treatment. Blast TBI was delivered using the Advanced Blast Simulator that models diffuse bTBI. On post injury days 1-5 the rats underwent vestibulomotor and neurological function assessments through Beam Balance and Beam walk, and Neuroscore behavioral assays. On post injury days 13-17, the animals were tested in a modified Morris Water Maze paradigm to assess for working memory. Beam Balance, Beam Walk and Neuroscore assessments did not reveal any significant differences among the 4 experimental groups (sham treatment + sham injury, sham treatment + bTBI, NPLT + sham injury, NPLT + bTBI). The working memory Morris Water Maze test showed that bTBI rats have a reduced T1-T2 latency (indicative of memory impairment) when compared to sham-injured rats on post-injury day 17 (sham=41.208±4.960, bTBI=15.958±6.731 p=.0084; mean+/-SEM, ANOVA). On the other hand, bTBI rats pre-treated with NPLT and sham-injured rats pre-treated with NPLT showed no significant difference compared to sham animals.These results show that, while bTBI did not affect vestibulomotor and neurological functions, it significantly impaired working memory. Moreover, pre-treatment with NPLT prevented bTBI-induced working memory deficits. Further studies are ongoing to determine the effect of NPLT pre-treatment on bTBI-induced histopathological changes.

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Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

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Program #/Poster #: P355.04

Topic: C.10. Brain Injury and Trauma

Support: DOD Grant W81XWH-18-1-0167
DoD Grant W81XWH-18-1-0166

Title: Neuroimmunomodulatory Treatment Prevents Post-Traumatic Hydrocephalus in Rats

Authors: *L. JANTZIE, **Y. KITASE**, M. FOUDA, S. HAMIMI, S. ROBINSON;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Young adults who suffer moderate to severe traumatic brain injury (TBI) are at risk of developing subacute post-traumatic hydrocephalus (PTH). In clinical studies, systemic inflammation increases the risk of PTH. We hypothesize that systemic inflammation precipitates the transition from TBI to PTH, and that neuroimmunomodulation after TBI can prevent PTH. On postnatal days 21 (P21) and P23, rats received 3mg/kg lipopolysaccharide (LPS) or sterile saline i.p. On P25, under anesthesia, rats received scalp incision and blunt cranial impact. Sham rats received anesthesia and incision without impact. For treatment, rats were randomized to a regimen of erythropoietin (EPO) plus melatonin (MLT) or sterile saline from P26-P36. Both sexes were used. At P45, opening pressure (OP) were measured. Brains underwent *ex vivo* MRI for structural T2 imaging. Ventricular volumes were quantified. Serum, CSF, and brains were collected. To quantify mRNA and proteins levels, qPCR, electrochemiluminescent assays, and immunoblotting were performed. Observers were blinded to experimental groups. Differences were compared with Kruskal-Wallis test with Dunn's posthoc, with $p<0.05$ indicating statistical significance. Results show that compared to controls (n=13) at P45, PTH-veh rats (n=19) had higher OPs ($p<0.001$), while PTH-EPO+MLT rats (n=8) had lower OPs ($p=0.04$). Ventricular volume was also larger in PTH-veh rats (n=5, $p<0.001$). mRNA levels of transcription factor YAP (yes-associated protein), which regulates ependymal motile cilia maturation and is modulated by inflammation, were reduced by half in PTH brains (n=7, $p<0.001$). Serum CCL2 (MCP-1), IL-1β, lipocalin 2 (NGAL) and TIMP (tissue inhibitor of metalloproteinases) were elevated in PTH rats and normalized with EPO+MLT treatment (n=7-10, all $p<0.05$.) Activity of the protease, calpain, was also elevated in ependyma from PTH rats, and normalized with EPO+MLT treatment (n=7-10, $p<0.05$). In conclusion, PTH complicates the recovery and burden of young adults with TBI. Systemic inflammation alters cerebrospinal fluid (CSF) dynamics, including ependymal motile cilia propulsion of CSF. Initial studies with our novel model of PTH support that chronic inflammation can be modulated by post-TBI treatment with the endogenous neurorestorative agents EPO and MLT.

Disclosures: L. Jantzie: None. **Y. Kitase:** None. **M. Fouda:** None. **S. Hamimi:** None. **S. Robinson:** None.

Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

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Program #/Poster #: P355.05

Topic: C.10. Brain Injury and Trauma

Support: New Jersey Commission on Brain Injury Research Grant No: CBIR19PIL010

Title: Intercellular adhesion molecule-1 antagonistic peptide protects the brain from the transmigration of leukocytes and formation of neutrophil extracellular trap and promotes functional recovery after traumatic brain injury

Authors: *P. M. ABDUL-MUNEER, S. BHOWMICK, D. CARUSO;
Hackensack Meridian Hlth. JFK Univ. Med. Ctr., Edison, NJ

Abstract: Traumatic brain injury (TBI) causes the blood-brain barrier (BBB) dysfunction and transmigration of inflammatory blood cells into the brain, an important mechanism underlying neurovascular damage and neuroinflammation. Exploring therapeutic methods against TBI is imperative because several clinical trials that have been performed in recent years have failed to demonstrate significant improvement in outcomes for TBI. We hypothesize that inhibition of intercellular adhesion molecule 1 (ICAM-1) using ICAM-1 antagonistic peptide (IAP) remodels the vascular system and promotes functional recovery after TBI. We are uncovering and targeting the significant roles of ICAM-1 in the transmigration of leukocytes to the brain, Neutrophil Extracellular Traps (NET) formation, and neovascularization. The experimental TBI was induced *in vivo* by fluid percussion injury (10 and 20 psi) in wild-type and *ICAM-1*$^{-/-}$ mice and *in vitro* by stretch-injury (3 psi) in human brain endothelial cells. We manipulate ICAM-1 pharmacologically and genetically and conducted several biochemical analyses to gain insight into the mechanisms underlying ICAM-1-mediated transmigration of leukocytes to the brain, and NET formation. We demonstrated the mechanisms of transmigration of blood cells across the BBB due to brain injury that IAP-mediated ICAM-1 inhibition mitigates leukocytes transmigration by disrupting the paxillin-FAK signaling pathway. Since we hypothesized that the adhesion and transmigration of blood cells lead to the formation of NET, depletion of NET and promoting faster neovascularization are of great therapeutic interest in treating a wide range of central nervous system diseases. Next, we tested whether IAP reduces ICAM-1 expression in neutrophils and inhibits NETs forming ICAM-1+ neutrophils promoting neovascularization. We used a cohort of behavioral tests that include sensorimotor functions, memory, and psychological stress analyses to validate the role of IAP in promoting functional recovery following TBI. Therefore, to validate the central hypothesis, we target a subset of events towards unraveling a larger picture of neurovascular remodeling and functional recovery after TBI by attenuating ICAM-1 activity using a novel small cyclic peptide developed in the PI's lab. This work was supported by New Jersey Commission on Brain Injury Research #CBIR19PIL010 to P.M. Abdul-Muneer.

Disclosures: P.M. Abdul-Muneer: None. **S. Bhowmick:** None. **D. Caruso:** None.

Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P355.06

Topic: C.10. Brain Injury and Trauma

Support: Private Donation

Title: Novel Cannabidiol (CBD)-Infused Absorbable Implant Delivery System for Neurotrauma

Authors: *L. K. FRIEDMAN, H. PENG, R. J. ZEMAN;
Cell Biol. and Anat., New York Med. Col., Valhalla, NY

Abstract: Brain and spinal cord injuries result in profound local hypoperfusion which restricts drug delivery to the site of impact so that peripheral treatment alone would have limited access to the site of injury during the most critical phases of neurotrauma. Cannabidiol (CBD), the major non-psychotropic cannabinoid constituent, has anti-convulsant, anti-inflammatory, anti-nociceptive, anti-oxidant, and immuno-suppressive properties which may abate neurotrauma-induced pathophysiology. Treatment of either neurotrauma with CBD would be restricted due to the acute hypoperfusion at the site of impact. We *hypothesized* that continuous local delivery of CBD directly to the contusion site overlying the dura of brain or spinal cord can attenuate the risk of excitotoxic Ca^{2+} dysregulation that causes progressive cell death leading to long-term behavioral and neuropathological sequelae, such as paralysis, locomotor impairment, memory and attention deficits, depression, as well as onset to intractable seizures. Therefore, we devised a patent pending CBD delivery system for brain and spinal cord in a pre-clinical rodent model of contusion. A controlled weight drop stereotactic apparatus was used to induce cortical or spinal cord injury. CBD was delivered over the dura at the contusion site in an infused gelfoam matrix followed by subcutaneous (s.c.) injection at 20 mg/kg 3x/week. Brains and spinal cords were paraffin sectioned, processed and analyzed with Nissl, NeuN and GFAP staining methods. In both brain and spinal cord trauma models of injury, post-administration of the CBD-infused implant with s.c. administration greatly reduced lesion volume that was associated with reduced levels of anxiety and restored locomotor function. In addition, CBD decreased the loss of neurons in the ipsilateral hippocampus, reduced the number of acidophilic injured neurons of the contralateral hippocampus, and inhibited astrocyte activation in the hippocampus bilaterally, which corresponded with improved learning and memory function in the alternating T-maze and increased time with novel objects compared to contusion alone consistent with restored cognitive function. The results suggest that dual therapy by targeting the site of injury internally with an infused CBD medical carrier that is supplemented systemically can offer a more effective countermeasure than systemic or implant treatment alone for opposing the deleterious effects of penetrating head and spinal cord wounds. Whether the beneficial effect of the dual CBD treatment was due to anti-inflammatory, anti-convulsant and anti-oxidative stress properties or other undefined mechanisms is yet to be elucidated.

Disclosures: L.K. Friedman: None. **H. Peng:** None. **R.J. Zeman:** None.

Poster

P355. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P355.07

Topic: C.10. Brain Injury and Trauma

Support: VA Grant RX003198

VA Grant RX003267
Barber Interdisciplinary Research Program
Wayne State University Undergraduate Research Opportunities Program

Title: Mitigation of pain and associated oxidative and neuroinflammatory pathology post-traumatic brain injury with photobiomodulation

Authors: *K. E. BOSSE[1], S. C. LLOYD[1], A. GOODWIN[1], J. I. MALEWICZ[1], B. A. BERKOWITZ[2], A. C. CONTI[1];
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Abstract: Chronic pain is a common complication post-brain injury, impacting and impairing the recovery of over 50% of traumatic brain injury (TBI) patients. Conventional therapies, such as opioids, have proven inadequate, often promoting risk of misuse, overdose, and suicide in these patients. Prolonged presence of reactive oxidative species (ROS) and pro-inflammatory mediators occurs across pain and TBI pathology, making them attractive targets for improving TBI pain management. Photobiomodulation (PBM), a non-invasive light therapy, attenuates excessive ROS production and inflammation, raising its possibility as a non-opioid intervention strategy. Our hypothesis is that PBM mitigates TBI-induced oxidative stress, inflammatory markers, and pain responsivity. C57Bl/6 mice (10-12 weeks old, n = 8-12/group) received a moderate closed-skull impact or sham surgery and were assessed for mechanical pain using von Frey (VF). TBI induced persistent, heightened VF sensitivity to at least 6 months post-injury that was comparable in males and females. Cortical and thalamic tissues showed concomitant, marked elevations in levels of both ROS and a host of pro-inflammatory cytokines (interleukin(IL)-1 beta, IL-12, and tumor necrosis factor alpha), determined using a fluorometric assay and ELISA. Repeated, but not a single, application of PBM (whole-body, 670 nm LED, 50 mW/cm^2, 90 sec/day for 7 consecutive days), initiated 24 hours post-injury, significantly reversed the pronociceptive response detected in TBI mice compared to controls and normalized cortical and thalamic ROS and IL-1 beta levels. In defining the trajectory of this therapeutic effect, a reduction in VF responding was still evident in TBI subjects 48 hours after PBM cessation but they returned to a state of heightened nociception following a protracted (7 days) termination of PBM. These findings highlight processes that govern hypernociception following TBI and promote PBM as a clinically-translatable strategy to address pain post-TBI. Supported by facilities at the Detroit VA Medical Center, VA awards RX-003198 (KEB) and RX-003267 (ACC), the Richard Barber Interdisciplinary Research Program (JIM, BAB and ACC) and the Wayne State University Undergraduate Research Opportunities Program (JIM and ACC).

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Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.01

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Challenges and limitations of CatWalk XT: analyzing gait and locomotor parameters in spinal cord injured mice.

Authors: *A. M. HALLIBURTON, A. N. STEWART, E. P. GLASER, R. H. HAMMONS, J. C. GENSEL;
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Abstract: Up to 500,000 people sustain a spinal cord injury (SCI) annually. Consequently, locomotor abilities are reduced as a result. Locomotor abilities are the most frequently used outcomes to assess SCI injury and recovery in preclinical rodent models, of which subjective open field rating scores are the predominant test used. The Basso Mouse Scale (BMS) and Basso, Beattie, and Bresnahan (BBB) scales of locomotor recovery dominate the SCI outcome testing for thoracic SCI in mice and rats respectively. Unfortunately, this assessment has limitations such as being ordinal and not-continuous, as well as relying on the fallibilities of the human eye. The CatWalk XT objectively analyzes gait parameters and locomotor activity in mice and rats and has been used in models of SCI. However, there are major limitations to the use of Catwalk XT for SCI that require optimization to acquire efficient and useful results. This project used quantitative approaches to optimize methods for acquiring and analyzing data from SCI-mice using the Catwalk XT. We identified that the regularity index and base of support obtained from Catwalk XT were significantly correlated with functional improvements on the BMS. However, the ability of mice to cross the platform in a consistent uninterrupted pass was a major limitation to data acquisition, which became worse over subsequent days of testing. This poster will discuss our data-driven approach to circumvent difficulties with incompliant trials on the Catwalk XT that have allowed for acquiring regularity index as the best correlate to SCI injury severity. Specifically, this project has identified protocols to obtain the minimum standards for trial number, length of walkway, number of step cycles, and speed variance to obtain reliable, robust, and reproducible outcomes.

Disclosures: A.M. Halliburton: None. **A.N. Stewart:** None. **E.P. Glaser:** None. **R.H. Hammons:** None. **J.C. Gensel:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: JSPS KAKENHI Grant No. 19H03983

Title: Gait assessment in spinal cord injured mice by kinematic synergy

Authors: *Y. SATO[1,3], T. KONDO[4], H. OKANO[4], J. USHIBA[2];
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Abstract: Spinal cord injury (SCI) research to develop effective treatments has typically used rodent models whose gait functions are mainly assessed using subjective scoring or univariate kinematic parameters. However, these assessments may not correctly reflect gait deficits. Coordinated joint movements, called kinematic synergies, are known as a procedure to evaluate the basic components of gait (Courtine and Schieppati, *J. Neurophysiol.* 2004), but few studies have examined synergies in rodents. In the current study, we investigated whether kinematic synergies can be used to assess gait function in mice. Kinematic data were recorded from intact (n = 7) and SCI (n = 17) mice walking on a treadmill. Spinal contusion injuries were performed at Th10 with 70 kdyn. Then principal component analysis was applied to extract kinematic synergies from the coordinates of each joint tracked using DeepLabCut (Mathis et al., *Nat. Neurosci.* 2018). Extracted synergy patterns of SCI were classified based on the similarity of the synergy components. Locomotor function was also scored using the Basso Mouse Scale for locomotion (BMS) (Basso et al., *J. Neurotrauma* 2003). Finally, the degree of spared tissue in each group was compared to verify if the differences in synergy patterns reflect the underlying SCI neuropathology. In intact mice, we identified three synergy components: forward propagation, forward/backward bent, and upward/downward movement. The synergy patterns in SCI mice were categorized into three groups using hierarchical cluster analysis based on spatial components. We identified the different spatial components compared with those in intact mice in two groups, however in the remaining group, the spatial components were the same as in intact mice, but the temporal components were different. Moreover, a significant difference was observed between these three groups in histological damage of spinal cord ($F(2,15) = 18.93$, $p < 0.001$; one-way ANOVA with Tukey's post-hoc). On the other hand, a significant difference was not observed in BMS ($F(2,16) = 1.91$, $p = 0.184$). These results suggest that kinematic synergy reflects underlying SCI neuropathology and may provide a new assessment system in the gait of mice with SCI.

Disclosures: Y. Sato: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ALAN Inc. (not related to this study). **T. Kondo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ALAN Inc. (not related to this study). **H. Okano:** A. Employment/Salary (full or part-time):; K Pharma, Inc. (not related to this study). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. (not related to this study). **J. Ushiba:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University-based Startup, Connect Inc. (not related to this study).

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.03

Topic: C.11. Spinal Cord Injury and Plasticity

Title: A Placebo-Controlled Phase I Study in Healthy Subjects Assessing NVG-291, which Targets CNS Receptor Protein Tyrosine Phosphatase Sigma (PTPσ)

Authors: *M. DEPAUL, B. LAWRENCE, N. COLLETT, J. TOEWS, **D. MIKOL**;
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Abstract: Background: There are no approved neurorestorative treatments following damage to the CNS, whether due to trauma (e.g. spinal cord injury [SCI]) or disease-specific mechanisms (e.g. multiple sclerosis [MS], Alzheimer's disease [AD]). Substantial data from animal models of SCI, MS and AD support that chondroitin sulfate proteoglycans (CSPGs), the major plasticity-inhibiting component of the perineuronal net, are increased at sites of CNS damage and inhibit endogenous repair mechanisms. The inhibitory effect of CSPGs is mediated through protein tyrosine phosphatase sigma receptor (PTPσ), which is the principal receptor for CSPGs in the CNS. NervGen is developing a novel, first-in-class PTPσ inhibitor, NVG-291, a systemically administered peptide for treatment of nervous system damage due to trauma or disease. In animal models, NVG-291 and NVG-291-R (rodent analogue) improved functional outcomes by promoting axonal regeneration, remyelination and neuroplasticity, and were shown to cross the blood brain barrier, by virtue of their cell-penetrating tag.
Objectives: This randomized, triple-blind, placebo-controlled trial will assess the safety, tolerability, and PK of single (SAD) and multiple ascending doses (MAD) of NVG-291 administered subcutaneously once-daily in healthy subjects.
Materials and methods: Part 1 (SAD portion), which began in May 2021, is being conducted in up to 32 healthy adult volunteers randomly assigned into 6 cohorts of placebo or NVG-291 (doses ranging from 0.032 mg/kg to 0.864 mg/kg). The doses being tested are in the (human equivalent) range of doses that showed efficacy in several animal models including SCI and MS. Part 2 (MAD portion) will proceed after Part 1, and dose up to 18 subjects randomly assigned into 3 dose cohorts to receive NVG-291 or placebo once-daily for 14 days. CSF will be collected in additional subjects for analysis of NVG-291 concentration.
Results and Discussion: NVG-291 has been safe and well-tolerated to date. Parts 1/2 are expected to complete in October 2021 and March 2022, respectively. The study will establish the safety and tolerability of NVG-291 and will measure exposure in the plasma and CSF, to support advancement to clinical trials in patients with SCI, MS, and AD in 2022.

Disclosures: M. DePaul: A. Employment/Salary (full or part-time):; NervGen Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NervGen Pharma. **B. Lawrence:** F. Consulting Fees (e.g., advisory boards); NervGen Pharma. **N. Collett:** A. Employment/Salary (full or part-time):; NervGen Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NervGen Pharma. **J. Toews:** A. Employment/Salary (full or part-time):; NervGen Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NervGen Pharma. **D. Mikol:** A. Employment/Salary (full or part-time):; NervGen Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NervGen Pharma.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life
University of Texas at Austin Startup

Title: Investigating sex differences in mouse neuropathic pain after spinal cord injury

Authors: E. K. GREENOUGH, S. E. LEE, *A. D. GAUDET;
Univ. of Texas at Austin, Austin, TX

Abstract: Spinal cord injury (SCI) causes neuropathic pain in ~65% of injured individuals. Sex differences in neuropathic pain have been observed in patient populations and animal models. Previous studies investigating sex differences in neuropathic pain following SCI have not been in agreement; however, it remains unknown how pain symptoms are affected by injury severity or neuroinflammation. Here, we aimed to establish whether there are sex differences in mouse neuropathic pain symptoms, lesion size, and neuroinflammation after SCI. 20 male and 20 female mice received either T9 contusion SCI (60 kDyn) or T9 laminectomy (sham surgery). Pain symptoms were assessed over 28 days after sham or SCI surgery using established pain measures: von Frey and Hargreaves testing for mechanical allodynia and heat hyperalgesia, respectively. Both female and male mice showed similar locomotor deficits and recovery after SCI (Basso Mouse Scale). Thermal and mechanical pain symptoms were present in both male and female SCI groups after injury. Male mice with SCI exhibited increased mechanical sensitivity compared to females. Sex differences in heat sensitivity appeared at day 21 with females showing increased sensitivity compared to male SCI animals. Tissue will be analyzed to determine the effect of sex on lesion size and neuroinflammation after SCI. These findings highlight that sex differences in neuropathic pain are present in a moderate-severity SCI model, and suggest that sex differences in pain following SCI are dependent on injury severity. Continued investigation into the underlying mechanisms of sex differences in neuropathic pain will aid development of more effective pain-relieving treatments for SCI.

Disclosures: E.K. Greenough: None. **S.E. Lee:** None. **A.D. Gaudet:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life
University of Texas at Austin startup

Title: A novel heat-light conflict test for mice unmasks latent anxiety behavior in females after spinal cord injury

Authors: *S. E. LEE[1], E. K. GREENOUGH[2], L. K. FONKEN[3], A. D. GAUDET[2];
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Abstract: Anxiety disorders affect 32% of individuals across their lifetime, with a nearly 2x higher prevalence in females. Anxiety exhibits high comorbidity with chronic pain, which implies that anxiety and pain disorders may also share underlying physiological mechanisms. We aim to explore the relative salience of anxiety versus pain using our novel Thermal Increments Dark-Light (TIDAL) conflict assay. The TIDAL conflict assay allows mice to move freely in an apparatus with two connected chambers: one light chamber, maintained at 31°C; and one dark chamber, which starts at 31°C but then increases incrementally from 39 to 44°C. In the first experiment, we reveal that C57BL6/J mice displayed sex differences in the salience of heat vs. anxiety. Specifically, female C57BL6/J mice preferred the dark plate more than male mice despite increasingly hyperthermic temperatures. In the second experiment, we observed distinct TIDAL preference differences in mice with spinal cord injury vs uninjured mice; both male and female mice with spinal cord injury exhibited increased dark-heated plate preference on the TIDAL assay at all tested temperatures (31°C-44°C). Our new TIDAL conflict test unmasks increased salience of stimuli that elicit anxiety-like behavior (vs. heat) in females and after spinal cord injury. Therefore, conflict assays with freely moving mice can illuminate behavioral phenotypes that are concealed at baseline; these strategies could have important implications for understanding the relative salience of anxiety, pain, and other conditions in combination with sex or neurologic disorders.

Disclosures: S.E. Lee: None. **E.K. Greenough:** None. **L.K. Fonken:** None. **A.D. Gaudet:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Paralyzed Veterans of America Research Foundation #3166

Title: Quantifying Mouse SCI-related behavior changes using ELAN annotation software

Authors: *A. CHUANG[1], H. KLOEFKORN[2], S. HOCHMAN[3];
[1]Emory Univ., Decatur, GA; [2]Physiol., Emory Univ., Atlanta, GA; [3]Dept Physiol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Spinal Cord Injuries (SCIs) may cause physical disability, regulatory dysfunction, and chronic pain, which may alter behavioral phenotype. Changes in motor behavior may indicate underlying dysfunction while also providing predictive value in pathogenesis and therapeutic efficacy. While altered behavior is monitored after SCI clinically, pre-clinical analogues are cumbersome and expensive. We tested use of a freely available annotation software (ELAN) as a simple method to quantify rodent behavior to show SCI-related behavioral changes.
We videoed five adult female C57BL/6 mice for 12 hours (noon to midnight) in individual home cages before SCI (baseline, n=5) and twelve weeks after receiving a moderate (50kDyne impact, infinite

horizon impactor) T12 contusion SCI (SCI, n=5). As an initial proof of concept, one hour (3-4PM) of motor behaviors were manually scored before and after SCI. Behaviors (exploration, rearing, eating, drinking, grooming, resting) were quantified using the ELAN linguistic annotation software,[1] an open-source tool able to flexibly assign annotations to video and export in several formats. Video was imported then scanned frame-by-frame. Behavior transitions were video-tag and assigned the appropriate description. Once a video was fully annotated, it was exported to Excel for analysis.
Data were analyzed using two-tailed student's t-tests. SCI animals decreased the number of behavior transitions per hour relative to their baseline values ($p=0.03$), suggesting animals consolidate their behaviors after SCI. Additionally, rearing and exploration events lasted longer after SCI compared to their baseline values ($p=0.02$ and $p=0.02$, respectively) but were less frequent ($p=0.04$ and $p=0.03$, respectively). This may indicate initiating rearing may be more costly than maintaining rearing posture. As exploration includes myriad sub-behaviors (e.g. burrowing, sniffing, locomotion, and nesting), more detailed scoring will be needed to understand these changes. Eating event duration increased after SCI relative to their baseline values ($p=0.02$), however, cumulative eating time and animal weight did not change.
We conclude that ELAN is a simple and robust method to annotate mouse movement-related behaviors and their changes in relevant disease models. Here it enabled us to identify several significant differences in a SCI model (contusion) known to elicit neuropathic pain. Additional studies are planned to use ELAN-derived behavior scoring to develop algorithms that enable automated behavior scoring methods.
Funded by PVA Research Foundation (#3166).
1.Wittenburg, P. et al. *Proc. 5th Int. Conf. Lang. Resour. Eval. Lr.*, 2006.

Disclosures: A. Chuang: None. **H. Kloefkorn:** None. **S. Hochman:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD Grant SC190134

Title: Molecular MRI and PET imaging link changes in neuroinflammation to locomotion deficits in contusion injured spinal cord

Authors: C. MU[1], *J. REED[2], M. N. TANTAWY[2], F. WANG[2], J. C. GORE[2], L. M. CHEN[2];
[1]Biomed. Engin., Vanderbilt Univ., Nashville, TN; [2]Vanderbilt Univ. Inst. of Imaging Sci. & Dept. of Radiology and Radiological Scienc, Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Spinal cord injury (SCI) severity and recovery are influenced by complex pathological mechanisms, including demyelination/remyelination, glutamate excitotoxicity, scar formation, and inflammatory responses. The overall goal of this study is to develop and validate noninvasive, mechanism-based imaging biomarkers of these processes to assist evaluation of injury severity, guide interventions, predict recovery, and provide objective measures of treatment outcomes. We used

quantitative chemical exchange saturation transfer imaging (CEST) MRI and translocator protein (TSPO) PET to quantify dynamic molecular changes associated with neuroinflammation over 8 weeks in a contusion lumber (L1) SCI rodent model. 14 SCI and 5 sham control rats were studied. Standard measures including BBB scores, open field, Von Frey filaments, gait analysis, and hot plate test were used to correlate behavioral deficits to the imaging measurements. Data from ROIs in high resolution CEST images were converted to Z-spectra and were fit to a 5-pool Lorentzian peak model. The peak amplitude of the nuclear Overhauser effect (NOE) pool (at RF offset -1.6 ppm) during the 1st week post-op was significantly lower for SCI compared to the sham rats, and amplitude increased progressively through 8 weeks post-injury. The NOE (-1.6 ppm) pool has been linked to mobile macromolecules, such as lipid and membrane proteins, that could be disrupted due to neurodegeneration effects triggered by elevated release of glutamate and pro-inflammatory cytokines at the injury site. PET images acquired within 10 days post injury demonstrated elevated TSPO at and rostral to the injury epicenter. BBB scores for the hindlimbs decreased during the first week of injury, along with decreased normalized open field movement. Motor function began improving within 7-10 days post-injury, while sensory deficits were detected well past 10 days post-injury, with minimal responses to filament strengths up to 60g. Hot plate responses indicated increased pain sensitivity, with decreased hot plate withdrawal times for SCI rats. BBB scores, open field activity, and Von Frey measurements strongly correlated with the -1.6 ppm NOE peak amplitude decrease during Week 1 and subsequent recovery over time. The results indicate that the molecular information provided from CEST and PET measures can be used as biomarkers of neuroinflammation dynamics. These imaging biomarkers for SCI severity and longitudinal recovery progress can be readily translated for human clinical applications. The novel information will help further development of treatments targeting specific pathological mechanisms in preclinical studies.

Disclosures: C. Mu: None. **J. Reed:** None. **M.N. Tantawy:** None. **F. Wang:** None. **J.C. Gore:** None. **L.M. Chen:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation

Title: Depression like behavior following spinal cord injury in male and female rats is associated with a decline in cognitive performance

Authors: *A. STEFANOV, R. M. JOSEPH, A. HEMPHILL, R. DUNDUMULLA, K. BRAKEL, J. RAU, K. S. MONTGOMERY, M. HOOK;
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Abstract: Each year, the global incidence of traumatic spinal cord injury (SCI) is estimated to number in the hundreds of thousands. On top of the disruption of physical and physiological function already complicating their recovery, 26% of SCI patients also suffer from major depressive disorder (MDD) and

60% experience impairments in cognition. Evidence suggests that these comorbidities may share molecular and neuroanatomical correlates. We aimed to investigate the association of depression and cognitive deficits following a lower-thoracic contusion SCI in young and middle-aged male and female Sprague-Dawley rats. Before spinal injury, and at acute and chronic time points after, components of depression-like behavior such as anhedonia, decreased sociability, and learned helplessness were tested using our behavior ethogram. We found that depression-like behavior manifests within a month post-SCI in 30-45% of subjects, commensurate with the clinical incidence, and persists into the chronic phase of recovery. To examine cognition during this phase, we trained rats in the Barnes Maze. We found that the subset of SCI subjects displaying depression-like behavior also demonstrated poor spatial learning strategies compared to their non-depressed SCI and sham counterparts. Our findings suggest an association between depression in acute spinal cord injury and cognitive decline in chronic stages of recovery, and indicate that our rodent SCI model is a powerful tool to investigate the molecular mechanisms underlying these outcomes.

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Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.09

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 546123

Title: Role of MRI Biomarker in Prognosticating Recovery Following Spinal Cord Injury In a Yucatan Animal Model

Authors: J.-W. KIM[1], M. SHARMA[2], *M. NEGAHDAR[3], R. J. BERT[3], M. L. MORGAN[2], R. U. AHMED[2], D. R. HOWLAND[2], S. E. DAVISON[4], L. C. SHERWOOD[4], M. D. BUDDE[5], J. XU[1], **M. BOAKYE**[2];
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Abstract: Background and Objectives: The Yucatan minipig model has increasingly been used as a large animal model of SCI. However, in vivo imaging using this model is lacking. Our goal is to investigate the role of MRI biomarkers in prognosticating recovery following spinal cord injury (SCI) in a large animal model. **Materials and Methods:** Eleven minipigs were scanned after 1 week from thoracic contusion injury (short-term). Four of them were scanned again after 12 weeks from injury (long-term). Anatomic Imaging. Three anatomic sequences were acquired: T1, T2, and STIR. Each sequence was performed with a sagittal large FOV to evaluate the whole spine, a sagittal small FOV for higher resolution to cover the site of injury, and axial imaging in several locations distal and proximal to the injury site. Inner-volume-imaging DTI data were collected superior to the site of the injury centered at T3

vertebra including 12 axial slices with 5 mm thickness each. DTI data acquisition was gated to oxygen saturation signal (SpO2) to reduce motion artifact. After the DTI volumes of each axial slice were registered using 2-dimensional x- and y-translation and DTI maps were generated. White matter regions of interest (ROIs) were manually defined based on mean b0 images, mean diffusion-weighted images, and DTI fractional anisotropy (FA) maps. Average DTI measures were calculated for the whole slices, inferior half slices, and superior half slices. **Results:**For short-term scans, the mean: standard deviation (SD) of FA across inferior half, superior half, and all slices were 0.74:0.05, 0.70:0.04, and 0.72:0.05, respectively, and those of radial diffusivity (RD) were 0.46:0.11, 0.51:0.09, and 0.48:0.09, respectively. For long-term scans, those of FA were 0.64:0.05, 0.74:0.03, and 0.68:0.02, respectively, and those of RD were 0.65:0.13, 0.39:0.05, and 0.52:0.04, respectively. In the inferior half slices, the FA values at long-term scans decreased > 7% for all 4 subjects ($p < 10^{-4}$) while RD values increased > 27% for 3 subjects ($p < 10^{-8}$) as compared to short-term scans. In the superior half slices, 2 subjects showed increased FA (> 9%, $p < 10^{-4}$) and decreased RD (> 29%, $p < 10^{-8}$) as compared to short-term scans. Others did not have statistically significant change over time. **Conclusion:** The decreasing FA and increasing RD distal to the injury region implies Wallerian degeneration. The normalization of FA and RD proximal to the injury region from 2 subjects indicates possible recovery after 12 weeks from injury. These data provide preliminary DTI data in a well-described thoracic contusion model in Yucatan minipigs.

Disclosures: J. Kim: None. **M. Sharma:** None. **M. Negahdar:** None. **R.J. Bert:** None. **M.L. Morgan:** None. **R.U. Ahmed:** None. **D.R. Howland:** None. **S.E. Davison:** None. **L.C. Sherwood:** None. **M.D. Budde:** None. **J. Xu:** None. **M. Boakye:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH 1F31NS117124-01A1

Title: Longitudinal neuromuscular connectivity and muscle function following spinal cord injury

Authors: *M. HARRIGAN, M. BALCH, W. D. ARNOLD, J. M. SCHWAB;
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Abstract: Objective electrophysiological measures are needed for effective cross-species translation, as prior work has uncovered pronounced fundamental differences in the anatomical and functional characteristics of the motor systems in primates versus rodents. The ability to factor neurobiological differences has been limited and constitutes an obstacle for the translation of rodent models to patients. The ability to assess different spinal cord regions and pathologies may be of particular benefit to SCI research. Additionally, low replicability and robustness of behavioral assays of functional recovery limit translation of findings in preclinical SCI models. Therefore, objective electrophysiological measures will optimize predictive value of experimental SCI studies. Compound muscle action potential (CMAP) and motor unit (MU) number estimation (MUNE) allow longitudinal monitoring of MU integrity in patients.

In analogy we refined these methods for assessing spinal MU input in the mouse hindlimb. We longitudinally applied these electrophysiological techniques over a period of five weeks in mice with thoracic SCI. Muscle contractility was also measured and compared to electrophysiological measures. Moving forward, CMAP and MUNE measures are putative electrophysiological biomarkers of forelimb and hindlimb MU integrity poised to guide and improve bi-directional translation in experimental spinal cord disease models.

Disclosures: M. Harrigan: None. **M. Balch:** None. **W.D. Arnold:** None. **J.M. Schwab:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS R01NS078494

Title: Sex-dependent cortical volume changes in patients with Degenerative Cervical Myelopathy

Authors: *T. C. OUGHOURLIAN[1], C. WANG[2], N. SALAMON[2], L. T. HOLLY[3], B. M. ELLINGSON[2];
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Abstract: Degenerative cervical myelopathy (DCM) is a chronic condition involving the progressive deterioration of osseocartilaginous structures within the cervical spine resulting in compression of the spinal cord and is the most common spinal cord impairment in people over the age of 55. Chronic cord compression from DCM can lead to neck pain, weakness in the upper limbs, loss of fine motor skills, and/or limb dyscoordination. Compared to healthy controls (HCs), studies have shown DCM patients experience structural and functional reorganization in somatosensory, motor, and cerebellar brain regions; however, sex-dependent cortical differences in DCM patients remains largely unexplored. In the present study, we investigate the role of sex differences on the structure of the cerebral cortex in DCM and determine how structural differences may relate to clinical measures of neurological function. T1-weighted structural MRI scans and modified Japanese Orthopedic Association (mJOA) scores were acquired in 85 patients with DCM. Structural MRI scans of 90 age-matched HCs were obtained from the Parkinson's Progression Markers Initiative database (www.ppmiinfo.org/data). Cortical segmentation, gray matter volume (GMV) computation, brain surface smoothing, standard space registration, and whole-brain GMV analysis were completed using FreeSurfer. A general linear model was used to determine vertex-level significant differences in GMV between the following groups 1) HC males and HC females, 2) DCM males and DCM females, 3) DCM males and HC males, and 4) DCM females and HC females. We observed no significant difference in GMV between HC males and females. However, DCM males exhibited larger GMV in motor, language, and vision related brain regions compared to female patients. In female subjects, DCM patients exhibited smaller GMV than HCs in the pericalcarine and lingual cortices, whereas in males, patients observed larger GMV in vision and language related

cortices compared to HCs. Both males and females demonstrated a significant positive correlation between GMV and mJOA score, in which patients with worsening neurological symptoms exhibited decreasing GMV primarily across somatosensory and motor related cortical regions. Interestingly, females exhibited a similar association, albeit across a broader range of cortical areas including those involved in pain processing. In sensorimotor regions, female patients consistently showed smaller cortical volume compared with male patients. Results from the current study suggest strong sex-related differences in GMV in patients with DCM, which may reflect hormonal influence or differing compensation mechanisms.

Disclosures: T.C. Oughourlian: None. **C. Wang:** None. **N. Salamon:** None. **L.T. Holly:** None. **B.M. Ellingson:** None.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: OKC VA Pilot Award

Title: Disconnection of Stress from Visceral Pain in a Contusion Injury Model of Spinal Cord Injury

Authors: *A. JOHNSON;
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Abstract: Introduction: The Veteran Affairs (VA) health care system is the largest single network of spinal cord injury (SCI) care in the nation. Many SCI patients develop complications involving the gastrointestinal (GI) tract including constipation and chronic visceral pain. We have previously demonstrated that activation of limbic brain areas can enhance colonic motility and sensitivity, but it is unknow if the brain-gut connection is maintained following SCI. Our hypothesis is that brain-gut connections can be re-wired following SCI and that activation of specific central networks may offer treatment opportunities for patients with SCI-induced bowel problems. **Methods:** Male Fischer 344 rats were randomized to receive a contusion (300 kdyne impact, Infinite Horizons model 400) SCI at T10 or Sham-SCI (incision without damage). The Basso, Beattie, Bresnahan (BBB) scale was used to assess locomotion one day prior to injury and weekly following the injury. Fecal pellet output in the home cage was assessed daily. On day 21-post injury, rats were randomized to receive 7 days of water avoidance stress (WAS) or Sham-WAS. Colonic sensitivity to distension was measured at 28-days after injury. Results were analyzed with a repeated measure two-way ANOVA with Bonferroni's post-hoc analysis (mean ± standard deviation). **Results:** Rats with SCI displayed a persistently low functional score in injured animals (median BBB score: 3/21 at one week, 7/21 at four weeks in rats with SCI, 21/21 at all weeks for Sham-SCI), indicating impairment of hindlimb function. While there was only any acute decrease in fecal pellet output during the first week after injury, rats with SCI could still elicit increased fecal pellets in response to WAS, suggesting that a connection between the brain and gut could be stimulated by stress despite the SCI. Assessment of colonic sensitivity measured by the visceromotor

response following T10 SCI was not possible due to the lack of hindlimb control. **Conclusions:** We demonstrated that stress-induced colonic motility was maintained following SCI, suggesting that some brain-gut connections can be remodeled to promote GI function following SCI. These finding support further studies using central modulation as a potential option for restoring GI function in in veterans with SCI.

Disclosures: A. Johnson: A. Employment/Salary (full or part-time):; OKC VA Health Care System, University of Oklahoma Health Sciences Center.

Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DoD Grant SC190100

Title: Noninvasive measurement of gastrointestinal motility following spinal cord injury in pigs

Authors: *R. U. AHMED[1], **C. A. KNIBBE**[1], F. WILKINS[1], J. ETHRIDGE[1], M. V. VADHANAM[1], C. M. MOORMAN[1], M. L. MORGAN[1], S. E. DAVISON[2], L. C. SHERWOOD[2], S. S. BARVE[3], D. R. HOWLAND[1], J. SEMLER[1], T. L. ABELL[3], M. BOAKYE[1];
[1]Dept. of Neurolog. Surgery and Kentucky Spinal Cord Injury Res. Ctr., [2]Comparative Med. Res. Unit, [3]Dept. of Med., Univ. of Louisville, Louisville, KY

Abstract: Autonomic nervous system disruptions after SCI (spinal cord injury) lead to severe gastrointestinal (GI) dysfunction that directly impact quality of life and chronic morbidity. The SmartPill™ (Medtronic, MN) is a novel, non-invasive tool that actively transmits pH, temperature, and pressure when ingested. We administered the Smartpill™ with normal diet in three pigs that underwent direct T10/T11 SCI impact with contusion from a 10cm drop height to assess feasibility of the SmartPill as a tool to assess GI functionality. Pigs were administered the SmartPill™ with a regular diet, both before injury and at two and six weeks post-injury. Tributyrin, a triglyceride reported to influence the gut microbiome and improve gut dysbiosis, was administered to pigs 1 and 2 post-injury. Gastric Emptying Time (GET), Colon Transit Time (CTT), Small Intestine Transit Time (SITT), antrum maximum pressure (AMP), and minimum pH (min pH) were recorded by MotiliGI®software and analyzed. We observed the following pre-injury transit times in animals 1 and 2, respectively: GETs of 4:06:30 and 7:21:10 and CTTs of 19:55:55 and 17:27:30. We observed the following times at two weeks post-injury in animals 1, 2, and 3, respectively: GETs of 12:06:35, 99:07:37, 8:36:10 and CTTs of 21:58:18, 26:25:03, and 18:08:05. At six weeks post-injury, we recorded the following times in animals 1, 2, and 3, respectively: GETs of 6:58:00, 8:13:51, and 8:41:40 and CTTs of 36:29:15, 22:00:27, and 86:13:05. We observed pre-injury min gastric pHs of 0.4 and 0.3, 2-week post-injury min gastric pHs of 0.5, 0.3, 0.2 and 6-week post-injury min gastric pHs of 0.5, 0.5, 0.3 in pigs 1, 2, and 3, respectively. We also noted pre-injury AMPs of 13451.92 and 8624.08, 2-week post-injury AMPs of 7204.76, 5920.24, and 11208.56, and 6-week pressures of 12609.13, 5928.46, and 7358.97 mmHg*sec for pigs 1, 2, and 3, respectively. These

findings suggest delays in GETs and CTTs post-injury but have minimal impact in SITTs or on minimum gastric pH. The prolonged GET and CTT can influence absorptive capacity in the gut, though it is unclear with the addition of Tributyrin how absorption is influenced and further studies are needed. The min gastric pHs indicate there is no notable changes in gastric acid secretion, though upper duodenal pH due to the interplay of bicarbonate and acid secretion is still of interest. There are decreases in AMP after injury, which could indicate autonomic dysfunction of the pyloric sphincter. These preliminary results support the utility of the Smartpill™ in pigs to assess GI function by reliably collecting metrics that accurately reflect post-injury conditions.

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Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Krembil Research Institute post-doctoral fellowship

Title: The changes in systemic monocytes in humans undergoing surgical decompression for degenerative cervical myelopathy may influence clinical neurological recovery

Authors: *P. VIDAL VERA[1,2], A. ULNDREAJ[3], L. TETREAULT[4], J. HONG[2], M. FEHLINGS[2]; [1]Univ. Catolica De La Santisima Concepcion, Concepcion, Chile; [2]UHN, Div. of Genet. & Development, Krembil Neurosci. Ctr. and Spine Program, Canada, ON, Canada; [3]UHN, Div. of Genet. & Development, Krembil Neurosci. Ctr. and Spine Program, Canada, ON, Canada, Canada, ON, Canada; [4]Grad. Entry Medicine, Univ. Col. Cork, Ireland, Ireland

Abstract: Background: Degenerative cervical myelopathy (DCM) is the most common cause of non-traumatic spinal cord injury worldwide. Surgical decompression is recommended as the preferred treatment strategy for DCM as it halts disease progression and improves neurologic symptoms. We previously demonstrated that neuroinflammation, including monocytes, plays a critical role in the pathobiology of DCM and in ischemic-reperfusion injury (IRI) following surgical decompression. Monocytes are able to enter the spinal cord and brain tissues due to damage to the blood spinal cord and blood brain barrier following injury. Studies have demonstrated that stroke patients and individuals undergoing hip replacement surgery have increased systemic levels of monocytes. Additionally, changes in the signalling responses of monocytes are associated with post-surgical recovery or with ischemic neural tissue damage. Herein, we investigated the role of systemic monocytes as a predictive biomarker for clinical recovery following decompressive surgery for DCM. **Findings:** There was a 2-fold increase in the number of monocytes in DCM patients at 24 h following decompression as compared to baseline levels, which was associated with a significant improvement in the modified Japanese Orthopedic

Association scale (mJOA) at 6-months after surgery ($p < .0001$). In a mouse model of DCM, depleting acute monocytes reduced the non-classical ($Ly6C^{low}$) subset from circulation ($p < .05$) and resulted in a 1.8-fold increase in CD11b expression in the spinal cord at 5 weeks following decompression. Acute monocyte depletion was accompanied by a modest decline in long-term overground locomotion, as evidenced by significantly reduced hindlimb swing speed. **Conclusions:** This work demonstrated that decompressive surgery leads to an acute increase in peripheral monocytes in human DCM patients, which is modestly associated with clinical recovery. We anticipate that this work could contribute to the implementation of routine measurements of blood monocyte subsets, their activation state, and production of cytokines following decompressive surgery. This information could help to select perioperative anti-inflammatory treatments that can enhance the beneficial effects of decompressive surgery and reduce the incidence of post-operative complications, while avoiding a reduction in systemic monocytes.

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Poster

P364. Spinal Cord Injury: Animal Models and Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P364.15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Leona M. & Harry B. Helmsley Charitable Trust 2016PG-MED001

Title: Urinary biomarkers in persons with chronic spinal cord injury

Authors: *S. KAPP[1], S. C. ASLAN[3,1], B. UGILIWENEZA[3,1], D. WANG[3,1], E. WYLES[3,1], K. JOHNSON[3,1], J. CAI[1,2], M. MERCHANT[2,1], T. CUMMINS[2,1], A. H. HERRITY[3,1];
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Abstract: Neurogenic bladder dysfunction after spinal cord injury (SCI) results in involuntary bladder contractions and simultaneous contractions of the urinary sphincter, producing high internal bladder pressure, which can lead to urinary reflux into the kidney, potentially damaging the upper urinary tract. A loss of normal elasticity in the bladder results in poor compliance and is one of the greatest risk factors for long-term complications to the kidneys, such as hydronephrosis and renal failure. The inability to effectively empty the bladder also increases the risk of urinary tract infections (UTIs), which are the single most common secondary medical complication after SCI. Urinary proteomics can be used to investigate the intracellular molecular pathways perturbed after SCI and reveal the protein component directly reflecting the dysfunction of cells within the urinary tract. In the current study, a total of 22 participants (non-disabled, n=10; SCI, n=12) provided clean-catch second morning urine samples. Urine samples from those with SCI were collected midstream, via urethral catheterization. Quantitative proteomic analysis of urine samples was conducted with qualitative and quantitative LC-MS/MS approaches implementing a urine-modified Filter-Aided Sample Preparation (U-FASP) method. Up and downregulated proteins were measured in comparison with non-disabled (ND) controls. In total, 1314

urine proteins were identified and quantified using a strict 1% FDR (false discovery rate) cutoff and 2-peptide identification for further bioinformatics analysis. Informatic analysis using Metaboanalyst 5.0 and PANTHER classification revealed that urine immunoglobulin and calmodulin-related proteins were significantly upregulated in samples from individuals with SCI relative to ND controls. Immunoglobulins can play an important role in the body's immune response mechanisms to bacteria, such as from chronic UTIs. Importantly, urinary excretion of calcium binding proteins may be related to stone formation, which can be attributed to the alkaline pH of infected urine as well as due to chronic catheterization. The data indicated significant changes in the urinary protein concentrations of from individuals with SCI relative to controls, suggesting the potential presence of early biomarkers within urine samples. Since the majority of the urinary proteins are generated by the kidney, the diverse urinary composition provides a comprehensive view of the local and systemic physiology. Current studies are investigating differences in the urinary proteomic profile between those intermittently catheterizing versus those using suprapubic catheters.

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Poster

P390. Pain Models: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P390.01

Topic: D.03. Somatosensation – Pain

Support: Department of Defense PR182408

Title: Evaluation of recombinant GABAergic cells releasing MVIIA in models of chronic pain in rats

Authors: K. LIEBMANN*, S. JERGOVA, M. HERNANDEZ, B. MARIN, D. QADIR, J. SAGEN; Univ. of Miami, The Miami Project, Miami, FL

Abstract: The underlying mechanisms of chronic pain are caused by pathophysiological processes within multiple pain signaling pathways. Clinical treatment of chronic pain is negatively affected by development of various side effects to pharmacological agents and often provides only moderate pain relief for many patients. Recombinant cell-based therapy provides a new avenue for the management of chronic pain because it can continually produce and secrete analgesic substances at local pain processing sites in the spinal cord.
Transplantation of GABAergic neuronal cells may restore the inhibitory potential in the spinal cord and replace dysfunctional interneurons. Grafted cells may also release analgesic peptides by means of genetic engineering to further enhance the benefits of a cell-therapy approach. The omega-conopeptide, MVIIA, an N-type Ca2+ channel blocker, was one of the earliest tested treatments for severe pain in animal models and is in clinical use marketed as FDA approved Prialt (Ziconotide). However, due to its poor penetration through the blood brain barrier it must be delivered intrathecally. The goal of this project is to develop transplantable recombinant GABAergic cells releasing MVIIA that can alleviate pain-like behavior following peripheral and spinal cord injury.

Rat models using chronic constriction of the sciatic nerve and spinal clip compression injury were used to induce chronic neuropathic pain. Male and female Sprague Dawley were tested weekly for the presence of tactile, cold and heat hypersensitivity. Rat embryonic E14 neuronal progenitors were harvested from medial ganglionic eminence and transfected with p_lenti_MVIIA. Their viability, proneuronal phenotype, and the ability to release recombinant MVIIA were confirmed via immunostaining and FLISA analysis. Recombinant and control cells were intraspinally injected into animals when signs of chronic pain were detected.
An analgesic effect of the transplant treatment was observed in both pain models in both sexes, with a stronger and longer lasting outcome in the recombinant group compared with non-recombinant control neural progenitor cells. Conditioned place preference with gabapentin revealed significant reduction of ongoing pain in animals with the grafts. Inflammatory biomarkers Iba-1, IL1-β, and TNF-α were reduced in treated animals compared to controls. The recombinant cells were detected up to 1 mm distance from the injection site. FLISA analysis confirmed the presence of MVIIA in the spinal homogenate.
Our results demonstrate the beneficial and targeted effect and potency of recombinant cell-based therapy in the management of chronic pain.

Disclosures: K. Liebmann*: None. **S. Jergova:** None. **M. Hernandez:** None. **B. Marin:** None. **D. Qadir:** None. **J. Sagen:** None.

Poster

P390. Pain Models: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P390.02

Topic: D.03. Somatosensation – Pain

Support: NIDA DA044999

Title: Sex and dose-dependent antinociceptive effects of the JNK (c-Jun N-terminal kinase) inhibitor SU 3327 are mediated by CB_2 receptors in female, and CB_1/CB_2 receptors in male mice in an inflammatory pain model

Authors: *J. GUINDON[1], M. MCHANN[2], H. BLANTON[1];
[2]Pharmacol. and Neurosci., [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Activation of c-Jun N-terminal kinases (JNKs) has been implicated in the development and persistence of inflammatory and neuropathic pain in animal models. Moreover, JNKs have been involved in the maintenance of chronic pain, as well as development of tolerance to antinociceptive agents in the opioid and cannabinoid class of compounds. In this study, we evaluated the antinociceptive effects of the JNK inhibitor SU 3327 (0.3 to 30 mg/kg) in the formalin pain model with an emphasis on the sex-specific actions of this compound. In wild-type C57BL6J mice, SU 3327 produced strong antinociceptive effects in the formalin pain model which were mediated by CB_2 receptors in females, and both CB_1 and CB_2 receptors in males. SU 3327 at a dose of 10 mg/kg produced antinociception, hypothermia, motor impairment, and hypolocomotion to a similar extent in both males and females. The antinociceptive effects of SU 3327 were more potent in males at lower doses (1 and 3 mg/kg), however hypothermia,

motor impairment and hypolocomotion were absent in both sexes at this lower dose range. Analysis of spinal cords, using qPCR following SU 3327 administration in the formalin test, revealed changes in cannabinoid, tolerance and inflammatory markers in females only, and only in the high (10-30 mg/kg) doses conditions. Indeed, females shown increase in mRNA levels of cannabinoids (CB_2), but a decrease in tolerance (β-arrestin 1) and inflammatory (TNF-α, IL-1β, IL-6)-associated markers. The differences between males and females, in this study, support sex as an important factor in nociception and antinociceptive responses mediated by JNK and the endocannabinoid system.

Disclosures: J. Guindon: None. **M. McHann:** None. **H. Blanton:** None.

Poster

P390. Pain Models: Pharmacology I

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P390.03

Topic: D.03. Somatosensation – Pain

Support: Conacyt grant A-S1-40015

Title: Spinal dopaminergic D1-like receptors contribute in a sex-dependent manner to fibromyalgia-like pain in rats

Authors: *Y. DE LA LUZ-CUELLAR[1], F. MERCADO[2], V. GRANADOS-SOTO[1];
[1]Ctr. De Investigación Y De Estudios Avanzados, Ciudad DE Mexico, Mexico; [2]Dirección de Investigaciones en Neurociencias, INPRFM, Ciudad de Mexico, Mexico

Abstract: Fibromyalgia (FM) is a chronic widespread pain syndrome that mainly affects women. It is believed that reduced serotonin, noradrenaline and dopamine (DA) levels in serum and cerebrospinal fluid in FM patients leads to an aberrant transmission of nociceptive stimuli. Activation of D2-like receptors in spinal cord produces antinociceptive effects while stimulation of D1-like receptors is related to pronociceptive effects in inflammatory and neuropathic pain models. However, the role of spinal DA receptors in FM-like pain is unknown. Moreover, gonadal hormones are known to drive sex differences in chronic pain. The aim of this study was to investigate the role of spinal DA receptors and their possible sex-dependent modulation in a reserpine-induced model of FM in rats. FM-type pain was induced by reserpine (RES) injections (1 mg/kg, s.c. for 3 days) in adult female and male Wistar rats (n=6). Tactile allodynia and muscular hyperalgesia were assessed with Von Frey filaments and the Randall-Selitto test, respectively. RES-treated rats were intrathecally (i.t.) injected with the D2-like receptor agonist pramipexole (15 nmol), or the D1-like receptor antagonist SCH-23390 (30 nmol). To study a possible hormonal influence over DA receptors function, estrous cycle of reserpinized rats was monitored by vaginal smears before drug injection so they were divided in two groups: high 17β-estradiol (E2, proestrus and estrous) and low E2 (metestrus and diestrus). In addition, we injected RES in ovariectomized (OVX) rats and reconstituted them with E2 24 h before the treatment with dopaminergic drugs. To further confirm the influence of E2, another group of OVX reserpinized rats were i.t, injected with estrogen receptor α (ERα) inhibitor MPP before the treatment with drugs. RES produced tactile allodynia and muscle hyperalgesia 5 and 7 days after last injection, respectively, in male and female rats.

I.t. injection of SCH-23390 and pramipexole had a small antinociceptive effect on male rats but reversed RES-induced nociceptive behaviors in female rats. Both drugs showed a greater antiallodynic effect in rats with high E2 compared to those with low E2. Accordingly, ovariectomy depleted SCH-23390-induced antiallodynic effect whereas that systemic reconstitution with E2 restored it. MPP treatment, but not vehicle, blocked E2-restored antiallodynic effect of SCH-23390, suggesting that its anti-nociceptive effect depends on E2-induced ERα signaling. Results suggest that spinal D1-like receptors contribute in a sex-dependent manner to the nociceptive hypersensitivity induced by RES in rats. Moreover, the pronociceptive D1-like receptors function is modulated by E2.

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Poster

P390. Pain Models: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P390.04

Topic: D.03. Somatosensation – Pain

Support: NIDA DA044999

Title: Influence of sex on ACEA antinociception in inflammatory and chronic pain models

Authors: *H. DE SELLE, C. L. DANCEL, M. C. MCHANN, H. BLANTON, J. GUINDON; Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Inflammatory and chronic pain continues to be a common complication associated with patients. Currently, sex differences and its connection to the endocannabinoid system is an ongoing focus of preclinical and clinical research. Indeed, there is evidence that pain, response to analgesics and tolerance is influenced by sex (Blanton et al., 2021). Cannabinoid (CB) receptor agonists are promising therapeutic agents in the alleviation of inflammatory and chronic pain. Selective activation of CB1 receptors via arachidonyl-2-chloroethylamide (ACEA) administration causes anti-nociception and reveals important sex differences in several rodent pain models. In this study, we investigated the dose and sex-dependent role of ACEA in alleviating inflammatory and chemotherapy-induced pain in male and female wild-type mice. In these experiments, we used the formalin test (2.5 % formalin intraplantar) to evaluate inflammatory pain and chemotherapy-induced peripheral neuropathy using cisplatin (5 mg/kg i.p.) as a chemotherapeutic agent. Our results demonstrate that there are sex differences in the response to ACEA alleviating inflammatory (formalin test) pain when used at different doses (between 0.1 - 1 mg/kg i.p.) in male and female WT mice. Furthermore, we evaluated the effect of ACEA on alleviating mechanical (Von Frey) and cold (acetone) allodynia induced by the chemotherapeutic agent cisplatin. We found that ACEA reverse mechanical and cold allodynia in both male and female WT mice. Our results also show that females developed tolerance faster than male. Indeed, females are tolerant to the antinociceptive effect of ACEA after 5 days whereas the males become tolerant after 8 days. Moreover, we also evaluated the oestrous cycle and found that ACEA disrupt the oestrous cycle toward the metestrus stage of the cycle. Taken together, our results suggest a clear interaction between sex, pain and analgesia. In order to shed light on these differences and better understand the mechanisms of action involved, we need to

scientifically recognize the importance of sex in influencing pain responses in order to develop better therapies and improve treatment of chronic pain in patients.

Disclosures: H. De Selle: None. **C.L. Dancel:** None. **M.C. McHann:** None. **H. Blanton:** None. **J. Guindon:** None.

Poster

P390. Pain Models: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P390.05

Topic: D.03. Somatosensation – Pain

Support: NIDA DA044999
TTUHSC SOM 121035

Title: Acea dose and sex dependent antinocicpetive effects in cisplatin induced peripheral neuropathy and changes in the estrous cycle

Authors: *M. MCHANN[1], H. BLANTON[1], I. CASTRO-PIEDRAS[2], J. GUINDON[2];
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Abstract: Introduction: Chemotherapy induced peripheral neuropathy (CIPN) is a chronic painful experience that has minimal treatment options. Cannabinoids have shown great promise for future treatment of CIPN. Sex differences in pain have been demonstrated by numerous studies and are also found during treatment with cannabinoids (Blanton et al., 2020). In this study, we used S426A/S430A mutant knock in mice. These mice have a mutation at the CB1 receptor for GRK and β-arrestin, showing delay in tolerance to cannabinoids. The 426 and 430 serines are turned into alanines preventing GRK from phosphorylating CB1, therefore the CB1 receptor is not desensitized as quickly.**Methods**: The objective of our current work is to find the efficacy of three different doses of the CB_1 selective agonist ACEA (0.25mg/kg- 0.75mg/kg) in alleviating chemotherapy-induced peripheral neuropathy using cisplatin (5mg/kg i.p.) in KI (S426A/S430A) male and female mice, which was administered once a week for four weeks. Mechanical and cold allodynia was evaluated with the von Frey and acetone tests respectively in S426A/S430A mutant knock-in mice. The sex differences were evaluated at the different doses of ACEA in respect to efficacy and tolerance. Additionally, we evaluated vaginal smears of the vehicle cisplatin females and the 0.75mg/kg females to see if ACEA interfered with the normal estrous cycle of the female mice. **Results**: We found that all doses of ACEA had an anti-nociceptive affect in both males and females, with 0.25 mg/kg showing a partial reversal of neuropathy and 0.5 mg/kg - 0.75 mg/kg showing full reversal of neuropathy. However, mechanical allodynia demonstrated sex differences in tolerance; the 0.25mg/kg dose showed that females developed tolerance two days before the males, the 0.5mg/kg and 0.75 mg/kg dose showed that females developed tolerance three days before the males. The cold allodynia also demonstrated sex differences in the development of tolerance to ACEA, with the 0.25mg/kg dose females developing tolerance two days before the males, the 0.5 mg/kg dose females developing tolerance one day before the males and the 0.75mg/kg females developing tolerance three

days before the males. **Conclusions**: In this study, we demonstrated that ACEA is effective at alleviating partially (low dose) or completely (high doses) chemotherapy-induced peripheral neuropathy at three different doses (0.25mg/kg- 0.75mg/kg) in S426A/S430A mutant mice. Sex differences in response to cannabinoids is demonstrated by ACEA since females develop tolerance to mechanical and cold allodynia faster than males and there is changes oestrous cycle with a predominance of the metestrus-diestrus phases.

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Poster

P390. Pain Models: Pharmacology I

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Program #/Poster #: P390.06

Topic: D.03. Somatosensation – Pain

Support: NSERC
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Healthy Brains for Healthy Lives
Ron Melzack Postdoctoral Fellowship

Title: Urinary volatiles from pregnant mice produce stress-induced analgesia in male mice

Authors: L. V. LIMA[1], S. ROSEN[1], C. CHEN[1], R. NEJADE[1], M. ZHAO[1], E. TOPRAK[1], S. N. TANSLEY[1], **A. S. ZUMBUSCH**[1], S. SOTOCINAL[1], J. MOGIL[2];
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Abstract: Stressors in the laboratory environment have a significant impact on the reproducibility of experiments. While testing mice for pain sensitivity, we observed that male mice being tested in the same room as pregnant females had elevated pain thresholds (hypoalgesia). Here we show that this hypoalgesia is a stress-induced olfactory-mediated phenomenon that is testosterone dependent. The olfactory chemosignal is mediated by volatile compounds found in the urine of pregnant and lactating female mice and that the compounds alone, even without an actual female mouse, can produce stress and stress-induced hypoalgesia. Chemical and behavioural testing of the specific compounds elevated in the urine of pregnant female mice revealed that *n*-pentyl-acetate, banana odorant, produced a concentration-dependant increase in hypoalgesia and plasma corticosterone levels. This olfactory cue likely signals potential female aggression aimed at preventing attacks from stranger males. Research examining rodent chemosignaling has primarily focused on the effects of such signalling from male-to-female or female-to-female mice and how olfactory signals relate to sexual behaviours. Thus, the results presented here represent a novel female-to-male chemosignal, mediated by a urinary volatile, that is important both as a finding in and of itself and as a consideration for avoiding experimental confounds in preclinical research.

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Poster

P390. Pain Models: Pharmacology I

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Topic: D.03. Somatosensation – Pain

Support: GACR 20-19136S
RVO67985823

Title: Chemokine CCL2 prevents opioid-induced inhibition of nociceptive synaptic transmission in spinal cord dorsal horn

Authors: *M. HELES, P. MROZKOVA, D. SULCOVA, P. ADAMEK, D. SPICAROVA, J. PALECEK;
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Abstract: Opioid analgesics remain widely used for acute and neuropathic pain treatment, despite serious side effects such as opioid tolerance and opioid-induced hyperalgesia (OIH). Increased levels of inflammatory chemokines such as C-C motif chemokine ligand 2 (CCL2) in the spinal cord dorsal horn and their interaction with μ-opioid receptors (MOR) may play a significant role in modulation of nociception and side effects development during pathological conditions. Here we report results suggesting the presence of crosstalk between CCL2, MOR, and transient receptor potential vanilloid 1 (TRPV1) receptors in the spinal cord dorsal horn. To study the modulation of acute opioid-induced depression of excitatory synaptic transmission by CCL2 and TRPV1 we used whole-cell patch-clamp recordings of miniature (mEPSC) and dorsal root stimulation-evoked excitatory postsynaptic currents (eEPSC) from superficial dorsal horn neurons in rat spinal cord slices. To investigate the modulation of opioid-induced analgesia in vivo we measured paw withdrawal latency (PWL) to thermal stimulation after intrathecal (i.t.) application of MOR agonist DAMGO ((D-Ala2,N-Me-Phe4,Gly-ol5)-enkephalin) (0.01 μg) and CCL2 (1.4 μg). DAMGO (1 μM) decreased frequency of mEPSC to 60.8 ± 4.0 % ($P<0.001$, n=16) and amplitudes of eEPSC to 33.0 ± 5.3 % ($P<0.001$, n=15) while induced increase of eEPSC amplitudes 15 minutes later in a subpopulation of recorded neurons (166.6 ± 21.5 %, $P<0.01$, n=9). CCL2 (10 nM) diminished the DAMGO-induced inhibition of mEPSC (82.4 ± 3.9 %, n=11) and eEPSC (97.4 ± 10.7 %, n = 11). Minocycline (100 μM), a commonly used inhibitor of microglial activation, attenuated the CCL2-induced effect on eEPSC amplitudes (56.4 ± 8.4 %, $P<0.001$, n=8). TRPV1 antagonist SB366791 (10 μM) prevented the delayed DAMGO induced increase of eEPSC (98.8 ± 16.3 %, n=9). In behavioral experiments, i.t. DAMGO application increased PWL (196.9 ± 12.5 %, n=5) and this thermal hyposensitivity was diminished by i.t. CCL2 injection before DAMGO (121.7% ± 10.2%, n=5). Minocycline (intraperitoneal, 45 mg/kg) prevented the effect of CCL2 on DAMGO induced analgesia. In conclusion, TRPV1 receptors may mediate the development of hypersensitivity described as OIH during opioid withdrawal. CCL2 diminishes the inhibitory effect of DAMGO on nociceptive synaptic transmission *in vitro* and analgesia *in vivo* and this effect is at least partially dependent on activation of microglia. Our results suggest that increased levels of cytokines during pathological conditions may lead to substantial attenuation of opioid-induced analgesia.

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Poster

P390. Pain Models: Pharmacology I

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Topic: D.03. Somatosensation – Pain

Support: NIH grant T32DA035165
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Title: Low frequency stimulation of TRPV1-expressing peripheral afferents enhances the excitability of spino-periaqueductal gray projection neurons

Authors: *C. L. BREWER, J. A. KAUER;
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Abstract: Inflammatory injury potentiates peripheral sensory neuron synapses onto spinal neurons projecting to the midbrain periaqueductal gray (spino-PAG PNs). Although this suggests that inflammation strengthens excitatory spinal input to the PAG, the output of spino-PAG PNs after peripheral inflammatory injury has not been examined in depth. Investigating C fiber-induced action potential (AP) firing in spino-PAG PNs can reveal how inflammatory injury affects the output of these neurons to the PAG, a region critical to pain processing. To stimulate C fibers, we used 3-6 week old male and female mice expressing Cre recombinase driven by expression of TRPV1 gene, which is expressed in virtually all C fibers, and Cre-dependent channelrhodopsin. Spinal PNs were retrogradely labeled from the dorsal/lateral PAG using diI. We performed whole-cell patch-clamp recordings in spino-PAG PNs using a semi-intact spinal cord preparation. Current-clamp recordings included spontaneous activity—and intracellular current injections to measure AP threshold and evoked firing. Stimulation of TRPV1-expressing (TRPV1+) peripheral afferents induced burst firing in virtually all spino-PAG PNs sampled. Inflammation increases the spontaneous firing rates of nociception-associated C fibers to 1-2 Hz; therefore, we used low frequency stimulation (LFS; 1 ms 470 nm LED pulses at 2 Hz for 2 mins) to replicate inflammatory injury. LFS induced a long-lasting (at least 20 min) increase in the number of APs within a C fiber-induced burst (n=10, p=0.029), rise in the frequency of synaptically evoked afterdischarge (n=10, p=0.0004), and decrease in intraburst afterhyperpolarization (n=10, p=0.037). Furthermore, LFS induced a transient membrane depolarization (n=12, p<0.0001). These LFS-induced effects may be dependent on G protein signaling, as they were blocked using GDPβs in the intracellular solution. Finally, these effects may in part be driven by altered intrinsic excitability in spino-PAG PNs—as the AP threshold (measured via intracellular current injection) decreased after LFS (n=14, p=0.015). However, LFS had no effect on the membrane potential, spontaneous firing frequency, or evoked firing frequency of spino-PAG PNs. Taken together, these results suggest that LFS increases G protein-dependent TRPV1+ afferent-induced excitability in spino-PAG projection neurons, likely leading to a lasting increase in the activation of supraspinal PAG circuits.

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Poster

P390. Pain Models: Pharmacology I

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National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) (No. 2021R1F1A1060919)

Title: Interleukin-1beta attenuates mechanical allodynia and GluN1 phosphorylation in a murine model of neuropathic pain: involvement of sigma-1 receptor

Authors: *S.-R. CHOI[1,2], H. HAN[2], A. J. BEITZ[3], J.-H. LEE[2];
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Abstract: The sigma-1 receptor (Sig-1R) plays an important role in spinal pain transmission by increasing phosphorylation of the *N*-methyl-D-aspartate (NMDA) receptor GluN1 subunit (pGluN1). As a result Sig-1R has been suggested as a novel therapeutic target for prevention of chronic pain. Here we investigated whether interleukin-1β (IL-1β) modulates the expression of the Sig-1R in spinal astrocytes, and whether this modulation affects the development of central sensitization and neuropathic pain following chronic constriction injury (CCI) of the sciatic nerve. Repeated intrathecal (i.t.) administration of IL-1β from days 0 to 3 post-surgery significantly reduced the increased pGluN1 expression at the Ser896 and Ser897 sites in the ipsilateral spinal cord, as well as, the development of mechanical allodynia and thermal hyperalgesia in the ipsilateral hind paw of CCI mice, which were restored by co-administration of IL-1 receptor antagonist with IL-1β. Sciatic nerve injury increased the expression of Sig-1R in astrocytes of the ipsilateral spinal cord dorsal horn, and this increase was suppressed by i.t. administration of IL-1β. Agonistic stimulation of the Sig-1R with PRE084 restored pGluN1 expression and the development of mechanical allodynia that were originally suppressed by IL-1β in CCI mice. Collectively these results demonstrate that IL-1β administration during the induction phase of neuropathic pain produces an analgesic effect on neuropathic pain development by controlling the expression of Sig-1R in spinal astrocytes.

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Poster

P390. Pain Models: Pharmacology I

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Topic: D.03. Somatosensation – Pain

Support: Research Endowment Fund, Dept of Anesthesiology & CCM, UNM HSC (S.R.A. Alles)
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NIH Grant R01DA042852 (R. Khanna)

Title: Slc7a5 (Lat1) inhibition alleviates neuropathic pain in rodent models

Authors: *S. R. A. ALLES[1], A. E. GOINS[1], K. GOMEZ[2], M. AFAGHPOUR-BECKLUND[1], M. MONTERA[1], A. MOUTAL[2], R. KHANNA[2];
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Abstract: High-impact chronic pain is suffered by 1 in 5 patients in the US and globally. Effective, non-addictive, non-opioid therapeutics are urgently needed for the treatment of chronic pain. Slc7a5 (Lat1), also known as system L-neutral amino acid transporter, is involved in a number of physiological processes related to inflammation. Transcriptomics studies have shown that Slc7a5 and its binding partner Slc3a2 are expressed in neurons of the dorsal root ganglia (DRG) and spinal dorsal horn, which are critical to the initiation and maintenance of nociception and pathophysiology of chronic pain. In addition, Slc7a5 is a transporter for the first-line anti-allodynic gabapentinoid drugs and binds to ion channels implicated in nociception and chronic pain including the voltage-gated sodium channel Nav1.7 and the voltage-gated potassium channels Kv1.1 and Kv1.2.
Our preliminary data show that blocking Slc7a5 with intrathecal or intraperitoneal administration of the drug JPH203 alleviates allodynia in the spared nerve injury (SNI) rodent model of neuropathic pain. Western blot studies show an increase in Slc7a5 protein levels in the spinal cord of SNI mice compared to naïve mice and a reduction in mice treated with an anti-allodynic drug. We performed whole-cell electrophysiology from small (<30 µm) cultured DRG neurons from SNI mice and established that excitability of neurons was reduced following JPH203 treatment in agreement with its behavioral effects. We also showed that JPH203 reduces peak tetrodotoxin-resistant (TTX-R) sodium current recorded from naïve rat DRG neurons. These results demonstrate that Slc7a5 is dysregulated in chronic neuropathic pain and can be targeted to provide relief of hypersensitivity.
Therefore, Slc7a5 is a promising target for neuropathic pain. Future work will involve the design of more selective Slc7a5 inhibitors for chronic pain and screening using human/human-derived neurons.

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Poster

P408. Non-Opioid Treatments

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Program #/Poster #: P408.01

Topic: D.03. Somatosensation – Pain

Support: NIH UH3NS115631

Title: Practical closed loop strategies for deep brain stimulation: lessons from chronic pain

Authors: *J. PROSKY[1,4], J. CAGLE[5], K. K. SELLERS[1,4], C. DEHEMPTINNE[5,6], A. SCHMITGEN[1,4], P. A. STARR[1,4,2], E. F. CHANG[1,4,2], P. SHIRVALKAR[1,4,7,3];
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Abstract: Deep brain stimulation (DBS) is a promising therapy for various neurological disorders, and many available devices for DBS can operate in both an open- and closed-loop mode. Using a closed-loop protocol mitigates many drawbacks of open-loop stimulation. We offer a practical guide for the implementation of a closed-loop DBS system, using examples from patients with chronic pain. Focusing on two research devices from Medtronic, the Activa PC+S and Summit RC+S, we provide details on the steps involved in closed-loop programming from a clinician's perspective. These devices contain many adjustable parameters that control how the closed-loop system operates, and these often require a combination of empirically and clinically informed decision making to optimize. As such, we provide an example of combining our understanding of chronic pain with data-driven heuristics in the context of selecting some of the most significant parameters. Additionally, we discuss other practical considerations that a clinician must be aware of when programming a closed-loop device.

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Poster

P408. Non-Opioid Treatments

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Program #/Poster #: P408.02

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DA047967

Title: Antinociceptive effects of α_2/α_3-selective $GABA_A$ receptor positive allosteric modulators on opioid-induced hyperalgesia

Authors: *K. L. WOODHOUSE[1], J. M. COOK[2], J.-X. LI[1];
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Abstract: Opioids have been increasingly prescribed to treat chronic pain since the 1980s, despite evidence that long-term use of opioids may lead to tolerance and pain sensitization called opioid-induced

hyperalgesia (OIH). OIH has been demonstrated in both preclinical models and healthy human volunteers, but is understudied and there is need for novel analgesics capable of mitigating OIH. α_2/α_3-selective $GABA_A$ receptor positive allosteric modulators (PAMs) act specifically at subunits of the $GABA_A$ receptor found to mediate analgesia, and have demonstrated antinociceptive effects in models of chronic inflammatory and neuropathic pain. However, the efficacy of these compounds at relieving opioid-induced pain hypersensitivity have not yet been investigated. This study systematically examined the antinociceptive effects of α_2/α_3-selective $GABA_A$ receptor PAMs alone and in combination with acetaminophen in an OIH rat model wherein repeated treatment with the opioid fentanyl induces mechanical hyperalgesia. The von Frey test was used to measure mechanical nociception. Duration of actions of α_2/α_3-selective $GABA_A$ receptor PAMs (KRM-II-81, NS16085, HZ-166) alone were studied, and combinations of KRM-II-81 and acetaminophen were also studied at fixed ratios (1:1, 1:3, 3:1). Dose-addition analysis was used to assess the antinociceptive interactions between KRM-II-81 and acetaminophen. α_2/α_3-selective $GABA_A$ receptor PAMs were able to fully reverse mechanical sensitivity caused by OIH. Furthermore, KRM-II-81/acetaminophen combinations produced additive to supra-additive interactions depending on the drug mixture ratios. These findings support the idea that α_2/α_3-selective $GABA_A$ receptor PAMs could serve as novel analgesics for treating OIH, and may interact favorably with other non-opioid analgesics.

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Poster

P408. Non-Opioid Treatments

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Topic: D.03. Somatosensation – Pain

Support: NIH AR073187
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Title: Select Androgen Receptor Modulator Microparticles Reverses Pain in Mouse Model of Chronic Widespread Muscle Pain

Authors: *J. LESNAK[1], D. S. NAKHLA[2], A. K. SALEM[2], K. A. SLUKA[1];
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Abstract: Currently, there is a need for the generation of non-opioid analgesics for treating chronic pain. Preclinical and clinical studies demonstrate the analgesic effects of testosterone. However, treatment with testosterone is not clinically feasible due to unwanted adverse effects. Select androgen receptor modulators (SARM) have been developed to overcome these limitations by selectively activating androgen receptors associated with anabolic effects while minimizing androgenic effects. The purpose of the current study was to develop a SARM-loaded microparticle formulation with a long-term release profile and test its efficacy in a preclinical model of chronic muscle pain. Chronic muscle pain was induced by 2 intramuscular injections of acidic saline (20µl, pH 4.0±0.1) into one gastrocnemius muscle 5

days apart in C57/BL6J male and female mice. Muscle withdrawal thresholds (MWT) were assessed with force sensitive tweezers applied to the gastrocnemius muscle before and weekly for 4 weeks after induction of the model. Efficacy of the SARM ((s)-3-(4-cyanophenoxy)-n-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide) was tested by daily systemic injections of the drug dissolved in vehicle (25mg/kg, s.c.) or 2 injections of SARM loaded into Poly(lactic-*co*-glycolic acid) (PLGA) microparticles (200mg, s.c.; 24h, 1wk) and compared to vehicle. Drug release profiles from the SARM microparticle formulation were assessed both in vitro and in vivo via HPLC-UV. To test for safety, liver and cardiac toxicity was analyzed from serum samples from animals receiving SARM microparticle or its vehicle. Statistical analysis for MWT was performed with repeated measures ANOVA. Daily systemic administration of SARM reversed the decreased MWT bilaterally ($p<0.01$) when compared to vehicle. Similarly, 2 injections of the SARM microparticle formulation reversed the decreased MWT in the gastrocnemius muscle bilaterally ($p<0.02$) when compared to vehicle. In vitro release studies showed SARM was steadily released from microparticles for up to 4 weeks. In vivo pharmacokinetics studies in mice detected SARMs in the systemic circulation for up to 5 weeks following a single SARM microparticle injection. Toxicity panels revealed no adverse effects of SARM microparticle treatment. The current study shows that SARMs can relieve muscle pain with daily administration. Long-term relief was observed with SARM microparticles with two injections, thus increasing its clinical utility. Future work will test SARM effectiveness in other pain models and clinical populations.

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Poster

P408. Non-Opioid Treatments

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Program #/Poster #: P408.04

Topic: D.03. Somatosensation – Pain

Title: Suvn-1301102, preclinical pharmacokinetic and pharmacodynamic profiling of a p2x7 receptor antagonist

Authors: V. GOURA, *V. PALACHARLA, R. KALLEPALLI, N. ASHTIKAR, V. MEKALA, N. MUDDANA, L. GUTTIKONDA, A. DAS, S. RAVELLA, A. MOHAMMED, P. JAYARAJAN, R. NIROGI;
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Abstract: Purine receptors play roles in peripheral and central sensitization, and are associated with neuropathic pain. Among all purine receptors, the P2X7 receptors (P2X7R) are well-defined therapeutic target for inflammatory and neuropathic pain. P2X7 receptors are widely expressed by several cell types involved in pain transmission, including the neurons, microglia, satellite glial cells and astrocytes located in the dorsal root ganglia, the trigeminal ganglia, and in the dorsal horn of the spinal cord. Existing P2X7 receptor antagonists are marred with low *in vitro* potency, poor pharmacokinetic properties and inadequate brain penetration. Herein, we describe the *in vitro* efficacy, pharmacokinetics and *in vivo* efficacy of SUVN-1301102. *In vitro* evaluations suggested SUVN-1301102 is a potent P2X7antagonist.

Pharmacokinetic evaluations carried out in male Wistar rats suggested good bioavailability with excellent brain penetration. SUVN-1301102 was evaluated for analgesic activity in neuropathic pain models such as streptozotocin (STZ) induced diabetic neuropathic pain (DNP) and chronic constriction induced (CCI). Paw withdrawal thresholds were evaluated using Vonfrey filaments. SUVN-1301102 showed significant increase in paw withdrawal thresholds at all the tested time points, when compared to vehicle group. SUVN-1301102 showed analgesic like activity in the rodent models. Further, SUVN-1301102 was evaluated in rota rod task for motor coordination. In this assay, SUVN-1301102 did not show decrease in latency to fall. Additional efficacy and safety profiling for this compound and similar compounds from this series is currently in progress.

Disclosures: V. Goura: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Kallepalli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Ashtikar:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Mekala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **L. Guttikonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Das:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Ravella:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

P408. Non-Opioid Treatments

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P408.05

Topic: D.03. Somatosensation – Pain

Support: Institutional funds from the University of Arizona

Title: Terpenes from Cannabis sativa induce anti-nociception in chemotherapy-induced peripheral neuropathy (CIPN) via activation of the adenosine A2a receptor

Authors: *A. SCHWARZ[1], A. I. KERESZTES[2], J. M. STREICHER[2];
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Abstract: The terpenes α-Humulene, β-Pinene, Linalool, β-Caryophyllene (BCP), and Geraniol are found in medium to high quantities in *Cannabis sativa*. We have observed that when administered, these terpenes elicit decreased pain response and antinociception in mice and have the potential to be used as therapeutic agents for pain relief. Previous work from our lab suggests these terpenes activate cannabinoid receptor 1 (CBR1) and adenosine receptor A2a (A2a). However, it is not clear if these ligands will produce pain relief in chronic pain models. We thus induced chemotherapy-induced peripheral neuropathy in male and female CD-1 mice by injection of paclitaxel (2 mg/kg, days 1-7). We measured mechanical allodynia using Von Frey filaments. The terpenes geraniol, linalool, α-humulene, β-pinene and BCP were injected at a 200 mg/kg dose IP on day 8, with the role of the CB1R and A2a tested

by pre-treatment with the CB1R inverse agonist rimonabant (10mg/kg, IP), the A2a antagonist istradefylline (3.2-10mg/kg, IP), or vehicle control. All terpenes produced robust acute anti-nociception in the CIPN model; mice treated with the CB1R inverse agonist rimonabant showed no significant difference in mechanical sensitivity to vehicle treated animals for any of the terpenes. This suggests no CB1R involvement in this pain model. However, istradefylline treatment partially or fully blocked β-Pinene, BCP, and Geraniol anti-nociception for both lower (3.2mg/kg) and higher (10mg/kg) doses. This suggests that the terpenes β-Pinene, BCP and Geraniol activate A2a receptors to contribute to anti-nociception in CIPN, while all terpenes produce anti-nociception in this pain model. We plan to confirm the action of the terpenes of interest on A2a receptors using a CRISPER-Cas9 Adenosine A2a knock down in the chronic pain CIPN model. These findings suggest that terpenes could be efficacious non-opioid, non-cannabinoid treatments for chronic pain, and further suggest specific receptor mechanisms in different pain models.

Disclosures: A. Schwarz: None. **A.I. Keresztes:** None. **J.M. Streicher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Botanical Results, LLC.

Poster

P408. Non-Opioid Treatments

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Topic: D.03. Somatosensation – Pain

Support: NSF CAREER 1844762
NIDDK R01 DK120824

Title: Targeting two-pore-domain potassium channels by mechanical stretch instantaneously modulates action potential transmission in mouse sciatic nerves

Authors: *J. LIU[1], N. GANESHBABU[2], N. SHALABY[1], L. CHENG[1], T. GUO[1], B. FENG[1];
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Abstract: Blocking action potential transmission in peripheral nerves effectively suppresses pain arising from the periphery without causing adverse off-target effects on the central nervous system. Despite centuries of research, the exact composition of ion channels that participate in action potential transmission in mammalian peripheral nerves remains undetermined. Recent reports indicate dominant roles of TRAAK and TREK-1 channels, i.e., mechanosensitive two-pore-domain potassium channels (K2P) at the nodes of Ranvier for action potential repolarization in mammalian peripheral nerves. Changes in peripheral nerve conduction by mechanical stretch were previously studied by recording compound action potentials, which lack the necessary resolution to detect the subtle neuromodulatory effects of mechanical stretch. In this study, we developed a novel in vitro approach that enables single-fiber recordings from individual mouse sciatic nerve axons while delivering computer-controlled stepped stretch to the sciatic nerve trunk. Axial stretch instantaneously increased the conduction delay in both myelinated A-fibers and unmyelinated C-fibers. Increases in conduction delay linearly correlated with

increases in axial stretch ratio for both A- and C-fibers. The slope of the increase in conduction delay versus stretch ratio was steeper in C-fibers than in A-fibers. Moderate axial stretch (14-19% of in vitro length) reversibly blocked 37.5% of unmyelinated C-fibers but none of the 8 myelinated A-fibers tested. Application of arachidonic acid, an agonist to TRAAK and TREK-1 to sciatic nerve blocks axonal transmission in both A- and C-fibers. Also, the application of an antagonist ruthenium red showed a tendency of suppressing the stretch-evoked increase in conduction delay. These results could draw focused research on pharmacological and mechanical activation of K2P channels as a novel neuromodulatory strategy to achieve peripheral nerve block.

Disclosures: J. Liu: None. **N. Ganeshbabu:** None. **N. Shalaby:** None. **L. Cheng:** None. **T. Guo:** None. **B. Feng:** None.

Poster

P408. Non-Opioid Treatments

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant 3R01AT009716

Title: Deciphering spinal mechanisms of green light-induced antinociception: A step towards an innovative complementary pain therapy

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Abstract: Numerous studies have shown how light exposure benefits multiple conditions such as seasonal affective disorders, circadian rhythm dysregulations, and neurodegenerative diseases. However, little is known about its potential benefits in pain management. Postoperative pain severely impacts quality of life and functionality, especially in the elderly. While current pharmacologic methods of pain management are effective in many cases, the associated side effects in elderly patients can limit their use. Non-pharmacological methods could minimize drug reliance, facilitating a reduction of the opioid burden. Green light therapy has been shown to be effective in reducing chronic pain in both humans and rodents; however, the underlying mechanisms of this therapy remain incompletely defined. This study unveils the potential of green light exposure in combination with drugs commonly used in pain management. Through behavioral and pharmacological assays in a postoperative pain model in aged rodents, we have demonstrated that exposure to green light potentiates opioid- and NSAID-induced pain relief. This can ultimately minimize dose requirements to achieve antinociception. Furthermore, these results provided directions to delve into the underlying mechanisms of green light in the spinal cord. We have shown that green light increased spinal endogenous opioid release, concomitant with reduced spinal inflammation. Through 3D-modelling analyses of microglial morphology, we have shown that a 4-day exposure to green light resulted in changes demonstrating evidence for deactivation of these immune cells. Following exposure, microglia soma volumes decreased by 30% with simplified arborization, which is characteristic

of resting states. Consistent with this deactivation, TNFα levels were decreased in the cerebrospinal fluid of the rats. Altogether, these results shed light on the mechanisms of green light therapy and provide crucial information about its use in combination with other drug therapies. This evidence is the foundation for future complementary therapies that will reduce drug prescription and consumption alongside their side effects.

Disclosures: L. Martin: None. **K. Cheng:** None. **S. Washington:** None. **T. Kranz:** None. **A. Patwardhan:** None. **M.M. Ibrahim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Green Light Patent Holder.

Poster

P408. Non-Opioid Treatments

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Topic: D.03. Somatosensation – Pain

Support: DA047858
DA041229
CA200417(AGH)

Title: In vivo profile and therapeutic potential of a CB1 positive allosteric modulator (ago-PAM)/CB2 agonist dualsteric ligand

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Abstract: Identification of safe and effective therapies for pain remains an urgent medical need. Activation of cannabinoid CB1 and CB2 receptors suppresses pain in animal models. However, unwanted side effects of direct acting CB1 agonists limits therapeutic use. Both CB1 positive allosteric modulators (PAMs) and CB2 agonists alone have been shown to reduce chemotherapy-induced peripheral neuropathy (CIPN) in rodents without producing tolerance or physical dependence (Slivicki *et al*. (2018) *Biological Psych* 84, 722-733; Deng *et al*. (2015) *Biological Psychiatry* 77: 475-487). In this study, we asked whether GAT1102, which behaves as a dualsteric CB1 PAM/CB2 agonist in vitro, would suppress behavioral hypersensitivities produced in models of paclitaxel-induced neuropathy or incisional injury. We also evaluated whether receptor mechanism of GAT1102 anti-allodynic action would differ based upon the specific pathological pain state or route of drug administration. GAT1102 attenuated paclitaxel-induced mechanical allodynia following either intraperitoneal or intraplantar administration in mice. GAT1102 did not produce tolerance following once daily injections over 10 consecutive days. The observation of elevated pre-injection mechanical paw withdrawal thresholds provided evidence that anti-allodynic efficacy of GAT1102 was maintained 24 h following each prior injection. Mice were also challenged with either the CB1 antagonist AM251, the CB2 antagonist AM630 or the combination of both antagonists to ascertain the relative contributions of CB1 and CB2 receptors to GAT1102-induced therapeutic efficacy. CB1 ago-PAM properties appeared to dominate the in vivo profile of anti-allodynic

efficacy in the paclitaxel-induced neuropathy model. However, the combination of CB1 and CB2 antagonists fully reversed the anti-allodynic effects of GAT1102. GAT1102 also suppressed paclitaxel-induced allodynia following local injection into the paw, consistent with a peripheral antinociceptive mechanism. GAT1102 was also effective in suppressing mechanical allodynia induced by intraplantar incisional injury. Efficacy of GAT1102 in the incisional injury model was reversed by either AM251 or AM630 alone, as well as by the combination of AM251+AM630 mixture. These observations suggest that GAT1102 behaves as a dualsteric ligand, exhibiting anti-allodynic efficacy consistent with both CB1 positive allosteric modulation and CB2 agonism. This favorable therapeutic profile of GAT1102 is observed in the absence of cardinal signs of CB1 activation.

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Poster

P408. Non-Opioid Treatments

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Topic: D.03. Somatosensation – Pain

Support: NIH grant R21 DE028096 (KNW, AK, RD)
Dr. John P. and Therese E. Mulcahy Endowed Professorship

Title: Single-chain fragment variable (scfv) antibodies targeting cholecystokinin-B receptor for chronic pain behaviors

Authors: *G. SANDHU[1], A. KUNAMNENI[3], K. N. WESTLUND[4,5], M. A. MONTERA[4], W. JESKE[1], J. FAREED[1], S. KAJA[2], R. DURVASULA[3];
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Abstract: Trigeminal neuropathic pain (TN) is a chronic pain condition that leads to a serious decline in quality of life with partial or no improvement from currently available treatments. Although not recommended, opioids are still prescribed to more than 40% of TN patients in the US, contributing to the opioid overdose crisis. Here, we investigated the role of the endogenous anti-opioid system mediated by cholecystokinin-B receptor (CCKBR) in TN. We hypothesized that CCKBR overactivity contributes to the nociceptive propagation in TN and that targeting CCKBR can serve as a novel efficacious non-opioid therapy for TN. Microarray gene expression profiling in an established mouse trigeminal nerve constriction model of TN revealed a 4.0- and 2.7-fold increase in CCKBR expression in the trigeminal ganglia (TG) on day 3 and day 21, respectively, after trigeminal nerve injury. Single-chain fragment variable (scFv) antibodies were generated as preferred non-opioid targeting therapy to block CCKBR. Engineered scFv antibodies feature binding affinity similar to monoclonal antibodies but increased tissue penetrability due to their smaller size. A mouse scFv antibody library recognizing a fifteen amino acid extracellular peptide fragment of the human CCKBR was generated from the immunized spleen.

Ribosome display was used for recombinant antibody selection and antibodies with high affinity, high specificity, superior stability, and solubility were developed further for *in vivo* and *in vitro* efficacy testing. A single intraperitoneal dose was given 3 weeks or 7 weeks after induction of trigeminal neuropathic chronic pain in mice. Mechanical and cold hypersensitivity was permanently reduced in both male and female mice through 10-12 weeks of testing. These preliminary data provide proof-of-concept that anti-CCKBR scFv improves the behavioral functionality in a murine TN model and support our hypothesis that CCKBR plays a role in nociceptive propagation in TN. To identify the mechanism of CCKBR-mediated analgesia, we investigated the expression of the μ-opioid receptor (MOR) and CCKBR in SH-SY5Y neuroblastoma cells using immunocytochemistry. MOR and CCKBR co-localized on the same neurons. These data support the notion that CCKBR may functionally antagonize endogenous MOR, thereby eliciting its pronociceptive effects. Our current work focuses on extending our mechanistic studies on the functional antagonism of MOR by CCKBR, and evaluating the feasibility of targeting CCKBR using an anti-CCKBR scFv as a novel efficacious non-opioid therapy in TN.

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Poster

P423. Olfactory Coding: Higher-Order Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P423.01

Topic: D.05. Olfaction and Taste

Support: Okinawa Institute of Science and Technology Graduate University

Title: Investigation of brain areas involved in delayed-action during olfactory tasks

Authors: *J. K. REINERT, S. LINDEMAN, S. NATH, I. FUKUNAGA;
Sensory and Behavioural Neurosci. Unit, Okinawa Inst. of Sci. and Technol., Onna, Japan

Abstract: Delayed actions, and the underlying neuronal activity that holds the information over time, are integral to behaviours across sensory modalities and typically involve higher cortical areas to achieve high task performance. However, it is not yet clear which anatomical regions are causally involved in rodents performing corresponding, odour-guided tasks. Here, we explored the involvement of several brain areas in mice performing a delayed-response task, discriminating binary odour mixtures of varying complexity.
We first sought to reveal two modes in which mice perform olfactory discrimination tasks, first, when

water arrives with a delay, and second, when reward arrives as soon as an action is taken. Towards this aim we first trained head-fixed mice to discriminate binary odour mixtures in a go/no-go paradigm with reward delivery occurring at a fixed delay of 3.5 seconds after offset of the 'go'-odour (mean reaction time 1436 ms, n = 25 mice). Upon reaching high discrimination accuracy, the timing of reward delivery was changed from this fixed delay to a variable delay, so that the reward was delivered as soon as mice licked on rewarded trials. This resulted in mice altering the onset of anticipatory licks to earlier time-points (mean change: -53.3%, n = 2 mice), similar to findings described for related go/no-go tasks and even classical conditioning experiments. Yet, when the delay was shortened but not under the animals' direct behavioural control, mice also altered the onset of anticipatory licks but to a lesser degree (mean reaction time 1063 ms, n = 16 mice vs. 730 ms, n = 13 mice; $H(3) = 17.3$, $p = 0.002$) Together this indicates that given no further incentive, mice will natively withhold reacting during a delay task.
To clarify which brain regions may maintain the odour-task related information during the delay period, we used *Vgat-Cre::Ai32* mice expressing the light-activated ion channel channelrhodopsin in GABAergic interneurons to selectively inhibit different brain regions during various timepoints of the delay phase. We found, that perturbing the activity in the anterior piriform cortex as well as in the ventral striatum altered the lick response of the mice significantly in a dose-dependent manner. In contrast, this was not observed when perturbing either the olfactory tubercle or the dorsal striatum activity.
Together our results indicate that olfactory-task related information is maintained not only in primary olfactory areas but may be distributed across brain regions at different stages throughout the delay period.

Disclosures: J.K. Reinert: None. **S. Lindeman:** None. **S. Nath:** None. **I. Fukunaga:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

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Topic: D.05. Olfaction and Taste

Support: JSPS KAKENHI Grant 18H05088
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Title: Odor-evoked behavioral signal map in each olfactory cortex subarea: ventral tenia tecta, the nucleus of the lateral olfactory tract, and anterior cortical amygdaloid nucleus

Authors: *Y. TANISUMI[1,2], K. SHIOTANI[3], Y. OSAKO[1,2], T. OHNUKI[1,2], S. TAKAMIYA[1,2], J. HIROKAWA[1], Y. SAKURAI[1], H. MANABE[1];
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Abstract: The olfactory cortex (OC), which consists of some distinct areas, receives both olfactory sensory signals from the olfactory bulb, and top-down signals from higher-order regions. It is unclear whether how each area of the OC codes for sensory and behavioral-related information from higher-order

regions. We specifically addressed this issue in rodents, especially focusing on three areas of the OC: the ventral tenia tecta (vTT), the nucleus of the lateral olfactory tract (NLOT), and anterior cortical amygdaloid nucleus (ACo). Here, our recent work has provided the first recordings of neuronal activity in the vTT, NLOT, and ACo of freely moving mice performing an odor-guided go/no-go task. First, we found some vTT neurons fired to both the go-cue and no-go-cue odor during the odor presentation phase without any preference for a particular cue odor. In contrast, many NLOT and ACo neurons showed cue odor selective responses. Second, we found neurons in the vTT NLOT, and ACo responded to not only the odor presentation phase but also the following odor-evoked behavioral scenes: the movement to the reward port, the waiting for the rewards, and the consumption of the rewards. Individual vTT neurons showed an excitatory response to a specific behavioral scene, with inhibitory responses relative to other scenes. On the other hand, NLOT neurons showed characteristic cue-associated behavioral responses: most of the go-cue preferred neurons excited during reward drinking behaviors. ACo neurons showed two types of odor-evoked anticipation signals: one neuron type exhibited gradual increases of activity toward reward delivery, while another type exhibited a phasic go cue-preferred activity during odor sampling as well as another phasic anticipatory activity for rewards. These results suggest that each area of the OC codes different sensory and behavioral-related signals. Finally, we anatomically elicited the possibility that the medial prefrontal cortex (mPFC)-to-vTT-to-OC pathway may be important as a candidate for the top-down input to the olfactory cortex. To test this hypothesis, we expressed inhibitory opsin Arch in the mPFC and recorded from vTT neurons with and without optogenetic inactivation of mPFC axons while head-fixed mice conducted the odor-outcome association task. Without mPFC-to-vTT inputs, the vTT state representations were degraded and less integrated. Taken together, our data suggest that vTT acts as a hub that sends context-dependent signals from the mPFC to broad olfactory areas.

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Poster

P423. Olfactory Coding: Higher-Order Processing II

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Topic: D.05. Olfaction and Taste

Support: BRAIN 1R01NS111673
TR01 5R01DC017876

Title: High-throughput sequencing of olfactory single neuron projections reveals non-random spatial organization

Authors: *Y. CHEN[1], X. CHEN[1], B. BASERDEM[3], H. ZHAN[1], Y. LI[2], M. DAVIS[1], J. M. KEBSCHULL[4], A. M. ZADOR[1], A. KOULAKOV[1], D. F. ALBEANU[1];
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Abstract: In most sensory modalities, neuronal connectivity reflects behaviorally relevant stimulus features, such as spatial location, orientation, and sound frequency. In contrast, the prevailing view of the olfactory system, based on reconstructions of dozens of neurons, is that it lacks structured connectivity, as suggested by reports of broad and distributed connections both from the olfactory bulb (OB) to the piriform cortex (PC) and within the cortex. These studies have inspired computational models of circuit function that rely on random connectivity. It remains, nonetheless, unclear whether the olfactory connectivity contains spatial structure. Here, we use high throughput methods (MAPseq and BARseq) to analyze the projections of 5,309 bulb (8 mice) and 30,433 piriform cortex (5 mice) output neurons in the mouse (C57BL6J, male, 8-10-week old) at single-cell resolution. Surprisingly, statistical analysis of this much larger data set revealed that olfactory connectivity is not random. We identify previously unrecognized spatial organization in connectivity along the anterior-posterior (A-P) axis of piriform cortex at 200 μm resolution. We find that both the bulb projections to the cortex and the piriform cortex outputs form orderly gradients along the A-P axis of piriform cortex. We further identify signatures of local connectivity within the piriform cortex. Specifically, we have uncovered a novel, but simple, principle of olfactory circuit organization and information processing: a triad. Thus, for example, a neuron in the olfactory bulb that targets the anterior portion of the piriform cortex likely also projects to the anterior olfactory nucleus (AON); and neurons in targeted (anterior) piriform locus complete the triad by also projecting to the AON. Moreover, the same triadic organization is replicated at different positions within the piriform cortex, along its anterior-posterior axis, for other functionally distinct targets, such as the cortical amygdala and lateral entorhinal cortex. The matched connectivity, reminiscent of residual neural networks (ResNet) architecture, enables parallel computations and further cross-referencing, since olfactory information reaches a given target region via both direct and indirect processing pathways. This triadic organization suggests that, as in other sensory modalities, olfactory information is routed at the earliest stages of processing in a coordinated manner to behaviorally appropriate targets.

Disclosures: Y. Chen: None. **X. Chen:** None. **B. Baserdem:** None. **H. Zhan:** None. **Y. Li:** None. **M. Davis:** None. **J.M. Kebschull:** None. **A.M. Zador:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cajal Neuroscience. **A. Koulakov:** None. **D.F. Albeanu:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

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Topic: D.05. Olfaction and Taste

Support: ISF 204/17

Title: Gamma-synchronization enhances transmission of sensory information in the brain

Authors: T. DALAL, ***R. HADDAD**;
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Abstract: Although gamma-oscillatory activity is ubiquitous across brain areas, how it contributes to sensory processing and cognitive function remain unclear. We investigated this in the mouse olfactory system, where local GABAergic granule cells in the olfactory bulb shape mitral/tufted cell (MTC) excitatory output from the olfactory bulb to the piriform cortex. By optogenetically modulating granule cell activity, we managed to dissociate MTC gamma-synchronization from firing rates. Recording odour responses in downstream piriform cortex neurons, we found that increasing MTC gamma-synchronization enhanced cortical odour-evoked firing rates, reduced their response variability, and improved the odour ensemble representation. These changes occurred despite a reduction in MTC firing rates, indicating that increased spike-synchrony can compensate for the reduction in spike rate. Furthermore, reducing MTC gamma-synchronization without a decrease in firing rates degraded piriform cortex odour-evoked responses and ensemble odour representation. Finally, direct optogenetic suppression of MTC firing rates reduced their gamma-synchronization and degraded piriform cortex odour responses. Thus, consistent with theoretical predictions, these findings provide the first causal evidence that increased gamma-synchronization enhances the transmission of sensory information in the brain. This may also point to a mechanism by which gamma-synchronization can affect cognitive functions in health and disease.

Disclosures: T. Dalal: None. **R. Haddad:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

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National Institute on Deafness and Other Communication Disorders grant R01 DC015426
National Institutes on Aging grants P30 AG013854
NIH Grant T32 AG020506

Title: Mapping the Connectivity and Microstructure of the Human Lateral Olfactory Tracts Using Diffusion MRI

Authors: *S. ECHEVARRIA-COOPER[1], G. ZHOU[1], C. ZELANO[3], F. PESTILLI[4], T. B. PARRISH[2], T. KAHNT[1];
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Abstract: Understanding the anatomy of the human olfactory tracts is important to understanding their function in health and disease. This is especially important in cases of neurodegenerative disease, such as Alzheimer's and Parkinson's diseases, where olfactory dysfunction is prevalent and predictive of future cognitive impairment. Historically, susceptibility and motion artifacts have prevented accurate characterizations of the human olfactory tracts *in vivo*, using diffusion MRI (dMRI). To address this, we

used an optimized dMRI method with readout segmentation of long variable echo-trains (RESOLVE) to reduce susceptibility artifacts, and individualized head stabilizers to prevent motion artifacts. Using these methods, we successfully segmented the olfactory tracts of 25 healthy young adult participants, using probabilistic tractography.Participants underwent olfactory perceptual testing with Sniffin' Sticks, a 1.5mm resolution RESOLVE dMRI scan (90 directions, b=1000s/mm^2, and 12 B0 volumes), and T1- and T2-weighted anatomical scans. We used a constrained spherical deconvolution model to perform probabilistic tractography. We placed seeding regions in the olfactory bulbs and at a midway point in the olfactory sulcus to segment the olfactory tracts.We successfully segmented the olfactory tracts in all subjects, but in most subjects we observed a small area of signal drop-out near the sphenoid sinus, resulting in two disjointed olfactory tract segments. We used natural cubic spline interpolation to estimate the path between the two segments. Using these data, we generated a probabilistic olfactory tract template in MNI space, which will be made publicly available.All subjects showed olfactory tract connectivity with the anterior olfactory nucleus, the piriform cortex, and the olfactory tubercle in at least one hemisphere, while 76% showed connectivity with the amygdala. Using our atlas, we calculated fractional anisotropy and mean diffusivity in the olfactory tracts and found that mean diffusivity measures were correlated with subjects' scores on an olfactory discrimination task. Our atlas may be used in future research to investigate the microstructural properties of the olfactory tracts in neurodegenerative diseases.

Disclosures: S. Echevarria-Cooper: None. **G. Zhou:** None. **C. Zelano:** None. **F. Pestilli:** None. **T.B. Parrish:** None. **T. Kahnt:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P423.06

Topic: D.05. Olfaction and Taste

Support: DFG Grant 458236353

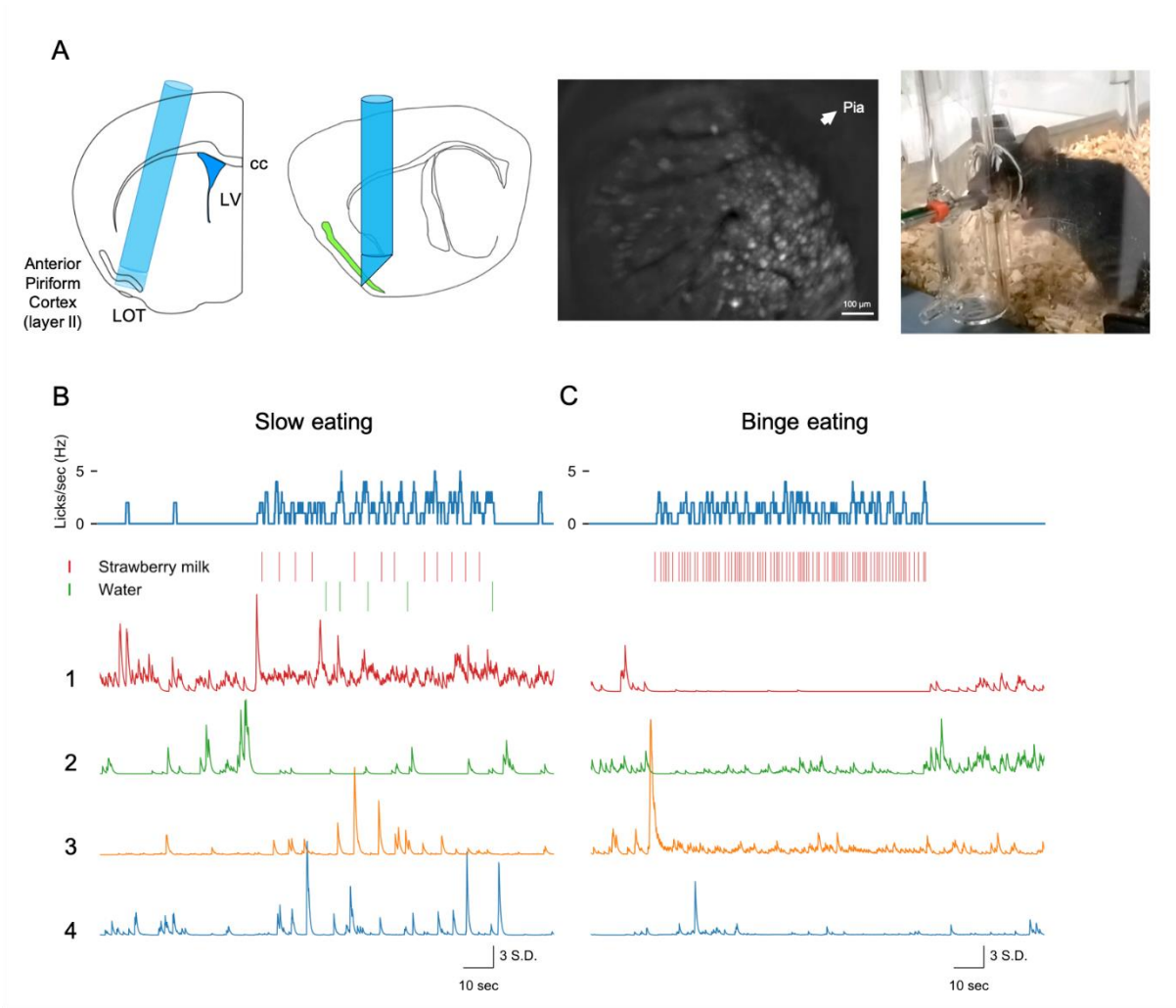
Title: Binge eating suppresses flavor representations in the mouse olfactory cortex

Authors: *H. LO[1,4], A. SCHOENHERR[1], M. L. TANTIRIGAMA[2,5,6], R. N. SACHDEV[3,6], K. STUMPENHORST[7], M. RIVALAN[7,5], Y. WINTER[7], D. SCHMITZ[3,4,5,8], F. W. JOHENNING[1,4]; [1]Neurosci. Res. Ctr., [2]NeuroCure Cluster of Excellence, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany; [4]Einstein Ctr. for Neurosciences Berlin, Berlin, Germany; [5]Cluster of Excellence NeuroCure, Berlin, Germany; [6]Inst. für Biologie, [7]Cognitive Neurobio., Humboldt Univ. zu Berlin, Berlin, Germany; [8]Ctr. for Neurodegenerative Dis. (DZNE), Berlin, Germany

Abstract: Energy homeostasis is achieved by the complex regulatory network that involves a feedback circuit between dietary intake behavior and nutritional state. The uncoupling of dietary intake and nutritional state results in overeating. Hedonic overeating can escalate into binge eating, a heritable trait associated with binge eating disorder and bulimia. One factor that modulates this feedback loop is the sensory perception of flavors. Olfaction is a critical element of flavor perception and greatly influences the qualitative and hedonic evaluation of foods. Patients with olfaction deficits commonly report a

reduced appreciation of food items. Current evidence also suggests that the olfactory system is necessary for triggering fasting-induced overeating. However, it is unclear how adaptations related to binge eating are reflected by the olfactory flavor responses.

To understand the relationship between olfactory perception and binge eating, we developed a hedonic feeding paradigm that repeatedly delivers hedonic food (flavored milk) to mice. We controlled the duration of inter-trial intervals so that mice can only activate the lick sensors and feed themselves with slow or fast paces. Implementing this paradigm with a head-mount miniaturized microscope allows us to measure neural responses upon slow eating or binge eating in the olfactory cortex (anterior piriform cortex, aPC) in freely moving mice (Fig. A). During slow eating, we observed distinct populations of excitatory piriform neurons responding to flavored milk and water (Fig. B). Surprisingly, during binge eating, we found the majority of excitatory neurons are rapidly suppressed in the aPC (Fig. C). Further investigation in inhibitory interneurons revealed both PV^{+} and SOM^{+} interneurons are not major contributors to this binge-induced global suppression. Whether this implies the involvement of neuromodulations during binging and/or whether the flavor representation adapts during the escalation of binging are the next steps of our examination.



Disclosures: H. Lo: None. **A. Schoenherr:** None. **M.L. Tantirigama:** None. **R.N. Sachdev:** None. **K. Stumpenhorst:** None. **M. Rivalan:** None. **Y. Winter:** None. **D. Schmitz:** None. **F.W. Johenning:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P423.07

Topic: D.05. Olfaction and Taste

Support: R01DC016063

Title: Taste-odor Integration in the Piriform Cortex of the Rat

Authors: *A. A. IDRIS[1], E. M. WALKER[2], J. X. MAIER[1], B. CHRISTENSEN[3];
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Abstract: Flavor perception is the amalgam of taste and odor qualities. During consumption, stimulation from gustatory and retronasal olfactory signals are combined to create it. Although the multisensory nature of flavor perception has been known and described in literature, its neural basis remains unknown.Previous work from our lab suggests that the piriform olfactory cortex (PC) may act as a site of flavor integration, as single PC neurons have responded to both taste and retronasal odor inputs. In this study we further quantified taste-odor convergence on single PC neurons, and characterized how bimodal inputs interact to influence their responses and information processing.To address this, we recorded spiking activity directly from single PC neurons of awake rats in response to taste, odor, and mixture stimuli using chronic electrode implants. Stimulus solutions were delivered via intraoral cannulae. Taste stimuli included all taste qualities; odor stimuli, a variety of monomolecular odorants (0.025%); multisensory stimuli, of binary mixtures of taste and odor stimuli.We recorded from 256 neurons in PC of 25 rats, 118 (46.1%) of which were responsive to intra-oral stimuli (response to all stimuli versus baseline). For these neurons, we analyzed responses to 408 mixture stimuli and their components. A total of 85 (20.8%) mixtures were associated with a significant odor response; 98 (24.0%) with taste response; and 31 (7.6%) with both components, demonstrating convergence of taste and odor inputs onto single PC neurons. To determine if bimodal inputs interact to influence the response, we compared unimodal component responses to mixture responses. For 53 (13.0%) mixtures, we found that neurons only responded to the mixture. For 43 (10.5%) mixtures, neurons only responded to at least one of the components. Thus, bimodal mixtures caused some neurons to become active, and others lost responsiveness relative to the unimodal component, suggesting nonlinear interactions between the two. We also compared mixture responses to the strongest unimodal component response for each mixture. A total of 24 (6.9%) mixtures showed direct evidence of multisensory interactions. Our data shows multisensory convergence onto single PC neurons, extending previous findings that PC is a site of multisensory convergence to both taste and odor stimuli. PC neurons also integrate their bimodal inputs, affecting responses to mixtures as compared to their components, resulting in unique spatial ensembles

activated by mixtures. Ongoing experiments will quantify the effect of taste context on discriminability of cortical odor representations, and determine the source of taste input to PC.

Disclosures: A.A. Idris: None. **E.M. Walker:** None. **J.X. Maier:** None. **B. Christensen:** None.

Poster

P423. Olfactory Coding: Higher-Order Processing II

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P423.08

Topic: D.05. Olfaction and Taste

Support: Cornell Sage Fellowship
NIH Grant DC014701

Title: Dynamical properties of interareal coherence and spike patterning in olfactory bulb and piriform cortex oscillations

Authors: *M. G. MARISCAL, T. A. CLELAND;
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Abstract: The coordinated timing of neuronal action potential firing, as evidenced by local field potential (LFP) oscillations, encodes information and facilitates interareal communication. During odor processing, a transition from gamma (50-90 Hz) to beta (12-32 Hz)-band LFP oscillations is observed in the olfactory bulb, with gamma thought to be generated within the olfactory bulb, and beta hypothesized to be generated either by the piriform cortex (after excitation by the olfactory bulb), or by the two structures together. Still, how exactly the olfactory bulb and piriform cortex generate beta, and what causes these oscillations to arise, is not yet known. Here, we analyze simultaneous multielectrode recordings from the olfactory bulb and piriform cortex collected as mice (n=13) were presented with 6 different odors for 10-15 trials each. In addition to the previously reported gamma-to-beta transition of oscillatory activity, we report a brief but consistent early beta oscillation in both olfactory bulb and piriform cortex. While late beta (>200ms after inhalation) arises simultaneously in the olfactory bulb and piriform cortex, this early beta (<150ms after inhalation) first arises in the olfactory bulb, prior to the onset of gamma. Granger causality analysis indicates though this early beta may begin in the olfactory bulb, the piriform cortex drives this oscillation. These early beta oscillations also co-occurred with strong spike patterning: a burst in firing in the olfactory bulb, followed immediately by a burst in firing in the piriform cortex, leading to a wave of inhibition in both areas. This pattern then repeats for multiple cycles on a beta timescale. Additionally, the strength of each oscillation differs between the brain areas. Gamma power is strongest in olfactory bulb, and olfactory bulb principal neurons synchronize strongly to gamma whereas piriform cortical neurons couple only weakly. In contrast, beta power is stronger in the piriform cortex; with both piriform cortical neurons (strongly) and olfactory bulb principal neurons (moderately) synchronizing to beta. Interareal coherence also is strongest for the beta oscillation, suggesting that beta may reflect communication between the two areas. These results further characterize the oscillatory dynamics of the olfactory bulb and piriform cortex during odor processing, and the mechanisms that drive the transitions

between these oscillatory modes. The recordings analyzed are drawn from the publicly available NSF CRCNS pcx-1 dataset (doi: 10.6080/K00C4SZB) by Bolding and Franks (2018).

Disclosures: M.G. Mariscal: None. **T.A. Cleland:** None.

Poster

P493. Perception: Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P493.01

Topic: H.02. Perception and Imagery

Support: KAKENHI 16H01873
KAKENHI 17H05933

Title: Top-down processing in body image processing: individuals with higher MMPI scale 1 (Hypochondriasis) showed greater activation in fusiform gyrus during evaluation of ideal body image

Authors: *Y. HAMAMOTO[1], S. SUZUKI[3], S. YAMAZAKI[2], K. MOTOKI[4], K. OBA[1], R. KAWASHIMA[5], M. SUGIURA[5];
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Abstract: Body image disturbance, overestimating and negative feelings toward one's body image, is known to be one of the greatest risk factors for eating disorders. Two independent body image processing are related to body image disturbance: actual body image processing (estimation of one's actual body size) and ideal body image processing (estimation of one's ideal body size). It is also suggested that different psychopathological personality traits influence each body image processing. Minnesota Multiphasic Personality Inventory (MMPI) can assess 10 psychopathological traits and we hypothesized the following relationships with each body image processing. Hypochondriasis and Hysteria scales are related to somatization, which is the tendency to experience psychological problems in the form of physical symptoms, and thus would influence the processing of actual and ideal body images. Psychasthenia scale would influence actual body image processing because Psychasthenia is related to obsession and the fixation of being overweight would influence the actual body image processing. Psychopathic Deviate and Social Introversion scales would influence ideal body image processing because these scales relate to sociability and ideal image is influenced by interaction with others. We investigated these relationships in 35 healthy young women by a task-based fMRI experiment. Participants viewed their silhouette images one by one in an MRI scanner that were distorted in width and performed two tasks: one in which they judged if each silhouette image was larger than their actual body (actual body task) and the other in which they judged if each silhouette image was larger than their ideal body (ideal body task). Based on the hypotheses, we conducted multiple regression analyses to examine relationships between particular MMPI scales and brain activities. We found that activation in the fusiform gyrus was positively correlated with Hypochondriasis during the ideal body task, which supported our hypothesis about the relationship between somatization and ideal body image processing.

Given that the fusiform gyrus is thought to process whole body image and higher Hypochondriasis scales represent greater concerns for one's body image, emotional and cognitive processing derived from concerns for body image may influence visual processing. The current study reveals part of the mechanism of body image disturbance.

Disclosures: Y. Hamamoto: None. **S. Suzuki:** None. **S. Yamazaki:** None. **K. Motoki:** None. **K. Oba:** None. **R. Kawashima:** None. **M. Sugiura:** None.

Poster

P493. Perception: Human Studies

Location: Virtual Only

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Program #/Poster #: P493.02

Topic: H.02. Perception and Imagery

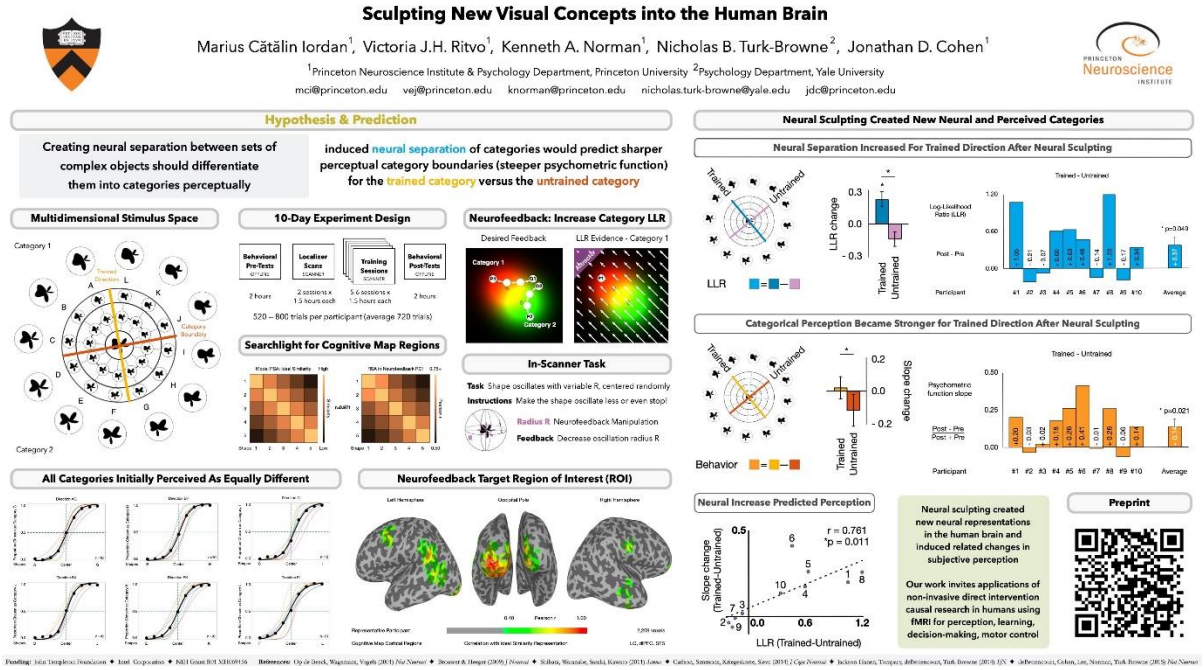
Support: Intel Corporation
John Templeton Foundation
NIH Award R01 MH069456

Title: Sculpting new visual concepts into the human brain

Authors: *M. IORDAN[1], V. J. H. RITVO[2], K. A. NORMAN[2], N. B. TURK-BROWNE[3], J. D. COHEN[1];
[1]Princeton Neurosci. Inst., [2]Psychology Dept., Princeton Univ., Princeton, NJ; [3]Psychology, Yale Univ., New Haven, CT

Abstract: Humans continuously learn through experience, both implicitly (e.g., statistical learning) and explicitly (e.g., instruction). As humans learn to group distinct items into a novel category, neural patterns of activity for those items become more similar to one another and, simultaneously, more distinct from patterns of other categories. We hypothesized that we could leverage this process using neurofeedback to devise a fundamentally new way for humans to acquire conceptual knowledge. Specifically, sculpting patterns of activity in the human brain that mirror those expected to arise through learning of new visual categories may lead to enhanced perception of the sculpted categories, relative to similar, control categories that were not sculpted. To test this hypothesis, we implemented a closed-loop system for neurofeedback manipulation using fMRI measurements recorded from the human brain in real-time (every 2s) and used this method to sculpt/create new neural categories for complex visual objects. After training, participants exhibited behavioral and neural biases for the sculpted, but not for the control categories, and we observed a significant positive correlation between the increase in behavioral discrimination and the increase of neural separation of the categories. Neural sculpting provides causal evidence (through direct experimental intervention) that distributed patters of activity evoked by complex visual stimuli can be formed de novo in high-level visual cortex to create categories that didn't previously exist in the brain or behavior. The ability to sculpt new conceptual distinctions in the human brain has broad relevance to many domains of cognition such as perception, decision-making, memory, and motor control. This also broadens the possibility for non-invasive clinical intervention in humans with fMRI (e.g., brain-machine interfaces, neuroprosthetics, neurorehabilitation) and hints at the distant possibility of

sculpting more extensive knowledge or complex concepts directly into the human brain, bypassing experience and instruction.



Disclosures: M. Iordan: None. **V.J.H. Ritvo:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None. **J.D. Cohen:** None.

Poster

P493. Perception: Human Studies

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Program #/Poster #: P493.03

Topic: H.02. Perception and Imagery

Support: Institutional funds from Penn State College of Medicine

Title: Perceptual dissimilarity analysis distinguishes grapheme-color synesthetes from non-synesthetes

Authors: *S. LACEY, M. GRAVENER, K. SATHIAN;
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Abstract: Synesthetes can be distinguished from non-synesthetes on a variety of experimental tasks because their concurrent synesthetic experiences can either facilitate or inhibit task performance if these experiences either match or conflict, respectively, with some aspect of the stimulus. Here, we tested grapheme-color synesthetes and age- and gender-matched non-synesthetic control participants (n = 20 in each group) using an online perceptual similarity task (Kriegeskorte & Mur, Front Psychol, 2012) to assess whether synesthetes' concurrent color experiences influence perceived grapheme similarity.

Participants iteratively arranged graphemes and, separately, their associated synesthetic colors in an online display, such that similar items were placed close together and dissimilar items further apart. The resulting relative inter-item distances were used to calculate the pair-wise (dis)similarity between items in the set, and thence to create separate perceptual representational dissimilarity matrices (RDMs) for graphemes and colors. On the assumption that synesthetes' similarity judgments for graphemes would be influenced by their concurrent color experiences, we predicted that grapheme and color RDMs would be more strongly correlated for synesthetes than non-synesthetes. We found that the mean grapheme-color RDM correlation was indeed significantly higher in synesthetes than non-synesthetes. In addition, synesthetes' grapheme-color RDM correlations were more likely to be individually statistically significant, even after correction for multiple tests, than those of non-synesthetes. Importantly, synesthetes' grapheme-color RDM correlations scaled with the consistency of their grapheme-color associations as measured by their Synesthesia Battery (SB: Eagleman et al., J Neurosci Meth, 2007) scores, thus providing a measure of convergent validity. By contrast, SB scores for non-synesthetes were only weakly, and non-significantly, related to their grapheme-color RDM correlations. Thus, perceptual dissimilarity analysis successfully distinguishes synesthetes from non-synesthetes, in a way that meaningfully reflects a key aspect of synesthetic experience.

Disclosures: S. Lacey: None. **M. Gravener:** None. **K. Sathian:** None.

Poster

P493. Perception: Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P493.04

Topic: H.02. Perception and Imagery

Title: Behavioral Oscillations in Rapid Face Detection

Authors: *X. LIU[1], E. BALESTRIERI[2], D. MELCHER[3];
[1]New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates; [2]Univ. of Muenster, Muenster, Germany; [3]Univ. of Trento, Rovereto, Italy

Abstract: Theories of rhythmic perception propose that perceptual sampling operates in a periodic way, with moments of high and low responsiveness to visual stimuli interleaving with each other. This rhythmic sampling seems to be modulated by brain rhythms and leads to oscillations in behavioral outcomes. Previous studies have revealed consistent theta-band behavioral oscillations in low-level visual tasks and object categorization. However, less is known about the oscillatory effect in face perception, for which the human brain has a highly dedicated network. To investigate this, we adopted a dense sampling technique and the dual-target rapid serial visual presentation (RSVP) paradigm. In each trial, a stream of object images was briefly presented at 30 Hz. Two identical face images (the target) were embedded among the baseline images with a randomly selected interstimulus interval (ISI) in between. The ISI varied from 0 to 646 ms in steps of 34 ms. The task was to indicate the presence of the target and its gender if present. There were 165 participants (mean age: 26.29 years old; 84 females; self-identified ethnicity: 46 Asian, 46 Black, 27 Latino, 46 White). We performed a Fourier transform and computed the phase-locked amplitude as an indicator of behavioral oscillations. Non-parametric permutation test was

used to test significance. A strong oscillation was found in the face detection task at 7.5 Hz (p = .005). Combining with previous studies, the results indicate a theta-band based oscillatory temporal organization underlying visual perception. The exact frequency differs from a previous study testing rhythms in face identification, suggesting the involvement of different feedback pathways in different face processes. Grouping the trials by target's gender, we found a significant oscillation at 7.5 Hz in male face detection (p = .023) and a trend to significant oscillation at 10.5 Hz in female face detection (p = .055), providing preliminary evidence that people might rely on different facial features in the rapid detection of female and male face.

Disclosures: X. Liu: None. **E. Balestrieri:** None. **D. Melcher:** None.

Poster

P493. Perception: Human Studies

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Program #/Poster #: P493.05

Topic: H.02. Perception and Imagery

Support: National Social Science Foundation of China (17ZDA323)

Title: Representation comparisons between human brains and hierarchical deep convolutional neural network in face perception reveal a fatigue mechanism of repetition suppression

Authors: *Z. LU[1,2,3,4], Y. KU[1,3];
[1]Dept. of Psychology, Sun Yat-sen Univ., Guangzhou, China; [2]Inst. of Cognitive Neuroscience, East China Normal Univ., Shanghai, China; [3]Peng Cheng Lab., Shenzhen, China; [4]Dept. of Psychology, The Ohio State Univ., Columbus, OH

Abstract: Repetition suppression (RS) for faces have long been studied, yet, the underlying primary neural mechanisms of RS remains debated, for example, fatigue or sharpening of neuronal activities. The present study used a hierarchical deep convolutional neural network (DCNN), which achieve the performance of face recognition at human level, as a tool to simulate the neural mechanism of facial repetition suppression as fatigue or sharpening of neurons and compared representations between human brains and DCNNs. First, pre-trained DCNN was better at distinguishing between different types of faces at human level than randomly-weighted DCNN. Afterwards, we constructed two RS models, fatigue model and sharpening model, to modify the activations of DCNNs, and conducted cross-modal representational similarity analysis (RSA) comparisons between dynamic processing in human EEG signals and layers in modified DCNNs. We found that facial representations of human brains were more similar to facial representations in fatigue-modified DCNN than sharpening-modified DCNN. These results indicated that the facial RS effect in face perception was more likely caused by the fatigue mechanism, which suggested that the activation of neurons with stronger responses to face stimulus would be attenuated more in facial RS. Also, human brains showed stronger and more consistent similarities with the fatigue-modified DCNN as the layer increased. Therefore, the current study supports the fatigue mechanism as a more plausible neural mechanism of facial RS. The comparison between

representations in the human brain and hierarchical DCNN provides a promising tool to simulate and infer the brain mechanism underlying human behaviors.

Disclosures: Z. Lu: None.

Poster

P493. Perception: Human Studies

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P493.06

Topic: H.02. Perception and Imagery

Support: NIH Grant R01-GM103894

Title: Degraded macroscale cortical hierarchy is unitary correlate ofhuman unconsciousness

Authors: *Z. HUANG, A. G. HUDETZ;
Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Background. Noninvasive neuroimaging in humans reveals that both pharmacological and neuropathological unconsciousness is associated with an extensive disruption of the functional connectome of brain networks. Here we ask whether these network alterations may relate to a system-level change in macroscale hierarchy affecting integration and segregation of unimodal and transmodal networks. Recent gradient mapping techniques in neuroimaging provide topological representations of human macroscale hierarchy in an abstract low-dimensional space by embedding the functional connectome into a set of axes (Huntenburg et al., Trends Cogn. Sci., 2018; Margulies et al., Proc. Natl. Acad. Sci. U. S. A., 2016; Murphy et al., Neuroimage, 2018; Vos de Wael et al., Commun. Biol., 2020). **Methods.** We analyzed fMRI datasets collected from participants and patients with various unconscious states induced by pharmacological (propofol and ketamine anesthesia, with distinct molecular targets) and neuropathological (unresponsive wakefulness syndrome, UWS) etiologies (Huang et al., Sci. Adv., 2020). We used gradient mapping methods to transform macroscale connectomes into a three-dimensional cortical gradient space (i.e., unimodal to transmodal, visual to somatomotor, and paralimbic to multiple-demand). We also applied a set of measures to quantify the range of each gradient, network eccentricity, and dispersion of global, within and between functional communities. **Results.** We found that unconscious states are associated with an overall degradation of macroscale hierarchy, which is characterized by a reduced functional distance from unimodal to transmodal regions. Further network analyses indicated dose-dependent, anesthetic-agent-dependent, and neuropathology-dependent effects. Moreover, the ventral attention network was most vulnerable to a change in the state of consciousness, of which decreased eccentricity of the cortical gradient space were consistently found during unconsciousness. **Conclusions.** These findings advance our understanding of functional reorganization in the unconscious brain, and offer a reference frame to accommodate conscious and unconscious states of diverse etiologies into a shared low-dimensional cortical gradient space.

Disclosures: Z. Huang: None. **A.G. Hudetz:** None.

Poster

P493. Perception: Human Studies

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Program #/Poster #: P493.07

Topic: H.02. Perception and Imagery

Support: BTMYoung RG Grant LV19-21_05

Title: Prestimulus fMRI activity predicts subjective Gestalt perception

Authors: *M. WILDING[1,2], C. KÖRNER[1,2], A. ISCHEBECK[1,2], N. ZARETSKAYA[1,2];
[1]Inst. of Psychology, Univ. of Graz, Graz, Austria; [2]BioTechMed-Graz, Graz, Austria

Abstract: The constructive nature of human perception sometimes leads us to perceiving rather complex impressions from simple sensory input. Bistable stimuli give us a rare opportunity to study the neural mechanisms behind this process. Such stimuli can be visually interpreted simple or more complex on the basis of the same sensory input. Previous studies demonstrated that the superior parietal cortex is selectively active when participants perceive a more complex illusory Gestalt impression compared to a simpler interpretation of individual elements. Here we tested whether activity related to the illusory Gestalt percept can be detected not only *during*, but also *prior* to it, by examining the slow fluctuations of resting-state fMRI activity before the stimulus onset. We presented 25 participants (10 women; mean age=24, SD=3.37) with a bistable motion stimulus, which can be perceived either as four moving dot pairs (local) or two moving illusory squares (global). This allows the isolation of specific neural mechanisms that accompany the experience of an illusion under matched sensory input. We used fMRI to measure brain activity in a combination of resting-state and event-related experimental design. The stimulus appeared around the fixation dot for 1s with a jittered inter-stimulus interval of 25-50s. Participants were required to respond either 'local' or 'global' depending on their subjective perception of the stimulus immediately after its presentation. We then performed a FIR-GLM analysis, which enabled us to examine the fMRI signal before and after the stimulus onset in both conditions. We observed that left superior parietal, precentral, and supramarginal areas were more active after the stimulus onset when participants perceived the stimulus as illusory squares compared to when they perceived it as local motion. This is in line with previous studies that examined activity related to perceptual grouping. Crucially, superior parietal areas were also more active for the global compared to the local condition *before* stimulus onset. Additionally, we found that global percepts were preceded by increased activity in the right putamen, which has also been linked to perceptual grouping before. Our results indicate that spontaneous fluctuations of activity in the parietal cortex and the putamen may bias the interpretation of subsequent sensory input in favor of illusory Gestalt perception. They also show that areas that are active during the illusion perception and areas that spontaneously increase activity prior to it partially overlap, suggesting that preactivation of the illusion-selective neural machinery is decisive for the subsequent illusion formation.

Disclosures: M. Wilding: None. **C. Körner:** None. **A. Ischebeck:** None. **N. Zaretskaya:** None.

Poster

P493. Perception: Human Studies

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Program #/Poster #: P493.08

Topic: H.02. Perception and Imagery

Support: Intramural Research Program of the National Institutes of Health ZIA-MH-002909

Title: Memorability is more than typicality or atypicality: evidence from brain, behavior, and computational modeling

Authors: *M. A. KRAMER[1], M. N. HEBART[2], C. I. BAKER[3], W. A. BAINBRIDGE[1];
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Abstract: A growing body of research has demonstrated that certain stimuli are consistently remembered more often than others, even across large heterogenous populations (Isola et al, 2011), leading many to ask, "what makes something memorable?" Recent studies targeting memorability - an intrinsic property of stimuli - suggest that memorability is not explained by single factor models (Bainbridge et al, 2017; Isola et al, 2014) or by linear combinations of traits (Bainbridge et al, 2013). Many of these studies hypothesize that memorability relates to typicality, with some indicating that less typical stimuli are more often remembered (Bylinskii et al, 2015; Lukavský & Děchtěrenko, 2017), some indicating that more typical items are more often remembered (Bainbridge, Dilks, & Oliva, 2017; Bainbridge & Rissman, 2018), and others suggesting a more nuanced relationship between the two (Koch et al, 2020). Here, to fully characterize the relationship between stimulus typicality and memorability, we examined THINGS, a large naturalistic object image database of 26,107 images across 1,854 categories with an associated 49-dimensional representational space consisting of both low-level visual features and high-level semantic features (Hebart et al, 2019). We leveraged the hierarchical structure of THINGS to analyze both image-to-concept typicality (e.g. the typicality of a specific penguin to the concept of a penguin) as well as concept-to-broader-category typicality (e.g. the typicality of penguins as an example of birds). We computed typicality in three ways: 1) similarity scores across visual and semantic dimensions, 2) behavioral judgments, and 3) similarity across layer activations from a deep neural network (DNN) as a proxy for visual processing. We uncovered a semantic primacy in the 49 dimensions with relatively low visual and shared variance, suggesting that the dimensions are semantically biased. We found that within-category typicality derived from the 49 dimensions correlated marginally with memorability, while behavioral within-category typicality and DNN based within-concept typicality values did not. Overall, we observe both positive and negative memorability-typicality relationships across concepts in all cases, suggesting that the relationship between memorability and typicality is more complicated than indicated by previous studies. We further characterize this memorability-typicality relationship by examining THINGS-fMRI/MEG (Contier et al, 2021), a neuroimaging dataset using the THINGS stimuli.

Disclosures: M.A. Kramer: None. **M.N. Hebart:** None. **C.I. Baker:** None. **W.A. Bainbridge:** None.

Poster

P493. Perception: Human Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P493.09

Topic: H.02. Perception and Imagery

Support: State of New York's Empire Innovator Program
NSF Grant 1734887
NIH Grant R01EY031971
NIH Grant R01CA258021

Title: An eye tracking investigation of Rubens' version of Titian's "Fall of Man"

Authors: *R. G. ALEXANDER[1], A. VENKATAKRISHNAN[1], J. CHANOVAS[2], S. L. MACKNIK[1], S. MARTINEZ-CONDE[1];
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Abstract: We conducted a psychophysical and eye-tracking study aimed at quantifying gaze dynamics during the free viewing of Rubens' version of Titian's "Fall of Man," as well as during the viewing of other similar paintings. Rubens' copy of Titian's masterpiece is very similar to the original in many ways, and virtually identical in some regards. By comparing gaze behavior during viewing of the two paintings, presented on a computer screen, we assessed the effects of Rubens' changes to Titian's composition on the viewer's experience. An EyeLink 1000 was used to record gaze binocularly from 33 participants as they viewed each of the images for 45 seconds. We analyzed multiple gaze parameters, including fixation duration, saccade and microsaccade production, fixation consistency across subjects, and others, as well as the natural image statistics of each painting. We found that participants gazed for longer durations at Eve's face in the Rubens' version of the painting than in Titian's original. In addition, gaze positions were more dispersed for the Titian painting than for the Rubens painting, indicating different allocations of viewer interest for each painting. Our combined results suggest that the above differences in gaze behavior can be attributed to critical variations in composition between the two paintings. Notably, Rubens changed the depicted characters' body arrangement and gaze direction, providing powerful joint attentional cues for viewers to focus their central vision on Eve's face. Thus, joint attention may be a key element in the viewer's experience of "The Fall of Man" as imagined by Rubens—though not by Titian.

Disclosures: R.G. Alexander: None. **A. Venkatakrishnan:** None. **J. Chanovas:** None. **S.L. Macknik:** None. **S. Martinez-Conde:** None.

Poster

P493. Perception: Human Studies

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Program #/Poster #: P493.10

Topic: H.02. Perception and Imagery

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Novartis Foundation for Medical-Biological Research Grant

University of Geneva (UNIGE) - University of Zurich (UZH) Joint Seed Funding Award
2020 Gorilla Grant for Online Behavioral Experiments

Title: Is Perceptual Adaptation Impaired in Healthy Individuals with Schizotypal Personality Traits?

Authors: *A. O. GIARRATANA[1,2], M. KALIUZHNA[3], S. KAISER[3], P. N. TOBLER[2];
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Abstract: Introduction and Background: Schizophrenia can be understood to exist on a spectrum; from non-clinical individuals with higher levels of schizotypal personality traits to patients with schizophrenia. Studying schizotypy in non-clinical populations can be extremely informative, given that schizotypy is positively correlated with an increased liability for the eventual development of a schizophrenia spectrum disorder. By studying schizotypy, researchers may be able to detect biomarkers for early detection of psychosis. To this end, we have developed a novel task that can be used either behaviorally only or together with neuroimaging. We previously found that neural adaptation to reward range is impaired in both healthy individuals with stronger schizotypal personality traits and in patients with schizophrenia. However, it remained unclear whether adaptive coding impairments in the schizophrenia spectrum are limited to reward or affect also other domains. **Specific Experimental Aims:** 1. To develop an fMRI friendly visual perceptual decision-making task with a measureable behavioral output that captures adaptation with narrow versus wide ranges of perceptual inputs. 2. To investigate if the adaptive coding performance in this task correlates negatively with levels of schizotypal personality traits in the healthy control population. **Methods and Design:** In each trial of our novel object discrimination task, participants decide whether a presented image is a face or a house. We present these morphed images in wide range blocks (2.50% - 97.5% face), and in narrow range blocks (27.5% - 72.5% face) to healthy individuals with different levels of schizotypy. **Results:** We find that participants behaviorally adapt to the range, such that for similar images, performance is more accurate in the narrow range blocks compared to the wide range blocks. With regard to the link between perceptual range adaptation and schizotypal personality traits, preliminary results reveal a trend-level negative relation. **Conclusions:** Our findings will speak to the generality of adaptive coding deficits in individuals with schizotypal personality traits, by investigating the perceptual domain with our novel task and its relation to the reward domain using fMRI. The results may provide leads for an early biomarker of schizophrenia burden.

Disclosures: A.O. Giarratana: None. **M. Kaliuzhna:** None. **S. Kaiser:** None. **P.N. Tobler:** None.

Poster

P506. Cross-Modal Processing In Humans III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P506.01

Topic: D.09. Multisensory Integration

Support: JSPS Grant-in-Aid for Early-Career Scientists, Grant Number 19K14319.
2019 QR Program (Qdai-jump Research Program) and Wakaba Challenge (reference number: 01296)

Title: Quantitative analysis method of color-odor association using Bayesian estimation

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Abstract: Olfactory inputs can influence human behavior and cognition. Odors can be associated with colors, even in the absence of visual information. While some color-odor associations seem to be shared widely (e.g., lemony smells and yellow), other odors can remind different people of different colors. The individual variance of a color-odor association likely indicates association strength, which could be estimated by observing the variation of associated colors and odors. We hypothesized that by observing the variation of associated colors with odor, we could estimate the strength of color-odor association. An appropriate measurement method was required, and the effect of verbal description also needed be considered. We proposed a quantitative method to measure the association between odor and color. Bayesian estimation was used for the statistical analysis because it facilitates the prevention of a type II error, which is caused by frequent hypothesis testing.
We estimated the variances of color responses by measuring associated colors with 13 types of odors as continuous variables in color space, CIEL*C*h*. This space comprises a hue axis (h), a chroma axis (C*), and a lightness axis (L*). It is created by converting Cartesian space, CIEL*a*b*, to a polar coordinate. Language descriptors for each odor were also examined. The Bayesian estimation method using Markov chain Monte Carlo (MCMC) was introduced to summarize color and descriptor responses. A total of 23 university students (female, n = 11, male, n = 12; mean age ± SD = 20 ± 1.6 years) participated in the experiment twice (on two separate days). They were instructed to sniff 13 different odorants and answer questions about the color and semantic descriptors associated with each odor. Their responses were quantified as continuous values and each odor's reproducibility and variability of associated colors were calculated.
This method enabled us to record colors associated with an odor as a continuous variable. Our measurement of associated colors revealed no significant variations between participants. These results supported the consistency of the measurement of associated colors with odor. In order to evaluate their variance, we measured the mean resultant vector length for hue data because CIEL*C*h space is a polar coordinate. Our method assessed the strength of intrinsic association of color-odor pairs by estimating the resultant length of associated color hues.

Disclosures: K. Tamura: None. **T. Okamoto:** None.

Poster

P506. Cross-Modal Processing In Humans III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P506.02

Topic: D.09. Multisensory Integration

Title: A Novel Electro-prosthetic Proprioception Reduces Visual-Proprioceptive Matching Error for Finger Aperture Control

Authors: R. RAVICHANDRAN[1], J. L. PATTON[2], *H. PARK[1];
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Abstract: Finger motor tasks often need high manipulation accuracy because the fingers are frequently used in sophisticated tasks. Finger aperture control in a finger reaching task is one of the critical maneuvers, especially in applications requiring right amount of force when touching a target object (e.g., a delicate tissue structure in surgery). The planning and execution of such a finger reaching task to control the finger aperture are based on proprioceptive feedback when vision on the fingers is blocked or occupied by other tasks. However, the visual-proprioceptive matching error, which is the mismatch between visually perceived distance and proprioceptively perceived distance, limits the capability of replicating the visual distance by the fingers and results in an error in the motor output. To address the visual-proprioceptive matching error and improve the control accuracy of the finger aperture, we introduce a novel technique, electro-prosthetic proprioception (EPP) that works as a new sensory reference, bridging vision and proprioception. EPP was rendered by electrical stimulation applied to the fingertip with a frequency inversely proportional to the finger aperture distance. We tested EPP could enhance accuracy in a conventional visuomotor training in a finger closing task without vision. We observed that aperture control accuracy significantly improved with EPP ($p<0.001$). More importantly, this accuracy was retained at 2 days post training ($p<0.001$) where conventional visuomotor training does not show any lasting effect at 2 days post training ($p=0.655$). We speculate that EPP affords a new schema of representing visual targets in working memory that reduces visual-proprioceptive matching errors, and may have broad application in enhanced feedback training paradigms, such as neurorehabilitation.

Disclosures: R. Ravichandran: A. Employment/Salary (full or part-time):; Texas A&M University. **J.L. Patton:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago. **H. Park:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

P506. Cross-Modal Processing In Humans III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P506.03

Topic: D.09. Multisensory Integration

Support: National Institutes of Health (National Cancer Institute Grant U01 CA193632)

Title: The role of superior colliculus in affective experiences during visual and somatosensory stimulation

Authors: *D. CHEN[1], P. A. KRAGEL[2,3], A. B. SATPUTE[1], P. SAVOCA[4], L. L. WALD[4], M. BIANCIARDI[4], T. D. WAGER[5], K. S. QUIGLEY[1,6], L. F. BARRETT[1,4], J. THERIAULT[1];
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Implementation Res. (CHOIR) and the Social and Community, Edith Nourse Rogers Mem. VA Hosp., Bedford, MA

Abstract: The superior colliculus (SC) is a small deep-brain structure in the midbrain. Non-human animal evidence shows that SC has strong anatomical connections with many sensory regions in the brain, including areas typically involved in vision, somatosensation, and interoception. Physiological and lesion studies also indicate SC involvement in multisensory stimulation that localized to specific layers, with visual activity localized to superficial layers and somatosensory activity to deep layers. SC intermediate and deep layers also receive inputs from brain regions that are implicated in affective experience. Despite this evidence, prior human studies have primarily focused on its role in visual processing and spatial attention. With limited previous human research, we hypothesize that, human SC plays an important role in affective experiences during multisensory stimulation through its widespread anatomical projections with the interoceptive-allostatic system and its multimodal responses. Using 7-Tesla ultra-high-field fMRI at 1.1mm resolution, we measured changes in BOLD activity within the SC during two affect-evoking stimulation, one using visual stimuli (picture viewing, N = 40, Sample 1) and another using somatosensory stimuli (pressure to left thumb; N = 40, Sample 2). Greater activity of whole SC was observed during unpleasant compared to neutral trials in both tasks. Notably, voxel-wise analysis of SC activity was localized to different SC subregions based on task modality: greater activity in bilateral *dorsal* SC was observed during the visual task, whereas greater activity in the right lateralized *ventral* SC was observed during the somatosensory task, consistent with the sensory organization of superficial-to-deep layers of non-human animal SC. Whole-brain functional connectivity from the SC was also examined across trials using subject-specific SC ROIs. Pending a full, planned preregistration of the connectivity analyses, preliminary results (N=3 for each task) showed that, for both tasks, whole SC demonstrated strong functional connectivity with the visceromotor hubs within the interoceptive-allostatic system, many of which have direct anatomical connectivity to the SC (e.g., anterior and mid cingulate cortex, amygdala, insula, periaqueductal grey, hypothalamus, nucleus accumbens, and thalamus). Narrowing the gap between non-human and human research, the results support our hypothesis that SC is involved in affective experience elicited through multiple sensory modalities, and to our knowledge, are the first to show human functional dissociation within SC through multimodal stimulation using high-resolution fMRI.

Disclosures: D. Chen: None. **P.A. Kragel:** None. **A.B. Satpute:** None. **P. Savoca:** None. **L.L. Wald:** None. **M. Bianciardi:** None. **T.D. Wager:** None. **K.S. Quigley:** None. **L.F. Barrett:** None. **J. Theriault:** None.

Poster

P506. Cross-Modal Processing In Humans III

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Program #/Poster #: P506.04

Topic: D.09. Multisensory Integration

Support: 5U01NS113339-02

Title: Seeing the Face of the Talker Normalizes BOLD Pattern Responses to Noisy Speech

Authors: *Y. ZHANG, J. F. MAGNOTTI, A. SONIG, M. S. BEAUCHAMP;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Viewing the talker's face improves comprehension of noisy speech. To investigate the neural computations underlying this perceptual benefit, we measured BOLD fMRI pattern responses in the posterior superior temporal gyrus and sulcus (pSTG/S) of 14 healthy participants who were presented with 2-second audiovisual recordings of single words (297 words from 12 different talkers) in 5 formats: clear audiovisual (AcV); noisy audiovisual (AnV); clear auditory-only (Ac); noisy auditory-only (An); and visual-only (V).fMRI data was collected with words presented in a silent interval inserted between acquisitions of the multiband pulse sequence. Participants reported whether the word was intelligible ("Y") or not ("N") with a button press after each presentation. For noisy auditory speech, seeing the face of the talker produced a large increase in intelligibility (odds-ratio = 7.0, $p = 10^{-8}$; 38% intelligible for An *vs.* 71% for AnV). The fMRI data from noisy auditory trials was *post hoc* sorted into "Y" and "N" trials, allowing for a comparison between trials that were physically similar but perceptually different. Voxel time series were analyzed using a GLM with 7 regressors of interest (AcV, AnV-Y, AnV-N, Ac, An-Y, An-N, V) in AFNI. The mean percent signal change across conditions was calculated for each voxel and subtracted from the response to each individual condition in order to increase the dynamic range of the fMRI pattern correlation. The fMRI pattern similarity between each pair of conditions was calculated by correlating the normalized percent signal change across the pSTG/S voxel in each of the 28 hemispheres. The response pattern evoked by AnV-Y speech was very similar to the response pattern evoked by AcV speech, even though they were physically very different, r(AcV, AnV-Y) = 0.66 +- 0.04 (mean ± SEM across hemispheres). In contrast, the response patterns evoked by AnV-Y and AnV-N speech were very different, even though the stimuli were physically similar, (AcV, AnV-N) $r = 0.13 \pm 0.13$. Intelligibility had a weaker effect on the response patterns for auditory-only speech, r(Ac, An-Y) = 0.49 ± 0.09 *vs.* r(Ac, An-N) = 0.45 ± 0.10, as confirmed by a significant interaction between intelligibility and stimulus format in a linear mixed-effects model. This demonstrates that intelligibility and the presence of visual speech are both important drivers of response patterns in pSTG/S. When noisy audiovisual words are intelligible, the pattern of brain response in pSTG/S is similar to that observed during clear audiovisual speech, suggesting that normalization of response patterns could be responsible for the perceptual benefit of seeing the face of the talker.

Disclosures: Y. Zhang: None. **J.F. Magnotti:** None. **A. Sonig:** None. **M.S. Beauchamp:** None.

Poster

P506. Cross-Modal Processing In Humans III

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Program #/Poster #: P506.05

Topic: D.09. Multisensory Integration

Support: NIH EB027586 (CRCNS)
BMBF 01GQ1805A,B,C (CRCNS)

Title: Depth-dependent somatovisual responses in human superior colliculus using 9.4T fMRI

Authors: *D. RESS[1], **A. QURESHI**[1], F. MOLLA[2], K. R. SITEK[3], M. HIMMELBACH[4], G. HAGBERG[5], K. SCHEFFLER[5];
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Abstract: OBJECTIVE: The superior colliculus (SC) plays an important role in representing the external environment across multiple sensory modalities. Ultra-high field MRI enables imaging and characterization of SC with a greater signal-to-noise ratio in smaller voxels. We investigate the role of deeper layers of SC in somatovisual integration (SVI) that uses tactile cues to guide a visual task. These responses are compared to a visual-only (VO) version of the same task. **METHODS:** MRI data were collected at 9.4T using a 16 (31)-channel transmit (receive) array. T1-weighted anatomical images were acquired with an MP2RAGE sequence (0.6 mm isotropic voxels). fMRI data were collected with 1-mm cubic voxels and 1.5-s TR (8 runs). A level-set scheme (Truong et al., Hum Brain Mapp 41, 2020) was used to quantify depth-dependence of the fMRI signal. Surfaces of each SC were divided into a 3x3 grid to allow across-subject averaging. Data were bootstrapped across subjects to quantify its reliability. Eight individuals participated in SVI and VO sessions, at least one each. Air puffs were delivered to their fingers during the SVI task to cue them to attend to a quadrant of the visual field. Subjects reported the total number of '+' patterns that appeared in this quadrant after each 6-min run, while ignoring other patterns. Single puffs were alternately presented to the index and ring fingers; a random double puff cued visual attention to the upper (index finger stimulation) or lower (ring finger stimulation) visual fields. Stimulation alternated between the left and right hands (cuing left and right visual fields) every 15 seconds, enabling coherence analysis. During the VO task, the target visual quadrant was cued by a color change without tactile stimulation.
RESULTS: We found that somatosensory stimulation drives lateralized responses in SC fairly globally. In rostral SC, responses were largely superficial. Deeper lateralized responses were found in caudal SC, as expected for forelimb stimulation. Compared to the VO responses, deep caudal SC responses were stronger in the SVI task, reaching significance at some depths. However, the SVI responses were noisier than those evoked by VO, and additional evaluation of noise sources is underway. **CONCLUSION:** We probed multisensory responses and studied the depth dependence of sensory processing within human SC using 9.4T fMRI, demonstrating its utility for investigating sensory responses within human midbrain structures. Consistent with prior animal studies, results suggest that the deeper layers of the SC represent multisensory information in a retinotopic fashion.

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Poster

P506. Cross-Modal Processing In Humans III

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P506.06

Topic: D.09. Multisensory Integration

Title: Three is better than two: how trimodal sensory information integrate in the double-flash illusion.

Authors: *A. TONELLI, A. BOLLINI, M. GORI;
Fondazione Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: The world, as we perceive it, is the result of integration among all our senses. In most cases, the combination of two senses allows improving the sensitivity of a perceived stimulus. However, in other situations, this combination can result in illusions. This is true for the 'Sound-Induced Flash Illusion' (SIFI), in which the rapid presentation of a single visual stimulus associated with two auditory 'beeps' produces the perception of two flashes, demonstrating that sound can alter vision even when there is no ambiguity in the visual input. Similarly, this happens also with tactile stimuli where a double touch induces the perception of two flashes, the 'Tap induced flash illusion' (TIFI). The specific time synchrony of this illusion is considered an indicator of multisensory integration, but what happens when more than two modalities are involved? Can sensory redundancy increase the effect of the illusion or interfere with it? In the present experiment, we tested whether the redundancy of sensory information could influence the visual illusion traditionally found in the SIFI and TIFI. During the experiment, we presented randomly three possible combinations of multisensory stimuli: (1) a single visual stimulus associated with two auditory 'beeps' (SIFI); (2) a single visual stimulus associated with two vibrations (TIFI); (3) a single visual stimulus associated with two vibration and two auditory 'beeps' (TMIFI - TriModal Induced Flash Illusion). The task was to count the number of flashes, regardless of the combination of stimulations. Results show around ~60% of illusion for both SIFI and TIFI conditions, in line with other studies in the literature; while in the tri-modal condition, in which there were two vibrations and two beeps with a single flash, participants perceived the illusion on ~75% of the trials. This result suggests that the redundancy of sensory information can boost the illusion effect. Moreover, we found that the effect in the TMIFI condition correlates positively with the illusion in both SIFI and TIFI, meaning that people with higher illusions in the bimodal conditions perceive a higher illusion in the tri-modal condition. Interesting, there is no correlation between SIFI and TIFI conditions. This result may indicate that when both tactile and auditory cues are presented with the visual stimulus, their influence is not a simple summation effect but rather an integration of the two that changes their effectiveness compared to the only tactile or auditory condition.

Disclosures: A. Tonelli: None. **A. Bollini:** None. **M. Gori:** None.

Poster

P506. Cross-Modal Processing In Humans III

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Program #/Poster #: P506.07

Topic: D.09. Multisensory Integration

Support: NIH Grant DC016297

Title: A temporally correlated visual signal improves the neural representation of auditory objects.

Authors: A. R. NIDIFFER, E. C. LALOR;
Biomed. Enginerring, Univ. of Rochester, Rochester, NY

Abstract: The auditory system is capable of processing complex acoustic environments, binding features of auditory signals into meaningful units called objects while also segregating objects from background noise and distractors. One cue that aids in this process is the common temporal dynamics of an object's features. Evidenced by behavioral, fMRI, and EEG data, humans can form objects from acoustic signals, called stochastic figure-ground (SFG) stimuli, based solely on temporally coherent frequency changes within that signal, despite spectro-temporal overlap between the stochastic figure and the background in which it is set. It is rare that events in the environment produce energy in a single sensory modality, and so we asked how a visual stimulus might affect object formation when observing these SFG stimuli. Specifically, we sought to determine how auditory object formation was affected by the presence of a temporally correlated, but otherwise uninformative, visual stimulus. While recording high-density electroencephalography (EEG), we presented these stimuli along with one of two visual streams: one with flashes timed to match frequency changes in the auditory object and one with independent flashes with similar temporal statistics. Via forward encoding models, we found neural representations of the object and the background in EEG in fronto-central electrodes typical of auditory signals. When the visual signal was correlated, the figure representation was enhanced relative to its background. Preliminary results from a second experiment suggest that alpha power tracked the correlation between the object and visual stimulus. Taken with previous findings, these results support a complex relationship between multisensory integration, attention, and binding that is susceptible to consistency across sensory features.

Disclosures: A.R. Nidiffer: None. **E.C. Lalor:** None.

Poster

P506. Cross-Modal Processing In Humans III

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Program #/Poster #: P506.08

Topic: D.09. Multisensory Integration

Support: NIH T32 MH 64913-18
Swiss National Science Foundation P300PB_164754

Title: Effects of motion coherence and congruency on evidence accumulation during audiovisual integration

Authors: *A. SCHOENHAUT[1], A. THELEN[1], A. NIDIFFER[2,3], N. VAN DER STOEP[4], R. RAMACHANDRAN[1,2], M. WALLACE[1,2];
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Abstract: Combining information from our different senses into a single, coherent percept in a process known as multisensory integration helps us make sense of our surroundings. The benefits of multisensory integration are especially clear when the incoming sensory information is degraded, such as in cluttered, noisy environments. While previous studies have investigated how static multisensory stimuli are processed, less is known about the principles underlying the integration of dynamic, ecologically valid

stimuli such as those that move. Here, we investigate the interaction between auditory and visual apparent motion cues as a function of stimulus reliability. To address this behaviorally, we employed apparent motion stimuli (i.e. random dot kinematograms and auditory motion embedded in noise) in a two-alternative forced choice reaction time task in which participants judged the direction of motion of unisensory alone (i.e., visual, auditory), directionally congruent audiovisual, and directionally incongruent audiovisual stimuli. By parametric manipulation of auditory and visual motion coherence in this task, we investigated their impact upon perceived motion direction and evidence accumulation. We found that adding directionally congruent, low-coherence visual motion to auditory motion decreased sensitivity to auditory motion, whereas adding congruent auditory motion of any coherence to visual motion increased sensitivity to visual motion. Additionally, we found substantial inter-participant variability in sensory cue weighting when auditory and visual motion was directionally incongruent. To determine how strength of visual and auditory motion cues affected rate of multisensory evidence accumulation during motion direction discrimination, we modeled reaction times and accuracy from congruent multisensory trials using a hierarchical Bayesian estimation of drift diffusion modelling (HDDM). We found that adding congruent auditory motion to visual motion increased the rate of evidence accumulation across auditory and visual stimulus coherences. In contrast, adding visual motion that was more coherent than the auditory motion present increased the rate of evidence accumulation, while adding visual motion that was less coherent than the auditory motion present decreased the rate of evidence accumulation. Taken together, our results suggest a greater reliance upon visual information than auditory information when discriminating the direction of audiovisual motion, but with striking inter-individual differences in the respective weighing of the auditory and visual cues.

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Poster

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Topic: D.09. Multisensory Integration

Support: JSPS KAKENHI (19H01087)

Title: One-hour interval induces the adaptation to the driving scene that causes simulator sickness.

Authors: *M. HAYASHI[1], Y. ITAGUCHI[3], M. MIKI[4], T. KIMURA[4], M. MIYAZAKI[1,2];
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Abstract: Driving simulators can be used to safely evaluate the behavior of drivers under various virtual conditions but they often cause simulator sickness. To use driving simulators more effectively, this problem needs to be addressed. In this study, we focused on adaptation as a strategy to reduce simulator sickness. Previous studies showed that simulator sickness is reduced by repetitive experience of

simulators with intervals of one day or more. If the adaptation occurs in intervals shorter than a day, simulator sickness is more effectively reduced. In our previous study, we tested whether adaptation can be induced by a six-minute interval between two sessions in a motorcycle simulator (Hayashi et al., 2021, SfN Global Connectome). However, this six-minute interval did not reduce simulator sickness, suggesting that six-minute intervals are too short to induce adaptation. In the current study, we tested whether a time interval of one hour can induce adaptation. Twenty students participated in the experiment. The participants sat on the chassis of a motorcycle and watched two six-minute motorcycle driving scenes on a winding road from a first-person perspective using a head-mounted display. There was a one-hour interval between the first and second driving scenes. During the experiment, the participants verbally reported the degree of simulator sickness every 30 s using a number from 0 (no sickness at all) to 20 (severe sickness) (Fast Motion Sickness scale, FMS). The FMS scores during the second driving scene were significantly lower than those during the first driving scene. Moreover, we compared the FMS scores between our current (one-hour interval) and previous (six-minute interval) experiments. For the first driving scene, there was no significant difference in the FMS scores between the two experiments, indicating that there were no difference in baseline sickness before the intervals between the two experiments. For the second driving scene, however, the FMS scores were lower in the current experiment with the one-hour interval than in the previous one with the six-minute interval. These results indicate that the one-hour interval induces adaptation to the driving scene and reduces simulator sickness. We discuss a possible mechanism of our results based on the sensory conflict theory and the consolidation theory for sensorimotor learning.

Disclosures: M. Hayashi: None. **Y. Itaguchi:** None. **M. Miki:** None. **T. Kimura:** None. **M. Miyazaki:** None.

Poster

P508. Eye Movements I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P508.01

Topic: E.01. Eye Movements

Title: Functional development of extraocular motor neurons in the larval zebrafish

Authors: *P. LEARY[1], D. GOLDBLATT[2], S. HUANG[1], K. HAMLING[1], D. SCHOPPIK[1];
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Abstract: To stabilize gaze, extraocular motor neurons are tasked with correctly contracting particular eye muscles. Individual motor neurons must therefore encode parameters associated with head and body movements. While much is known about eye movement behavior and the spatial organization of extraocular motor neuron pools, the factors influencing motor neuron activity development remain unclear. We will present results that define the response of developing zebrafish extraocular motoneurons to vestibular stimulation. We first generated transgenic lines that permit targeted expression of the calcium indicator GCaMP6s in the oculomotor (nIII) and trochlear (nIV) nuclei. We next performed whole-body vestibular stimulation in the pitch and roll axes while we measured motor neuron activity

during multiphoton imaging. We investigated changes to activity patterns by repeatedly recording from the same cells over early development. Preliminary findings are as follows: We observed reliable responses that increased in magnitude following stimulation in the preferred direction. The slope of the relationship between stimulus amplitude and increasing activity varied considerably between cells. Further, individual motor neurons had different response kinetics, such as timescale of response, basal activity levels, and post-inhibitory rebound. Between 3 and 10 dpf, we observed systematic changes to the motor neurons. These included changes to the slope of the relationship between stimulus amplitude and activity, indicating changes in sensitivity to body tilts, as well as changes in the sensitivity to pitch vs roll axis stimulation.Taken together, this suggests developmental changes due to cell-specific properties or extrinsic properties, such as establishment of new inputs into motoneuron pools. Work is underway to characterize molecular correlates of these developmental changes using transcriptomic approaches and targeted photoablations of motor neuron inputs. Our work will speak to the factors that shape extraocular motor neuron activity for gaze stabilization.

Disclosures: P. Leary: None. **D. Goldblatt:** None. **S. Huang:** None. **K. Hamling:** None. **D. Schoppik:** None.

Poster

P508. Eye Movements I

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Program #/Poster #: P508.02

Topic: E.01. Eye Movements

Support: K08EY023265
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R01EY017039
Zegar Foundation
Keck Foundation
Kavli Foundation

Title: The Role of Oculomotor Proprioception in the Accommodative Reflex and Vergence Eye Movements

Authors: S. E. STELLA[1], M. E. GOLDBERG[2], S. G. LOMBER[3], *L. D. SUN[1];
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Abstract: Previous research has shown that cortical ocular proprioception is implicated in fixation stability and alignment of interocular eye position, but it is unknown if it plays a role in the accommodation reflex. This reflex allows the eyes to focus on near targets and involves three simultaneous motor movements in what is known as the “near triad” which includes: binocular convergence, pupillary constriction (miosis), and lens accommodation. We hypothesized that ocular proprioception controls eye position alone and that it would have no effect on accommodation as

measured by pupil size. To test this, we reversibly inactivated area 3a of the somatosensory cortex via a cooling probe implanted in the right central sulcus of a single head-fixed rhesus macaque while tracking interocular angles and pupil diameter. LED fixation targets were presented at near (27 cm) and far targets (1-2 m). Physiological responses were monitored during an alternate-cover task and compared in control, cooled, and warmed states. We assessed approximately 250 trials for each state over five different recording days for the response of the covered and uncovered eye. There were differential contralateral and ipsilateral effects on the pupil during unilateral inactivation of cortical ocular proprioception for near targets. For the covered contralateral eye, there was a significant 3.4% increase in pupil diameter during inactivation which returned to baseline after rewarming (two-tailed Wilcoxon Signed-Ranks Test, $Z=7.93$, $p<1e-14$). The pupil diameter of the covered ipsilateral eye increased by 0.25% during inactivation of area 3a which was not significantly different from the control condition ($Z=0.30$, $p=0.76$). Thus our experiment showed that the contralateral eye saw interference of pupillary constriction during fixation to near targets while cortical proprioception was inactivated (the covered contralateral pupil enlarged and the eye moved laterally). But there was no significant interference ipsilaterally, showing contra-ipsilateral differential control. These results suggest that cortical ocular proprioception plays an additional underlying role in the near triad by modulating pupil and vergence tone, disproving our initial hypothesis of only eye position involvement.

Disclosures: S.E. Stella: None. **M.E. Goldberg:** None. **S.G. Lomber:** None. **L.D. Sun:** None.

Poster

P508. Eye Movements I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P508.03

Topic: E.01. Eye Movements

Title: Neuronal populations trajectories during smooth pursuit and motion perturbations in area MT

Authors: K. K. NONEMAN[1], *J. MAYO[2];
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Abstract: Natural vision involves unexpected moving objects, self-induced motion, and expectations about motion in the world. The medial temporal area (MT), a sensory response region of the primate visual cortex, plays a critical role in visual motion processing and consists of direction- and speed-sensitive neurons. MT neuronal responses to motion are often described by a dominant sensory component, driven by the presented stimulus, that is modulated by top-down cognitive factors such as visual attention. But the sensory and cognitive aspects of the neuronal mechanisms involved in rapid sensory-motor transformations (~100 ms), such as smooth pursuit eye movements, are unclear. One possibility is that the oculomotor response to motion onset during pursuit is rapid enough to dampen or preclude the effects of top-down modulation. Alternatively, extrasensory signals unrelated to stimulus identity may be an unavoidable part of most behaviors. To begin to address these issues, we designed a task that allowed us to define a ***sensory axis*** based on the responses of neurons to brief motion pulses at various speeds, as well as a ***cognitive axis*** based on well-characterized changes in temporal attention (i.e., expectation) during fixation. We first asked if these two axes were meaningfully separable across

recording sessions. We then evaluated the potential cognitive contributions of pursuit initiation by measuring changes in population trajectories relative to the sensory axis caused by 1) stimulus motion onset, and 2) subsequent eye movement-induced motion. We recorded from small populations of neurons in macaque area MT using linear multi-contact electrode arrays and analyzed neuronal responses to brief motion pulses (50 ms duration) during sustained periods of fixation and pursuit (15 deg/sec). We asked if motion pulses of various speeds (i.e., sensory input) during fixation drive population activity along a similar trajectory as eye movements (i.e., sensory and reafferent input). To find the relevant dimensions for understanding the data, we employed dimensionality reduction techniques to transform the high-dimensional spiking data into lower-dimensional space. Our overarching goal is to delineate the differences in sensory processing and cognition that are at times not readily apparent at the level of individual neurons by using simultaneously recorded populations of MT neurons to better understand the neural mechanisms of motion perception in the natural world.

Disclosures: K.K. Noneman: None. **J. Mayo:** None.

Poster

P508. Eye Movements I

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Program #/Poster #: P508.04

Topic: E.01. Eye Movements

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Title: Fixational drift is driven by diffusive dynamics in central neural circuitry

Authors: N. BEN-SHUSHAN[1], N. SHAHAM[3], M. JOSHUA[2], *Y. BURAK[2,1];
[1]Racah Inst. of Physics, [2]Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: During fixation and between saccades, our eyes undergo diffusive random motion called fixational drift. In the foveal region of the visual field, where receptive fields are dense, fixational drift causes stimuli to move across many receptive fields. The role of this motion in visual coding and inference has been debated in the past few decades. On one hand, it has been proposed that fixational motion may assist high acuity vision. On the other hand, it has been argued that fixational drift poses a challenge for high acuity visual inference, as it precludes the possibility to overcome spiking noise by simple temporal averaging. While the consequences of fixational drift have been extensively studied from a normative perspective, the mechanisms that underlie this motion remained unknown. In particular, it has been unclear whether fixational drift arises from peripheral sources, or from central sources upstream of the muscles. To address this question, we analyzed simultaneous recordings of neural activity of ocular motoneurons (OMNs) in the Rhesus monkey, alongside precise measurements of eye position obtained using implanted eye coils. Single OMNs are too noisy to identify a correspondence between spiking

activity and eye position during fixation over a single trial, but by analyzing data from 58 OMNs over hundreds of eye trajectories for each cell, we show that the two are correlated, and that on average, the correlated component of the single OMN activity accounts for a large fraction of the eye motion variability during fixation. Several lines of reasoning indicate that most of the motion must arise from a central origin, upstream of the motoneurons. This is the first demonstration that fixational drift is correlated with central neural activity. We propose that the primary source of the motion resides in noise-driven random diffusion within the oculomotor integrator. We support this hypothesis by constructing a mathematical model of central and peripheral contributions to eye dynamics: the stochastic dynamics of the oculomotor integrator, combined with the dynamics of the ocular motoneurons and ocular plant. With biologically plausible parameters this model accounts both for the magnitude of the fixational motion and for its detailed statistics, as measured from the data. Thus, we propose that fixational ocular drift provides a direct observation of diffusive dynamics in a neural circuit responsible for storage of continuous parameter memory in persistent neural activity.

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Poster

P508. Eye Movements I

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Program #/Poster #: P508.05

Topic: E.01. Eye Movements

Support: NIH Grant EY024831
NIH Grant EY030667
NIH Grant EY022854

Title: Spiking activity and local field potentials along the dorsoventral axis of the superior colliculus during visually-guided eye movements: instantaneous correlational analysis

Authors: *N. J. GANDHI, C. BOURRELLY;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC), a neural structure involved in the sensorimotor transformation, is functionally organized along its dorsoventral axis: neurons in superficial layers exhibit a visual response, neurons in deeper layers present a movement response, and neurons in intermediate layers show both responses. Whereas it is known that the action potentials are the output of neurons, local field potentials (LFP) are believed to reflect the input. However, the exact nature of the LFPs remains unclear. In our companion abstract we state that the LFP signal shares general properties with spiking activity - visual response for the most superficial layers, a movement response for the deeper layers, and both visual and movement responses for intermediate layers - and that the onset of LFP modulation occurs earlier than the onset of visual burst in superficial layers. Recently, in the macaque visual cortex, a trial-by-trial correlation analysis has shown that the LFP activity is coupled to the spiking activity. This study showed that the spiking activity is a good predictor of the LFP amplitude occurring later. We hypothesized that, in the superficial layers, after the onset of its modulation, the LFP signals are coupled with preceding

spiking activities. Using multi-contact laminar electrode, we simultaneously recorded LFPs and spikes in the SC in two rhesus monkeys performing a visually guided delayed saccade task. We computed correlations between instantaneous LFP and spiking modulations as a function of depth around the time of the visual burst. We regressed the time-series signals of the residual spiking activity with the residual LFP activity for each trial ("within trial" analysis). The strongest correlations were observed when the LFP activity lagged the visual spiking activity by ~10 msec. Also, the magnitude of the correlation decreased with depth. To study the instantaneous correlation during the visual burst, the residual spiking activity across all trials at one time point was regressed against the residual LFP activity at different delays ("across trials" analysis). We found that, throughout the visual burst, the instantaneous residual spiking activity was correlated with later instantaneous residual LFP activity. The preliminary results of both within trial and across trials analysis on the motor response seem to show similar trends. Altogether, our results support the idea that, after its onset, the LFP modulation could be driven by the spiking activity.

Disclosures: N.J. Gandhi: None. **C. Bourrelly:** None.

Poster

P508. Eye Movements I

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Program #/Poster #: P508.06

Topic: E.01. Eye Movements

Support: NIH EY024831
NIH EY030667
NIH EY022854

Title: Spiking activity and local field potentials along the dorsoventral axis of the superior colliculus during visually-guided eye movements: visuomotor features and response onset

Authors: *C. BOURRELLY, N. J. GANDHI;
Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a brain structure involved in the visuomotor transformation. Previous studies have shown that the SC is functionally organized across depth: neurons in superficial layers present a visual response, neurons in deeper layers exhibit a movement response, and neurons in intermediate layers show both visual and movement responses. It is known that the spiking activity is the output of neurons. In contrast, local field potentials (LFP) presumably represent the input. The nature of LFP signals in the SC remains largely unexplored. Previous studies, based on single electrode recordings, have shown that LFP signal shares spatial and temporal properties with spiking activity. Moreover, it has been shown that in both frontal eye fields and lateral intraparietal region, the onset of LFP modulations precede the spiking activity during the visual burst, whereas the spikes lead the LFP modulations during the motor response. Using multi-contact laminar electrode, we simultaneously recorded across depth spiking activities and LFPs in the SC in two rhesus monkeys performing a visually guided delayed saccade task. We hypothesized that the same general spatial properties described for the spiking activity

will be found in the LFP signal as a function of depth. We predict that the onset of the LFP modulation will precede the visual burst in the superficial channels whereas the motor burst will occur before the onset of LFP modulation in the deeper channels. As observed for spiking activity, the categorization of the LFP on each channel revealed a visual preference for the most superficial channels, a movement preference for the deeper channels, and both visual and movement responses for intermediate channels. Interestingly, the switch from the visual to the motor preference is observed on deeper channels on the LFP signal. Then, we examined the temporal properties of LFP modulations as a function of depth during the visual response. The analysis of the relative timing between the onset of LFP modulations and the onset of the spiking activity revealed a spatiotemporal pattern: the onset of LFP modulation occurred earlier than the visual burst on superficial channels. A preliminary analysis on the motor response seems to show a similar pattern: the motor burst strongly leads the LFP onset for deeper channels. All together, these results are consistent with the spatiotemporal representation of the input-output transformation in the SC. Nevertheless, it is still unclear if the spiking activity lags (or leads) the LFP activity throughout the visual (or motor) burst or solely at the earlier stage i.e. its onset. This question is addressed in a companion abstract.

Disclosures: C. Bourrelly: None. **N.J. Gandhi:** None.

Poster

P508. Eye Movements I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P508.07

Topic: E.01. Eye Movements

Title: Microsaccade dynamics in a spatial attention task with neutral cuing and varied stimulus configurations

Authors: *S. WILLETT, J. MAYO;
Dept. of Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Microsaccades are thought to be a behavioral measure of covert attention. Attentional cues can modulate the frequency and direction of microsaccades, as well as attention-related changes in firing rate across visual cortical areas. However, the precise relationship between attention and microsaccades remains unclear. First, many studies probe the microsaccade-attention relationship by using cues that always predict the target location (100% cue validity). This approach assumes the effects of attention remain constant at a single location, complicating the interpretation of the microsaccade-attention relationship for multiple items in more naturalistic settings. Second, because attention fluctuates as a function of cue validity and stimulus configuration, the dynamics of the microsaccade-attentional relationship are confounded by multiple interacting cognitive processes that are sometimes not experimentally manipulated. Here we analyzed monkey behavior in cued vs. neutral blocks of trials to measure attention in relation to microsaccades. Specifically, we investigated a) the frequency and direction of microsaccades aligned to stimulus onset, and b) changes in microsaccades as a function of stimulus configuration (e.g., one stimulus in each hemifield vs. two stimuli in a single hemifield). Monkeys were trained to perform an orientation change-detection task. Two oriented Gabors, sinusoidally

counterphased at 10 Hz, were presented simultaneously. Monkeys fixated (500-5000 ms) and reported an orientation change by saccading to the changed stimulus. Attention was cued to a stimulus location via a visual cue on instruction trials at the start of each block of trials. During cued blocks, the change occurred with 80% probability at the cued location and 20% probability at the other location. During neutral blocks, visual cues were presented at both stimulus locations during instruction trials, and the change occurred with 50% probability at each location. 5% of the total trials were catch trials in which no change occurred and monkeys were rewarded for maintaining fixation. This study investigated microsaccade frequency and direction in response to stimuli that varied in their location and their likelihood to change in orientation. Establishing the distribution of microsaccades across time, cue validity, and stimulus configurations helps elucidate the extent to which microsaccades can be used as a non-invasive indicator of visual spatial attention and the limitations of this approach. In future work, we hope to determine how changes in the moment-by-moment neuronal correlates of attention relate to the timing and direction of microsaccades.

Disclosures: S. Willett: None. **J. Mayo:** None.

Poster

P508. Eye Movements I

Location: Virtual Only

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Program #/Poster #: P508.08

Topic: E.01. Eye Movements

Support: JSPS KAKENHI Grant 19K11460

Title: Properties of visual search strategies based on eye-head coordination in athletes

Authors: *S. ONO[1], Y. YOSHIMURA[2], T. KIZUKA[1];
[1]Hlth. and Sport Sci., [2]Comprehensive Human Sci., Univ. of Tsukuba, Ibaraki, Japan

Abstract: In various sports situations, it is necessary to execute appropriate movements in response to visual targets such as a ball or opponent's movements. Visual motion information plays an important role in control of movements. In particular, skilled ball players are thought to acquire accurate visual information by using an effective visual search strategy with eye and head movements. For example, when tracking a moving object, the visual image is first captured in the central or peripheral visual field, and based on this visual information, the speed, trajectory and spatial location of the ball are estimated. In previous studies on visual search, eye movements were mainly analyzed to evaluate gaze, and the distribution of gaze was clarified from the viewpoint of where the gaze is mostly placed in the visual field. However, in actual sports situations, visual search based on the interaction between eye and head (whole body) movements are required. Therefore, the purpose of this study was to determine the characteristics of visual search strategies based on eye and head movements during a ball catching task in comparison between athlete and non-athlete groups. We examined the different patterns of gaze movement, head and eye movements among subjects during a catching task. Participants were fifteen tennis players (athlete group) and fifteen college students who are not experienced in ball sports (non-athlete group). The participants performed a one-handed catching task using a tennis ball-shooting

machine, which was placed at a distance of 9 m in front of the participants, and two conditions were set up: a low-speed condition (ball speed, 24 km/h) and a high-speed condition (ball speed, 32 km/h). Their head and eye movements were detected using gyroscope and electrooculography (EOG) during the task. Our results showed that peak eye and head velocities were lower in the athlete group than in the control group. In particular, when the head was tilted upward, downward eye velocity was induced in the non-athlete group. This result indicate that the non-athlete group shows vestibulo-ocular reflex (VOR) during head movements, whereas the VOR is suppressed in the athlete group. Furthermore, athletes showed smaller arm movements when catching the ball, suggesting that arm movements and head movements are linked to catching skills. Taken together, skilled ball players have relatively stable head and eye movements, which may lead to an effective visual search strategy.

Disclosures: S. Ono: None. **Y. Yoshimura:** None. **T. Kizuka:** None.

Poster

P524. Hand Control: Behavioral Studies

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.01

Topic: E.04. Voluntary Movements

Support: Israel Science Foundation Grant # 1634/19
German-Israel Foundation Grant # I-2535-409.10/2019

Title: Dissimilarity of finger individuation behavior between flexion and extension

Authors: *O. RAJCHERT, Y. MELUL, F. MAWASE;
Biomed. Engin., Technion - Israel Inst. of Technol., Haifa, Israel

Abstract: The ability to individuate fingers imparts high motor flexibility and requires accurate coordination of different finger flexor and extensor muscles. Although most everyday hand movements involve coordination of flexor muscles for both gross and fine activities (e.g., grasping, typing), the role that extensor muscles play in these types of movements is unclear. Here, we investigated two aspects of independence of the digits during single and multi-finger isometric force assessments, *individuation* - the degree to which all uninstructed digits remain still during instructed movement of a particular digit, and *stationarity* - the degree to which a particular uninstructed digit remains still during movements of all instructed digits. The study was split up into 2 experiments. In Exp. 1, participants (n=13) used a hand robot (Tyromotion's Amadeo®) and producing finger forces, each time with a different single finger, to maintain one of four levels (20,40,60,80% of the maximal voluntary contraction) in both the extension and flexion directions. Participants then performed multi-digit chords (2-digit, 3-digit, and 4-digit) in each direction. We found that during single-digit tasks, individuation and stationarity were significantly lower for extension ($p<0.0001$). Interestingly, we found dissimilar involvement of the opposite muscle direction for uninstructed digits when comparing extension and flexion. While exertion of single-digit extensor forces revealed that in the uninstructed fingers extensor muscles were primarily involved, single-digit flexor forces involved flexors of the adjacent uninstructed digits and extensors of the non-adjacent uninstructed digits. In the multi-digit task, accuracy was reduced for fingers during exertion of force in

the extension direction ($p<0.0001$) and chords with 2 or 3 digits were less accurate for both flexion and extension compared to chords with 1 or 4 digits. Next, we studied the extent to which mechanical coupling between muscle extensors and flexors limits finger independence by studying passive individuated finger movements (Exp. 2). Our data suggest that when the robot passively moved each of the fingers, the reduced mechanical coupling for the extensors could not fully explain the reduced individuated extensor muscles' behavior we encountered during Exp. 1. Overall, our data suggest that finger individuation is dissimilar for extension and flexion and that this disparity is attributed to neuromuscular control, rather than passive mechanical coupling. This study sheds light on characterization of a more complete mechanism of hand function taking into account not only flexion, but also extension.

Disclosures: O. Rajchert: None. **Y. Melul:** None. **F. Mawase:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.02

Topic: E.04. Voluntary Movements

Support: University of Nebraska Omaha Graduate Research and Creative Activity Grant 27265
Biomechanics Rehabilitation and Manufacturing Initiative

Title: Use of Immersive Virtual Reality for Assessing Gross Hand Dexterity

Authors: *S. PARKER[1], E. BUCKLEY[2], K. COULTER[2], B. RICKS[2], J. ZUNIGA[1], B. KNARR[1]; [1]Biomechanics, [2]Computer Sci., Univ. of Nebraska, Omaha, Omaha, NE

Abstract: Virtual Reality (VR) is a promising technology that allows for tasks to be performed in a virtual environment that uses less physical space. Previous studies have reported increased functional outcomes with screen-based VR systems[1-5]. However, it is not well known whether immersive VR elicits similar functional outcomes and brain activation as conventional manual therapy. The purpose of this study is to assess the use of immersive VR as a modality for testing total hand dexterity in adults while performing the Box and Block (BBT) test under observation with functional near-infrared spectroscopy (fNIRS). We hypothesize that there will be no difference in the magnitude of contralateral motor cortex (CM1) activation between Manual and VR condition for both the left and right hands. The contralateral activation was chosen in accordance with previous studies that support CM1 activation during arm & grasping tasks[6,7]. Ten participants (5M/5F, age: 26.9±6 years, height: 1.7±0.3 m, weight: 80.1±21 kg, hand dominance: 8 right/2 mixed) were included in analysis. Participants were asked to complete the BBT Manually and in VR (Oculus Rift, Oculus) with their left and right hands for 3 one-minute trials each. A block study design was implemented with one-minute breaks given between trials and three-minute breaks between hands and conditions. The order of BBT condition and hands were randomized for each participant. fNIRS (NIRSport2, Nirx) was used to record levels of CM1 activation for each condition. CM1 activation was calculated using a group level general linear model (GLM) analysis with the NIRS AnalyzIR toolbox[8,9]. The beta values were used in a 2x2 Anova to determine the main effect difference

between VR and Manual conditions for both hands with significance correction. The behavioral outcome measure was BBT score for each condition. Two paired t-tests were performed using BBT scores comparing the Manual and VR conditions for both hands. All statistical analyses were performed in Matlab R2018a (Mathworks) with significance at $\alpha \leq 0.05$. The Manual condition exhibited a significantly higher BBT score compared to the VR condition for both left (Manual: 61±10, VR: 40±13, $p = 0.003$) and right (Manual: 62±7, VR: 42±10, $p < 0.001$) hands. This reduction in functional VR BBT score may be a result of reduced tactile input from the VR controllers combined with the VR being a novel task. There is no significant interaction in CM1 activation between the Manual and VR BBT conditions (all channels $q > 0.05$). CM1 activations were comparable between Manual and VR conditions, suggesting that VR systems may elicit similar cortical responses compared to the conventional Manual BBT.

Disclosures: S. Parker: None. **E. Buckley:** None. **K. Coulter:** None. **B. Ricks:** None. **J. Zuniga:** None. **B. Knarr:** None.

Poster

P524. Hand Control: Behavioral Studies

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Topic: E.04. Voluntary Movements

Support: H2020-EU.1.3.3. - PLATYPUS - No. 734227
H2020-EU.1.2.2. - MAIA - No. 951910

Title: Horizontal target size perturbation during grasping movements modifies sizes perception and saccade amplitude

Authors: P. SANZ DIEZ[1,2], *A. BOSCO[3,4], P. FATTORI[3,4], S. WAHL[1,2];
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Abstract: Action and perception are crucial aspects of our daily activities. Based on the dual-visual stream theory, it is now accepted that action and perception are not separated processes, but they interact and influence each other. However, it is still unknown how object perception may be affected by unpredictable changes in object size during grasping movements. In this study, we aimed to determine whether size perception and related saccade amplitude before and after grasping movements were modified by horizontal perturbations of target size during movement execution and under the presence (TF) or absence (NoTF) of tactile feedback exerted on the fingerprints by vibration motors. We have tested twenty-one participants (mean 25.05±4.08years) in 4 blocks of 30 trials where the blocks were divided into two categories: TF and NoTF. Trials consisted of 3 sequential phases: pre-grasping size perception, grasping, and post-grasping size perception. During pre- and post- phases, participants were required to execute a saccade towards a horizontal bar and to perform a manual size estimation of the bar size by extending the index finger and thumb. During the grasping phase, participants were asked to execute a saccade towards the bar and to make a grasping action towards the screen matching the edges of

the displayed bar by extending the index finger and thumb. During the grasping phase, 3 horizontal size perturbation conditions were applied after the onset of the grasping movement: non-perturbation, shortening, and lengthening. 30% of the trials presented perturbation, meaning a symmetrically shortened or lengthened by 33% of the original size. Participants' hand and eye positions during the estimation phases were assessed by a motion capture system and a mobile eye-tracker, respectively. In both NoTF and TF, the difference between perceptual responses in pre- and post- phases revealed significant adjustments. After grasping, size estimation was significantly reduced in lengthening ($p=0.002$; Wilcoxon) and non-perturbation conditions ($p<0.001$; Wilcoxon), whereas shortening condition did not induce significant adjustments ($p=0.86$; Wilcoxon). After grasping, saccade amplitude became significantly longer in shortening condition ($p<0.001$; Wilcoxon) and significantly shorter in lengthening condition ($p<0.001$; Wilcoxon). Non-perturbation condition did not display significant adjustments ($p=0.95$; Wilcoxon). These results suggest that the horizontal size perturbation occurring during the grasping action is reflected on size estimation and saccade amplitude measured in the subsequent perceptual phase.

Disclosures: P. Sanz Diez: None. **A. Bosco:** None. **P. Fattori:** None. **S. Wahl:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.04

Topic: E.04. Voluntary Movements

Title: Humans modulate gripping forces on a stationary, handheld object in response to mere expectation of rapid movement

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Abstract: Recent studies show that while manipulating hand-held objects, the grip force (GF) is not as tightly coupled with the load force (LF), as previously thought. Rather, the predictability of the LF imposed by volitional object movement influences the GF magnitude and the GF-LF coupling. Here, we study the anticipatory modulation of GF to understand further the sensorimotor control of prehension. Previous studies explored the GF-LF coupling while the object was in motion. Hence, we studied GF control during the *foreperiod* of a choice reaction-time (CRT) task, when an object is held static, but participants expect to move it in response to a visual cue. The goal was to identify how GF exerted on a static object changes in response to a mere expectation of object movement. Since GF increases with task uncertainty, we hypothesized that GF would increase when participants expect to move but are uncertain about the time and direction of movement. Healthy adults ($N = 16$; 24 ± 4 yrs.) held an object in a pinch grasp in their dominant right hand and tracked a target provided on a computer screen by moving the object vertically. Digit forces and object position were measured using force transducers and motion capture. Visual feedback of the object's position was provided as a cursor on the screen. In steady tasks, participants were aware that the target will not move. They did not expect to move the object, and held the object static so that the cursor remained inside the target. CRT tasks began like steady tasks, but

participants expected the target to jump either up or down at any moment. They were required to track the target as quickly as possible by moving the object. We compared the mean GF for steady tasks and during the foreperiod of CRT tasks before object movement began. As predicted, the GF increased by 13% when movement was expected versus when it was not expected ($t_{(15)} = 3.1$, $p < .01$). This is a novel finding: GF increased in response to mere expectation of movement, even as the LF remained constant. By increasing GF, the central nervous system (CNS) may increase tactile feedback to improve predictive control of digit forces. Tactile feedback is thought to be intermittent for predictable manipulation tasks. However, when upcoming movements are uncertain and involve significant state changes, more frequent feedback will yield superior current state estimates, which, in turn, would facilitate motor planning and execution. Also, when upcoming movements are uncertain, the CNS may prepare and optimize multiple plans associated with possible movements. Increased GF may be a manifestation of such optimization since the GF eventually increases after the foreperiod during both up and down movement.

Disclosures: A.S. Naik: None. **S. Ambike:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.05

Topic: E.04. Voluntary Movements

Support: Johns Hopkins Malone Center Seed Grant

Title: Individuated finger control in fine manipulation introduces a cost of decreased trajectory smoothness

Authors: *J. XU[1], T. MA[2], S. KUMAR[3], K. OLDS[4], J. BROWN[4], J. CARDUCCI[4], A. D. FORRENCE[5], J. W. KRAKAUER[4];
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Abstract: Humans possess remarkable skills in fine object manipulation. This ability is presumably enabled by increased individuated finger control due to enlarged corticospinal tract (Lawrence & Kuypers, 1968). In the motor control field, it's been established that good control manifests as smooth trajectories (Flash & Hogan, 1985, Harris & Wolpert, 1998). However, what is the role of individuation ability in smooth control in object manipulation is not clear. Here we investigated this question by directly comparing people's finger individuation and their trajectory qualities in precision grip. We developed a sensitive device to measure subtle isometric forces at all fingertips in three-dimension (3D), and designed 3D individuation and three precision-grip tasks. We hypothesize that increased finger individuation may be an important factor of smooth manipulation.
Healthy college-aged participants (N=22 for Individuation and Grip 1, N=17 for Grip 2&3) placed their hands in the device in a comfortable resting posture. In the individuation task, participants were required to move a dot in a 3D virtual cartesian space by exerting isometric forces at one of the fingertips while keeping other fingers immobile. Movement of the dot along virtual xyz axes reflected forces exerted by

MCP ab/adduction, PIP flexion/extension, and MCP flexion/extension, respectively. In the 3 grip tasks, participants attempted to grasp a small spherical object in the 3D virtual space with their thumb and index/middle finger (max force < 3N). The object was placed in the middle of the straight line between the two fingers. In Grip 2 task, the two fingers had to enter tunnels before the grip; in Grip 3 task, they attempted to first grasp a small dial of the same diameter and then turn the dial with +/-20 or +/-45 degrees to match the 12 o'clock position.
From the force traces recorded during the entire trial, we derived Individuation Index, initial and final grip angles, and trajectory smoothness (jerk cost). Our results showed that individuation ability did not play a role in final grip angles ($p = 0.27$) but was a significant factor in the initial positioning of fingers in Grip 2&3 tasks ($p<0.001$), where individuation ability was demanded. Contrary to our prediction, in these two tasks grip trajectory were jerkier than those in simple grips (Grip 1 task) ($p = 0.008$), and individuation ability were negatively correlated with smoothness ($p < 0.01$). In the dialing task, trajectories became jerkier when the angle to be adjusted was smaller (20 deg.) ($p = 0.00005$). We conclude that the evolutionarily new finger individuation system entails a cost of increased movement variability in fine manipulation tasks.

Disclosures: J. Xu: None. **T. Ma:** None. **S. Kumar:** None. **K. Olds:** None. **J. Brown:** None. **J. Carducci:** None. **A.D. Forrence:** None. **J.W. Krakauer:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.06

Topic: E.04. Voluntary Movements

Support: Japan Society for Promotion of Science, KAKENHI (grant numbers 17H06345 and 20H01785)

Title: Re-optimization processes to gravitational perturbation in reach-to-grasp movements

Authors: *L. ANDO[1], Y. ITAGUCHI[2];
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Abstract: In a daily life, we often experience arm weight changes when using tools or lifting of objects. Most of the studies of motor adaptation in force-field have investigated adaptation processes to force applied in the horizontal plane, but not to force in the gravitational direction. In this study, we investigated the re-optimization processes to forearm-weight increase in the trajectory planning of reach-to-grasp movement. We hypothesized that the height of movement trajectory is modulated to reduce disturbances due to signal-dependent noises in the gravitational direction. To confirm this hypothesis, we conducted 400 trials of reach-to-grasp movement tasks under three weight conditions; no-weight 200 g, 400 g weight condition, which was also supposed to induce muscle fatigue. Signal-dependent noise can be increased by two factors: increased muscle force against the forearm weight and muscle fatigue. We thus set two predictions; first, the movement trajectory will be higher in the weight conditions than the

no-weight condition, and second, the movement trajectory will continue to increase as a function of trials in the 400 g weight condition.In the experiment, right-handed 14 participants performed reach-to-grasp movements on a desk. They reached for and grasped a target object located 30 cm in front of the starting point and transported it 10 cm right of target position with their right-hand. The participants performed eight blocks per each condition, and one block consisted of 50 trials. They experienced each of the three weight conditions alternatively every other month. Under the no-weight condition, the participants performed the movements without any weight. Under the 200 g and 400 g weight conditions, they performed the movements with 200 g or 400 g weight attached to their forearm except in the first and last block. We calculated max height and MGA (maximum grasp aperture); max height was defined as the maximum height of the wrist position from the desk, and MGA was defined as the maximum distance between the tips of the thumb and index finger. The results showed that max height was evidently higher compared with the baseline block in the 200 g and 400 g conditions and continued to increase as function of trials only in the 400 g condition. These results support our hypothesis that participants might re-optimize their movement trajectories to the increase in forearm weight by raising the height, which can reduce disturbances due to signal-dependent noises attributed to increased muscle force against the forearm weight or muscle fatigue.

Disclosures: L. Ando: None. **Y. Itaguchi:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.07

Topic: E.04. Voluntary Movements

Support: PRODEX, Belgium
CNES, France

Title: Grip dynamics during object manipulation on the International Space Station

Authors: *L. OPSOMER[1,2], J.-L. THONNARD[1,2], F. CREVECOEUR[1,2], J. MCINTYRE[3,4,5], P. LEFEVRE[1,2];
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Abstract: During object manipulation, the brain must predict the consequences of arm movements to adjust grip force anticipatively and ensure a stable grasp. Parabolic-flight studies have shown that the temporal coordination between grip force and load force is preserved during object manipulation in extreme gravito-inertial environments, such as Mars, Moon, hyper- or micro- gravity (Augurelle et al., 2003; White et al., 2005; Crevecoeur et al., 2009; Opsomer et al., 2018). However, it was also observed in these studies that participants tend to increase the grip-load force ratio in microgravity, probably to increase the safety margin against accidental slips. But what are the characteristics of the grip force/load force coupling in microgravity after long-term adaptation, i.e. when this environment is not novel

anymore? Do astronauts tune the grip force to the object mass and movement-induced inertial loads with the same accuracy as they do on Earth? To address this question, we asked six astronauts to perform rhythmic arm movements with an object held in precision grip, both on Earth and during long-term (>5-months) missions on the International Space Station. Various masses were used, as well as various oscillation frequencies. Corroborating the results from previous studies, a steady grip force/load force correlation was rapidly acquired, both on the ground and during space flight. Strikingly, the grip-load force ratio at the time of maximum load was independent of object mass, movement frequency or gravity level. This constant force ratio was achieved by offsetting the grip force as a function of load force range, consistent with the ability to estimate the slip ratio properly and suggesting that tactile and proprioceptive feedback are integrated quickly to update the anticipatory control of grip force. Interestingly though, even after several months of exposure to microgravity, up/down asymmetries were observed in the grip force modulations, despite symmetrical load force fluctuations.

Disclosures: L. Opsomer: None. **J. Thonnard:** None. **F. Crevecoeur:** None. **J. McIntyre:** None. **P. Lefevre:** None.

Poster

P524. Hand Control: Behavioral Studies

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.08

Topic: E.04. Voluntary Movements

Support: NINDS Grant NS122333

Title: A method to study prehension in primates

Authors: *A. R. SOBINOV[1], C. M. GREENSPON[2], E. V. OKOROKOVA[1], Y. YAN[1], S. J. BENSMAIA[2];
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Abstract: A hallmark of primate behavior is the exceptional ability to dexterously grasp and manipulate objects. Investigation of the neural mechanisms that support manual dexterity has been hindered by technical challenges. First, tracking the time-varying posture of the hand is difficult given its many articulated segments and the susceptibility of individual segments to occlusion. Second, characterizing the contact forces exerted on objects with sufficient precision is challenging given the exquisite sensitivity and spatial resolution of the sense of touch. Third, contact forces propagate down the limb in the form of joint torques and alter muscle activity. Measurements of limb state and object interactions is thus critical to understanding the neural mechanisms that mediate manual object interactions.
With this in mind, we have developed an experimental apparatus to overcome these challenges. First, the apparatus allows us to place an object anywhere in the workspace. Second, the objects size and orientation can be systematically manipulated. Third, the object is sensorized with thousands of pressure-sensitive elements that allow us to measure the forces exerted at each point of contact. Fourth, hand and arm movements are tracked using eight high-speed cameras, whose output is then processed using machine vision algorithms to track the positions of 34 markers on the limb in 2D for each camera. The

positions of the markers are then triangulated based on the 8 planar estimates (on from each camera) and used to obtain time-varying joint angles using a musculoskeletal model of the limb. Finally, we solve an optimization problem in a physics engine to adjust the object's position with respect to the hand to reproduce the pattern of exerted forces. Having reconstructed contact forces, applied to the corresponding contact locations on the hand, and reconstructed the posture of the entire limb, we can then calculate the torque at each joint using inverse dynamics. Together, these measurements provide a characterization of primate manual behavior with exceptional precision, which opens the door to an unprecedented investigation of the neural mechanisms of manual dexterity.

Disclosures: A.R. Sobinov: None. **C.M. Greenspon:** None. **E.V. Okorokova:** None. **Y. Yan:** None. **S.J. Bensmaia:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.09

Topic: E.04. Voluntary Movements

Title: Human and monkey hand kinematics during prehension

Authors: *Y. YAN[1], A. SOBINOV[3], S. J. BENSMAIA[2];
[2]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL; [3]West Virginia Univ., Morgantown, WV

Abstract: HUMAN AND MONKEY HAND KINEMATICS DURING PREHENSION Yuke Yan, Anton R. Sobinov, & Sliman J. BensmaiaThe human hand is a remarkably precise and versatile manipulative organ, enabling interactions with objects that range from the mundane – like grasping an object – to the extraordinary – epitomized by virtuosic instrumentalism. Our understanding of the neural mechanisms that mediate manual dexterity has relied heavily on experiments with non-human primates, and in particular macaques, whose hands and sensorimotor systems are similar to their human counterparts. Indeed, the anatomy of human and macaque hands is largely similar and homologs to the neural structures that support the sensorimotor control of the hand in humans have been identified in macaques. Qualitatively, manual behavior is also similar in humans and monkeys. Like humans, monkeys preshape their hand before grasp in an object-specific way and are capable of some degree of finger individuation. However, to our knowledge, human and monkey manual behavior has never been compared using detailed quantitative approaches that have been used to characterize manual behavior of either species separately. With this in mind, we systematically compared the prehensile behavior of humans and rhesus macaques using an identical experimental paradigm. In brief, humans and monkeys grasped a set of 35 objects handed to them by a robot while we monitored the time-varying joint angles of their hands using a computer vision algorithm. We then compared the hand kinematics of human and monkeys using a variety of quantitative approaches. First, we analyzed the range of motion, velocity, and acceleration of the kinematics. Second, we quantified the degree to which the kinematic subspaces of humans and monkeys are similar. Third, we assessed the interdependence of human and monkey joint movements. Finally, we decomposed the variance in hand postures into different task-dependent and

independent components. We found that, while hand kinematics of prehension are similar in humans and monkeys, these differ in subtle but systematic ways. For example, although thumb is the most independent digit in both species, other human fingers move more independently and adopt postures that are more tightly dependent on the object to be grasped. This careful comparison of human and monkey manual behavior provides a further assessment of the validity of the macaque sensorimotor system as a model of human manual behavior.

Disclosures: Y. Yan: None. **A. Sobinov:** None. **S.J. Bensmaia:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.10

Topic: E.04. Voluntary Movements

Support: ONR MURI Grant N000142012163

Title: Joystick-based Motor Control Task During Sympathoexcitation via Cold Pressor in Healthy Humans

Authors: *T. REISSMAN[1], P. KOMPA[2], K. DUFFY[2], S. COLLINS[2], M. REISSMAN[1], A. CRECELIUS[2];
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Abstract: Motor control performance is important in tasks that require piloting of a vehicle and thus it is of interest to understand the physiological changes that may impact motor control. Little work to date has been done that attempts to couple physiological measurements such as cerebral blood flow to motor control tasks, particularly in situations of enhanced autonomic nervous system activity. Here, we utilized a joystick-based virtual beam rotation task to assess motor control performance. After a familiarization trial, 24 young, healthy subjects (12M, 12F, age: 21±1 yrs) performed the task in either control conditions or with concomitant sympathoexcitation via cold pressor (CP; foot submerged in 4°C ice slurry), with the order counterbalanced across subjects. Throughout each trial, heart rate (HR; 3-lead ECG), beat-beat arterial blood pressure (BP; finger photoplethysmograph), end-tidal CO_2 (nasal cannula) and middle cerebral artery velocity (MCAv; transcranial doppler), an indicator of cerebral blood flow, were measured. The motor control task consisted of a virtual horizontal beam with a circular ball on its upper surface. A target section of the beam (one of 4 options, near and far on right and left of center) was identified with lines. Subjects were instructed to rotate the joystick in order to tilt the beam and cause the ball to both roll and slow down within the target area. The total motor control task consisted of 10 blocks, where the 4 locations were randomized within each block. Differences between control and CP were assessed with a paired t-test and differences across all timepoints were assessed via repeated-measures ANOVA with post-hoc pairwise (Sidak) test with *a priori* $p<0.05$). The CP elevated HR and BP as anticipated (74±11 vs 84±13 bpm, p=0.0002; 93±8 vs 95x±8 mmHg, p=0.00004). At 30 sec, MCAv significantly increased with motor control task in control (Δ 4.8±7.0%, p=0.007) and CP conditions (Δ 8.7±7.8%, p=0.0001), and this increase was greater for CP vs control (p=0.01). Results did not vary if

separated by sex. Motor control performance was quantified according to the tasks for the 2 near targets and the 2 far targets, as each pairing had the same difficulty level as per Fitts' law. Statistical differences were observed only within the first 30 sec. Total task completion time increased with CP vs control for both the near targets (Δ 0.89s or 21%, $p<0.001$) and the far targets (Δ 0.55s or 11.6%, $p=0.007$). Results indicate these increases were not due to changes in movement initiation but increased movement corrections. Taken together, we demonstrate that sympathoexcitation can negatively impact motor control performance despite increased cerebral blood flow.

Disclosures: T. Reissman: None. **P. Kompa:** None. **K. Duffy:** None. **S. Collins:** None. **M. Reissman:** None. **A. Crecelius:** None.

Poster

P524. Hand Control: Behavioral Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P524.11

Topic: E.04. Voluntary Movements

Support: Tufts CTSI (NIH UL1TR002544)
Northeastern Internal Grant

Title: Control of manipulative forces on the leg during walker ambulation is hard for human trainers

Authors: J. MANCZUROWSKY, *C. HASSON;
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Abstract: To provide effective physical assistance clinicians must implicitly know how to apply forces to patients' bodies to generate desired motions. This mapping between forces and motion can be framed as an internal model of patient dynamics. In gait rehabilitation these models can be complex, but nevertheless can be learned by non-experts as previously shown. One may expect that the clinical experiences of physical therapists (PTs) provides a foundational set of internal models that can be rapidly adapted to new patients. This study tests the hypothesis that PTs adapt to novel locomotor dynamics faster than non-PTs. We asked two groups of trainers (21-65 yrs), PTs and non-therapists, to reproduce a time-varying pattern of manipulative forces on the leg of a healthy individual walking on a treadmill (the walker). For experimental control all participants interacted with the same walker. The walker wore a right ankle brace that served as an attachment point for a force sensor sandwiched between the brace and a handle the trainers grasped. Walker leg motion and assistive force templates were created from data collected while a PT provided manual assistance to increase the (same) walker's step length. Trainers (PTs and non-PTs) first practiced two randomly presented control conditions without walker dynamics present: 1) trajectory-matching in which trainers tried to match the walker leg motion template while moving their hands in free-air, 2) force-matching where the trainers tried to match the force template by pushing on the walker's leg while the leg remained stationary. Next, trainers practiced two randomized conditions in which success depended on appropriately compensating for external forces from the walker's leg: 1) exerting zero force while holding onto the moving walker's leg, 2) producing forces to match the force template (on a moving leg). In these conditions the walker attempted to maintain the same

locomotor kinematics, aided by a real-time visual display of their motion overlaid with a target trajectory. Data collection is ongoing; preliminary results suggest that without needing to account for walker dynamics, both PTs and non-PTs can move their arms in the requisite leg trajectory and can apply time-varying forces that match the force template. However, both PTs and non-PTs had difficulty adjusting their motor commands to match the force template when the walker ambulated, with high force errors. Both trainer types adapted and improved with practice. Whether PTs have faster adaptation rates than non-PTs should become clear with additional data. Knowledge of how PTs interact with patient dynamics may help develop future approaches to enhance PT performance.

Disclosures: J. Manczurowsky: None. **C. Hasson:** None.

Poster

P586. Vocal/Social Communication: Avian IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.01

Topic: F.01. Neuroethology

Support: PSC-CUNY Grant TRADA-52-296
NIH Grant 5T32GM136499-02

Title: Social-context-dependent activation of the social behavior network in zebra finch songbirds

Authors: *K. L. ANDERSON, J. URAGA, O. WHITNEY;
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Abstract: As the environment presents both obstacles and opportunities to organismal fitness, the nervous system functions to evaluate stimuli encountered and generate context-appropriate, adaptive behavioral responses. Such decisions in animals involve brain mechanisms that are not well understood. Recent studies of species-specific adaptive behavior implicate evolutionarily conserved and reciprocally connected brain regions, termed the social behavior network (SBN). However, few studies have investigated the genomic response of regions within the SBN to social behavior stimulation of naturally behaving animals (i.e., not hormonally manipulated). Here, using zebra finch songbirds, we measure activity-dependent gene expression to investigate SBN activation during a non-social context of undirected singing and a social context of female-directed singing. We performed fluorescence *in situ* hybridization to map the transcription of cellular activity marker *EGR1* within the SBN of zebra finches. Three adult males from each experimental group (non-social undirected singing; socially directed singing) were housed individually in acoustic attenuation chambers. Singing males sang spontaneously for 45 mins at the beginning of their 14:10 light cycle in either the presence or absence of a female. Subsequently, brains were quickly excised and freshly frozen for serial coronal cryosectioning. Tissue sections were thaw mounted onto slides and hybridized to FITC-labeled *EGR1* RNA probes. Antibody detection of FITC revealed *EGR1* within regions of interest, which was quantified using ImageJ2 and standardized against DAPI nuclear DNA staining. Similar to previous studies, we found higher levels of *EGR1* in all cerebral vocal-control regions of undirected singing males (HVC, RA, lMAN, and Area X) compared to that in Area X and RA of directed singers. Compared to non-social undirected singing

controls, we found an upregulation of *EGR1* in the VMH, AH, and LS of socially directed singing males. Additionally, we found increased *EGR1* in the PVN, an area with known direct projections to the SBN, in socially directed singing males compared to non-social undirected singing controls. No hemispheric differences were found. These findings suggest that the social behavior network of zebra finches may be part of a larger social decision-making network regulating adaptive behavior in response to environmental challenges. Furthermore, the molecular signatures and epigenetic mechanisms in the SBN that are associated with socially motivated behavior may have a fundamental role in maintaining the neural circuits that direct organismal decision-making.

Disclosures: K.L. Anderson: None. **J. Uraga:** None. **O. Whitney:** None.

Poster

P586. Vocal/Social Communication: Avian IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.02

Topic: F.01. Neuroethology

Support: JSPS KAKENHI #19K16302
JSPS KAKENHI ##20H05075

Title: Social interaction shapes selective memory in the higher auditory area through the neuronal activities of Locus Coeruleus

Authors: *J. KATIC, Y. MOROHASHI, Y. YAZAKI-SUGIYAMA;
Okinawa Inst. of Sci. and Technol. (OIST) Grad. Univ., Okinawa, Japan

Abstract: Juvenile zebra finches learn to sing by engaging in social vocal communications with their fathers (tutors). Being socially exposed to a tutor singing is crucial for juveniles to learn songs. Here we show by recording extracellular single-unit activities in free-moving juvenile zebra finches that neurons in the locus coeruleus (LC), an attention control area, exhibited greater activities when juveniles vocally communicate with tutors. The LC neurons responded stronger to live tutor singing (LIVE TUT) than to playback of pre-recorded tutor songs (TUT playback) (mean response strength (RS) to TUT playback: 1.6 ± 0.4 (spikes/s), to LIVE TUT: 15.98 ± 2.8(spikes/s)). The LC neurons which were activated by LIVE TUT sent axons to the zebra finch higher auditory cortex, the caudomedial nidopallium (NCM), where early tutor song memories form. Previously we showed that a fraction of NCM neurons, which had broader spiking shape, responded selectively to TUT playback (TUT-selective neurons). Here we exposed juveniles to a live tutor for five days (60~90 min /day) and tracked auditory responsiveness of NCM neurons to LIVE TUT and TUT playbacks. We found TUT-selective neurons exhibited greater response to LIVE TUT than to TUT playback only in the first two days of tutoring. After hearing LIVE TUT (> 60 min) those neurons showed greater responses even to TUT playbacks for hours (mean RS before: 0.4 ± 0.2, after: 4 ± 0.67 (spikes/s)). We further found that proportions of TUT-selective neurons increased only for the first two days of tutoring. After the 3rd day of tutoring the neurons which showed responses to TUT playbacks did not increase response strength to LIVE TUT. To ask whether LC neurons directly influence song perception in the NCM, we optogenecially blocked LC terminal activities in the NCM

every time juveniles heard LIVE TUT and recorded NCM neuronal activities. The NCM neurons, which responded to TUT playbacks, showed reduced responses to LIVE TUT when paired with LC terminal inhibition (mean RS to TUT playback: 7.9 ± 0.88, to LIVE TUT with LC inactivation: 3.3 ± 0.73 (spikes/s)). Those neurons showed a reduced response to TUT playback hours after LC terminal inhibition but showed no response reduction to playbacks of other song stimuli. Finally, juveniles, which were hearing LIVE TUT for three days with LC terminal inhibition failed to copy tutor songs (similarity to TUT = 33.7 %, N=6), while control juveniles learned tutor songs well (similarity to TUT = 71.3 % N=6). Taken together, our data suggest that social vocal communication with a tutor modulates song perception in the auditory cortex and shapes selective auditory memories through neuronal activities of the LC.

Disclosures: J. Katic: None. **Y. Morohashi:** None. **Y. Yazaki-Sugiyama:** None.

Poster

P586. Vocal/Social Communication: Avian IV

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Program #/Poster #: P586.03

Topic: F.01. Neuroethology

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NIH/NINDS Grant R00NS102520

Title: Dopamine neurons evaluate natural fluctuations in performance quality

Authors: A. DUFFY[1], K. W. LATIMER[2], J. H. GOLDBERG[3], A. L. FAIRHALL[1], ***V. GADAGKAR**[4]; [1]Dept Physiol & Biophys, Univ. Washington, Seattle, WA; [2]Neurobio., Univ. of Chicago, Chicago, IL; [3]Dept. of Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [4]Zuckerman Mind Brain Behavior Inst., Columbia Univ., New York, NY

Abstract: Many motor skills are learned by comparing ongoing behavior to internal performance benchmarks. Dopamine neurons encode performance error in behavioral paradigms where error is externally induced, but it remains unknown if dopamine also signals the quality of natural performance fluctuations. Here we recorded dopamine neurons in singing birds and examined how spontaneous dopamine spiking activity correlated with natural fluctuations in ongoing song. Antidromically identified basal ganglia-projecting dopamine neurons correlated with recent, and not future, song variations, consistent with a role in evaluation, not production. Furthermore, dopamine spiking was suppressed following the production of outlying vocal variations, consistent with a role for active song maintenance. These data show for the first time that spontaneous dopamine spiking can evaluate natural behavioral fluctuations unperturbed by experimental events such as cues or rewards.

Disclosures: A. Duffy: None. **K.W. Latimer:** None. **J.H. Goldberg:** None. **A.L. Fairhall:** None. **V. Gadagkar:** None.

Poster

P586. Vocal/Social Communication: Avian IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.04

Topic: F.01. Neuroethology

Support: R56 NS110951

Title: Further exploration of the activation of the mTOR cascade throughout development in juvenile zebra finches.

Authors: *R. M. BUTLER[1], S. E. LONDON[2];
[2]Dept of Psychology, [1]Univ. of Chicago, Chicago, IL

Abstract: Early life experiences can result in long-term patterns of behavior when they occur when the brain is sufficiently mature to encode them as memories. An example is a Critical Period (CP), a restricted period of development during which a specific experience has profound and permanent effects on brain function and behavioral patterns. Here, we use a CP in sensory song learning in zebra finch songbirds to study mechanistic connections between juvenile maturation and experiential processes, and the emergence of adult brain function and behavior.
Adult male zebra finches sing a song that reflects a sensory memory of a "tutor's" song they formed during a CP. The process of forming this memory is known as Tutor Song Memorization (TSM) and requires the auditory forebrain. As adults, after the closure of the CP, the auditory forebrain's function changes to support song recognition learning. Females cannot sing, but behave in ways as adults that demonstrate they also form sensory song memories during development. The function of the adult female auditory forebrain appears equivalent to that of the male. But, we recently showed using phosphorylation of ribosomal protein S6 (pS6), a necessary step for protein translation and thus long-term memory formation regulated by the mTOR cascade, that male and female juveniles may in fact use different mechanisms to perform sensory learning, even if they are indistinguishable in adulthood. This prompts the question: what elements of development – maturational progression, experiential accumulation, and genetic sex – contribute to the observed change in molecular response to hearing song?
To answer this question, we used immunohistochemistry to quantify pS6+ cells within the auditory forebrain after males and females, aged to span the CP, heard song. We included males that allowed us to specifically test the role of accumulated tutor song experience, a crucial determinant of the CP close. We found the greatest density in pS6+ cells after hearing song at the onset of the CP compared to all other ages. We confirmed the previously reported sex difference at the onset of the CP, but found that this sex difference does not persist at older ages. We found that hearing song led to a greater increase in pS6+ cells in birds without prior song exposure compared to the birds that had accumulated song experience. These data suggest that a fundamental mechanism of developmental learning and memory, the phosphorylation of S6, is modulated by all elements of development, which need to be considered in studies linking early life experiences and adult behavioral patterns.

Disclosures: R.M. Butler: None. **S.E. London:** None.

Poster

P586. Vocal/Social Communication: Avian IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.05

Topic: F.01. Neuroethology

Title: Female vocalizations during song learning shape song performance by altering premotor neuron activity in juvenile zebra finches

Authors: *L. BISTERE, D. VALLENTIN;
Max-Planck-Institute for Ornithology, Seewiesen, Germany

Abstract: Learned motor behaviors are often shaped by social influences. For instance, human infants learn to speak through the process of observation learning, imitating and observing parental feedback. Similarly, young zebra finches learn their song from their fathers. To some extend young birds are also able to learn to imitate from playbacks of tutor song without direct feedback. So far, a possible contribution of female zebra finches to song learning has been largely neglected. To understand whether the presence of a female supports song learning, we raised two groups of juvenile males to match the same tutor song in an operant conditioning paradigm. Juvenile birds in each group were either exposed to a female bird or kept socially isolated during the song learning phase. We found, that female zebra finches have an impact on the learned song tempo. Male zebra finches raised with a female copied the tutor song tempo more accurately compared to birds, that were raised socially isolated. We then wanted to characterize the vocal feedback of female birds in respect to songs with different tempos. Therefore, we exposed female birds to playback of a song that was modified to match three different tempos. Female birds responded most to adult song with slow tempo, which suggests that females change their feedback depending on the temporal aspects of song. Next, we wondered how this vocal feedback is processed in the song production pathway of juvenile zebra finches. The premotor nucleus HVC is known to be involved in song learning and song production, but whether auditory feedback by females can also impact this circuitry to support song learning is not known. We performed intracellular recordings of premotor neurons in HVC in awake and listening juvenile zebra finches while presenting playbacks of female calls alone and bird's own songs that were accompanied by female vocalizations. We found that female calls in both contexts had the potential to alter the activity of premotor neurons. Taken together, these findings support the notion that auditory feedback by females contributes to neural plasticity within a premotor circuit which leads to improved learning of the song tempo in juvenile zebra finches.

Disclosures: L. Bistere: None. **D. Vallentin:** None.

Poster

P586. Vocal/Social Communication: Avian IV

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.06

Topic: F.01. Neuroethology

Support: JSPS 19H04743
JSPS 18H02531

Title: Axon retraction within a sensory-motor circuit coincides with the closure of a critical period for song learning

Authors: M. I. M. LOUDER[1], M. KURODA[1], Y. MOROHASHI[2], D. TANIGUCHI[1], ***Y. YAZAKI-SUGIYAMA**[2,1];
[1]Intl. Res. Ctr. for Neurointelligence, the Univ. of Tokyo, Tokyo, Japan; [2]Okinawa Inst. of Sci. and Technol. (OIST) Grad. Univ., Okinawa, Japan

Abstract: Young male zebra finches listen and memorize the songs of tutors (normally their father songs) during the auditory learning phase, and then in the following sensory-motor learning phase, match their vocalization to the memorized tutors' songs. Cumulative studies have suggested that the caudomedial nidopallium (NCM) serves as a primary site for the storage of auditory memories of the tutor song. Yet whether the stored auditory memory of the tutor song in the songbird auditory forebrain guides song development remains unknown. Here we investigated the anatomical connections for the subset of NCM neurons which were activated by hearing the tutors' song (Yanagihara & Yazaki-Sugiyama, 2016), and their functional relationship to song learning. We injected in the NCM of juvenile male zebra finches (40-45 DPH) with the adeno associated viral vector (AAV9-cFos-TetOn-EYFP-PEST) and induced EYFP expression in the activated neurons with playback of their tutor's song in the presence of doxycycline at 55-60 DPH. Using whole-brain tissue clearing and light-sheet microscopy, we identified axons of tutor-responsive NCM neurons with long-range projections to song system nuclei, including the song premotor nucleus HVC. We confirmed that NCM-HVC axonal projections were observed in juvenile males (2% area ± 1%, n=6) but not in adult male zebra finches (> 90DPH; 0.1% area ± 0.1%, n=6) in conventional brain sections. To test whether the stored memory in the NCM is involved in song learning, we selectively lesioned the tutor-responsive NCM neurons in juvenile males with a cocktail of viral vectors (AAV9-cFos-TetOn-CaCasp3 and AAV9-cFos-TetOn-dT) which induces apoptosis upon hearing the tutor song playback. After lesioning, we isolated the males and measured the song similarity to the tutor song at 70 DPH. Juveniles with lesions of tutor song-responsive NCM neurons produced songs with less similarity to the tutor song than controls, brothers which were not exposed to tutor songs ($p=0.03$, $d=0.86$, $n=18$). Consistent with the observation of a developmental retraction of NCM-HVC axonal connections in adults described above, lesions of tutor-responsive NCM neurons after the sensory-motor learning phase (> 90 DPH) did not affect song learning ($p=0.74$, $d=0.22$, $n=6$). Taken together, our results suggest that the auditory memory of the tutor song stored in the NCM is involved in instructing motor learning but is developmentally limited by axon retraction upon the closure of the critical period for sensory motor learning.

Disclosures: M.I.M. Louder: None. **M. Kuroda:** None. **Y. Morohashi:** None. **D. Taniguchi:** None. **Y. Yazaki-Sugiyama:** None.

Poster

P586. Vocal/Social Communication: Avian IV

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.07

Topic: F.01. Neuroethology

Support: DFG project 327654276 – SFB 1315

Title: Optogenetic manipulations of HVC interneurons in adult zebra finches lead to changes in song production

Authors: *F. HEIM[1], E. MENDOZA[2], C. SCHARFF[2], D. VALLENTIN[1];
[1]Max Planck-Institute for Ornithology, Seewiesen, Germany; [2]Freie Univ. Berlin, Berlin, Germany

Abstract: Juvenile male zebra finches learn their song from an adult tutor. They start babbling around one month after hatching, undergo a variable plastic song phase and after three months, a more or less accurate copy of the tutor's song is established and changes little thereafter. The premotor nucleus HVC (proper name) plays a key role in this process and also in adult song production. HVC contains four main cell types, including premotor neurons and inhibitory interneurons, which participate in song production and song learning. As the juvenile's song is being consolidated and becomes more similar to the tutor's song, GABAergic interneurons selectively inhibit premotor neurons during the presentation of song elements a juvenile has already mastered while inhibition is lower during elements that require more practice. Presumably, auditory-induced plasticity of HVC premotor neurons is selectively repressed by GABAergic interneurons. As a result, juvenile song plasticity is reduced and adult male zebra finches sing a stereotyped series of song elements, called motifs, which are strung together in a song bout. To investigate the specific contributions of HVC interneurons to adult song production and test whether altered inhibition can induce song changes in adult birds, we used a viral strategy to activate or inactivate HVC interneurons in male zebra finches. We bilaterally injected mDLX-driven AAVs in HVC to transduce GABAergic inhibitory interneurons and express light-sensitive depolarising or hyperpolarising channel proteins. This approach allowed us to use light stimulation to manipulate neural activity in a cell-type specific manner and assess its impact on song plasticity in freely moving birds. Depolarisation of inhibitory interneurons in HVC during song production resulted in shorter bouts containing fewer motifs. The magnitude of shortened song bouts was positively correlated with the viral transduction efficiency in individuals. Moreover, as predicted, new song elements were added to motifs when light-induced inactivation of interneurons was accompanied by song playbacks. These new song elements were preferentially added towards the end of the existing song. Our results suggest that the inhibitory network in HVC plays an important role in the maintenance of performance stability in adult song production. Precise and cell-type specific manipulations of this network might have the potential to alter and re-open a critical period for sensorimotor learning.

Disclosures: F. Heim: None. **E. Mendoza:** None. **C. Scharff:** None. **D. Vallentin:** None.

Poster

P586. Vocal/Social Communication: Avian IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P586.08

Topic: F.01. Neuroethology

Title: Assessing the effect of tutor song structure on avian vocal learning strategies

Authors: *A. F. TANNER, A. H. BAHLE, M. S. FEE;
McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: In both human infants and juvenile songbirds, vocal learning progresses from an unstructured 'babbling' phase to highly structured sequences that typify adult birdsong and human language. To produce these ordered vocal sequences, young pupils store a memory of adult vocalizations and compare this memory to their own productions, making continuous adjustments until their own productions form a close match with those of adults. One of the earliest signs of the transition from babbling to song is the emergence of "protosyllables" - acoustically variable vocalizations with a characteristic duration - from the random variations in vocalization length that occur in the babbling stage. Songbirds then alter these protosyllables to imitate the tutor's song. Songbirds use different learning strategies to achieve vocal imitation. For example, earlier work has suggested that some birds develop new syllables by hierarchical splitting of the protosyllable and simultaneous differentiation of multiple syllables (motif learner). More generally, we are interested in the role of the acoustic structure of the tutor song in biasing vocal learning toward different strategies. Do acoustically similar tutor syllables promote a splitting strategy, and where are the decision boundaries for such a process? Does the duration of the tutor syllable, in relation to the protosyllable, impact vocal learning? In cases where birds are tutored early, does the rhythmicity of the tutor song constrain the duration of emergent protosyllables? To study the effect of the temporal and acoustic structure of the tutor song on learning strategies, we built an automated audio-video tutoring device for presenting artificial songs with a range of rhythmic and acoustic properties to juvenile zebra finches. Preliminary experiments reveal that juvenile birds rapidly produce a protosyllable that is well matched to the rhythmic properties of the tutor song. In ongoing work, we are using carefully controlled stimuli to ask how different acoustic and temporal properties affect the trajectory of vocal learning. The form in which a tutor song memory influences the process of juvenile song learning may give us insights into the developmental course of complex motor behaviors.

Disclosures: A.F. Tanner: None. **A.H. Bahle:** None. **M.S. Fee:** None.

Poster

P586. Vocal/Social Communication: Avian IV

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Program #/Poster #: P586.09

Topic: F.01. Neuroethology

Support: Midwestern University Faculty Startup Funds

Title: Validation of a vitamin A deficiency (VAD) songbird model

Authors: *C. OLSON, **C. JAMES**;
Midwestern Univ., Glendale, AZ

Abstract: Vitamin A deficiency (VAD) is a global health problem with effects on brain development and cognition, particularly in young people. However, the specific effect of VAD on complex vocal-motor learning has not been studied. Songbirds possess a cortical brain circuit for vocal learning that relies on vitamin A signaling during the critical period of vocal learning. To study VAD in a vocal learner we developed a special diet from white rice and sunflower seed, two grains that are naturally low in vitamin A and carotenoids, with other essential vitamins and minerals added back. This diet was provided to zebra finch family groups during chick rearing to evaluate the ability of parents to feed the diet to their chicks and the effects of a VAD diet on serum and brain retinol, chick growth and development. We found that adult birds readily consumed the rice/sunflower seed diet and fed it to their nestlings. Adults that consumed the diet maintained the same caloric intakes compared to when fed the seed mix and although these birds showed some decline in body mass it remained within a normal range. Surprisingly, we detected a 28% decline in serum retinol after three weeks on the diet in adult finches, a response that makes songbirds a highly useful model to study VAD. Juveniles that were fed the diet by the adults beginning at hatch also were able to consume the food and thrive on it. Compared to controls, chicks on the VAD diet showed no effects on growth rate between 10-65 days, but the chick survival rate was 63% lower than that of controls with no chicks surviving beyond 65 days old. Chicks that were on the VAD diet did not exhibit sub-song behavior between 35-50 days (72 total hours of monitoring), whereas chicks that were on a seed diet or a rice/sunflower seed control diet (with retinol added back) showed song development. We also noted that VAD affected eye shape and appearance, consistent with what is found during VAD of non-avian models. Serum retinol of chicks on the VAD diet showed a 57% decline compared to controls. Further development of this model will require titration of the VAD to moderate levels that allow for song development and high chick survival. This study lays the groundwork for the use of modified diets in the songbird model to examine how VAD or other micronutrients may modulate neural development in the vocal circuit of a vocal learner, as well as open the door for the use of the model in high-fat diet nutrition experiments and lipid transport studies.

Disclosures: C. Olson: None. **C. James:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.01

Topic: F.04. Stress and the Brain

Support: NIH Grant R15MH116337

Title: Childhood stress is associated with enhanced fear acquisition and an overgeneralization of fear in female participants

Authors: *K. E. RENEAU[1], J. N. WEISER[1], S. J. HELWIG[1], C. N. CORDES[1], E. M. VIRDEN[1], C. K. THEBEAULT[1], C. L. PFISTER[1], B. A. GETNET[1], K. M. BOAZ[1], T. D. NIESE[1], B. R. RORABAUGH[2],

S. D. NORRHOLM[3], P. R. ZOLADZ[1];
[1]Psychology, Ohio Northern Univ., Ada, OH; [2]Pharmaceut. Sci., Marshall, Huntington, WV; [3]Psychiatry and Behavioral Neurosci., Wayne State Univ., Detroit, MI

Abstract: Research has shown that childhood maltreatment is associated with increased risk for trauma- and stressor-related disorders in adulthood. This increased risk might be caused by maltreatment-induced changes in the neural circuitry underlying fear learning, which results in pathological responses to adulthood trauma. To begin testing this hypothesis, we assessed whether childhood stress was associated with altered fear learning and fear generalization in adults. One hundred and ninety-nine undergraduate students learned to associate one geometrical shape (CS+), but not another (CS-), with an aversive stimulus (US) in a fear-potentiated startle paradigm. The next day, participants were tested for their fear generalization by measuring their fear responses to a variety of stimuli (generalization stimuli, GSs) that were similar to, but different from, the shapes observed on Day 1. Childhood stress was quantified using the Childhood Trauma Questionnaire, and participants were divided into high and low childhood stress groups based on methodology employed in previous work. According to the results, participants with high childhood stress reported significantly greater anxiety sensitivity, state and trait anxiety, symptoms of depression, and symptoms of post-traumatic stress disorder than participants with low childhood stress. Female participants with high childhood stress demonstrated significantly enhanced fear acquisition for the CS+ and significantly greater fear generalization than female participants with low childhood stress and male participants with high or low childhood stress. Moreover, during generalization testing, female participants with high childhood stress exhibited significantly greater US expectancy ratings for the CS+ and some GSs than female participants with low childhood stress. These findings suggest that, in females, exposure to childhood stress could result in greater fear learning and an overgeneralization of fear, which could increase the risk for certain psychological disorders in adulthood.

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Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.02

Topic: G.08. Other Psychiatric Disorders

Support: DGAPA-PAPIIT IN215218 to OPG
DGAPA-PAPIIT IA205218 to MMD
DGAPA-PAPIIT IN217221 to AERC

Title: Early life stressing experiences are risk factors for drug-taking, insomnia and severity of depression and anxiety symptoms during young adulthood

Authors: J. I. LÓPEZ-JUÁREZ[1], *U. CABALLERO-SÁNCHEZ[2], T. V. ROMÁN-LÓPEZ[2], I. ORTEGA-MORA[2], C. B. ROSAS-ESCOBAR[2], M. MÉNDEZ-DÍAZ[1], A. E. RUIZ-CONTRERAS[2], O. E.

PROSPÉRO-GARCÍA[1];
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Abstract: Early life stressing experiences are associated with brain and behavioral alteration during adulthood. This study evaluated how perceived abuse and care during childhood and adolescence impacts on some psychiatric symptoms during adulthood. For this purpose, 115 university students were recruited and answered the Parental Bonding Inventory (PBI), the Childhood Trauma Questionnaire, short form (CTQ), the Beck Anxiety and Depression Inventories (BAI and BDI, respectively), the Insomnia Athens Scale (IAS), the Resilience Scale for Mexican population (RESI-M), and a detection of use of psychoactive substances (tobacco, alcohol, cannabis, stimulants, opiates, cocaine, inhalants, and prescribed tranquilizers). Participants also provided their academic achievement (AA) in each level of education completed; and a cortisol and oxytocin sample during baseline and after watching a video of an ocular surgery, to cause discomfort or stress. Based in PBI and CTQ, Subjects were classified in those who perceived have been raised with optimal care (OC) by both parents, therefore with absence of any type of abuse (physical, emotional and/or sexual abuse, physical and/or emotional negligence); those who did not perceive have been raised with OC by both parents (i.e., negligent care, NC) albeit reported absence of abuse; and those who perceived have been raised with NC and at least one type of abuse (NC+A). Subjects in the OC group had better outcomes in PBI, CTQ, BAI, BDI, AIS, RESI-M and AA compared to those in NC and NC+A groups. Furthermore, according to odds ratio analysis, NC and NC+A were risk factors for presenting mild, moderate, and severe symptoms of depression and anxiety, and to suffer from insomnia, as compared with OC. Regarding to OC, NC+A was a risk factor for the intake of three or more drugs. No changes in cortisol or oxytocin were detected. Our results further support the relevance of Optimal Care during childhood and adolescence to prevent negative outcomes during adulthood.

Disclosures: J.I. López-Juárez: None. **U. Caballero-Sánchez:** None. **T.V. Román-López:** None. **I. Ortega-Mora:** None. **C.B. Rosas-Escobar:** None. **M. Méndez-Díaz:** None. **A.E. Ruiz-Contreras:** None. **O.E. Prospéro-García:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.03

Topic: F.04. Stress and the Brain

Support: Maine INBRE - NIGMS Grant P20GM103423

Title: From biomarkers to novel treatments: a multi-domain analysis of the developmental consequences of early life adversity and the role of therapeutic ketamine

Authors: S. N. ELLIS[1], A. CHEN[1], E. NOEL[1], S. BONAUTO[1], E. MCCUE[2], ***J. A. HONEYCUTT**[1];
[1]Bowdoin Col., Brunswick, ME; [2]Southern Maine Community Col., South Portland, ME

Abstract: An individual's early life environment critically shapes the developmental trajectory of brain and behavior, thereby influencing later-life outcomes. Early life adversity (ELA) via caregiver deprivation can set the course for increased risk for later emerging mental illnesses, particularly those characterized by affective dysfunction (i.e., anxiety, depression), with females showing higher prevalence rates than males. Individuals with a history of ELA exhibit disturbances in processing affective information and can exhibit contextually inappropriate hypervigilance and anxiety-like behaviors. Limbic regions, such as the basolateral amygdala (BLA) and the bed nucleus of the stria terminalis (BNST), are important for processing emotionally salient information. Specifically, they are thought to be involved in the initiation (BLA) and maintenance (BNST) of anxiety-like states in response to potential threat, with both regions receiving regulatory inputs from other cortical regions (i.e., prefrontal cortex). Our work utilizes a novel aversive ultrasonic vocalization (USV) playback paradigm to probe subtle psychosocial effects of ELA on excitatory/inhibitory neural recruitment in these regions, as well as on sex-specific behavioral outcomes and hypervigilance in rats in response to ambiguous threat. We then use a multi-domain approach to investigate the neural and epigenomic drivers of ELA-associated changes in anxiety-like behavior. In recent years the dissociative anesthetic, ketamine, has been of increasing interest for the treatment of persistent and treatment-resistant anxiety and depression in clinical populations; however, the neural mechanisms by which it has its effect remain poorly understood and the degree to which it shows therapeutic efficacy within ELA populations is understudied. Here, we provide evidence of sex-specific changes in anxiety- and depressive-like behaviors in rats following ELA, and their possible mitigation by an acute therapeutic dose of ketamine. In addition to behavioral outcomes, we also present preliminary evidence of epigenetic changes (specifically, changes in regional DNA methylation and inhibitory/excitatory neuron-specific methylation patterns) following ELA in both males and females, as well as their interaction with ketamine treatment. Taken together, these findings provide critical information regarding the lasting consequences of ELA across development as measured at the behavioral, neural, and genomic levels which will allow for the identification of key markers of behavioral risk/resilience, as well as predictions toward efficacy of ketamine treatment.

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Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

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Program #/Poster #: P604.04

Topic: F.04. Stress and the Brain

Support: Margaret Q. Landenberger Foundation

Title: Early life stress results in atypical defensive behavior in mice

Authors: *C. R. CODY, A. KISNER, A. M. POLTER;
The George Washington Univ., Washingon, DC

Abstract: Defensive behaviors are a crucial aspect of survival and conservation of species. The ability to correctly develop and execute defensive strategies in response to threats is a complex process. Adverse experiences during early life significantly enhance the risk for the development of emotional and threat-related pathologies. One paradigm used to study ELS in the mouse is the limited bedding and nesting (LBN) model, in which dams and pups are placed in a low resource cage for seven days. This leads to disrupted maternal care, and results in behavioral, anatomical, and physiological changes in the brains of pups (Walker et al). It remains unknown how these adaptations affect naturalistic defensive responses and contribute to the development of fear-related disorders, as well as how sex may contribute to these adaptations. In order to test the effects of ELS on defensive behaviors, we utilized a Looming Disk (LD) behavioral assay. In the mouse, looming stimuli mimic the approach of aerial predators, and evoke innate, species-specific defensive behaviors such as running and freezing. Our data indicates that ELS affects the selection of defensive responses in mice. We have identified a relationship between ELS and an increase in passive responses such as freezing, as well as atypical defensive responses such as darting. Control animals exhibited an increased preference for a flight response, with 50% of male and 79% of females engaging in flight. ELS mice show a decreased preference for flight, with only 34% of males and 50% of females utilizing this coping strategy. Conversely, ELS mice show an increased preference for passive and atypical responses, with 30% of male mice freezing and 23% engaging in darting, compared to only 11% and 19% of controls engaging in these respective behaviors. Female ELS treated mice show an even greater preference towards passive and atypical strategies, with 26% exhibiting freezing behavior and 24% exhibiting darting behavior, compared to only 9% and 12% of control females engaging in these respective behaviors. The results of this work indicate that atypical defensive responses to threatening stimuli occur as a result of ELS, and that ELS causes a shift in the preferred behavioral response in both sexes. This work is relevant for increasing our understanding of how altered early life environmental conditions may affect the development of stress related responses in humans later in life.

Disclosures: C.R. Cody: None. **A. Kisner:** None. **A.M. Polter:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.05

Topic: F.04. Stress and the Brain

Support: R56MH123147

Title: The role of early life adversity and pubertal timing in the development of the acoustic startle response in rats

Authors: L. E. GRANATA, A. E. R. PARAKOYI, H. C. BRENHOUSE;
Psychology, Northeastern Univ., Boston, MA

Abstract: Early life adversity significantly increases the risk of developing anxiety disorders later in life, particularly during and following adolescence. Hormonal changes during puberty affect the development of neural circuits subserving cognitive and affective regulation, creating a window of vulnerability.

Anxiety-related psychopathologies in humans are often characterized by increased sensitivity to potential threats, which can be modeled in rodents via the acoustic startle response, a reflex modulated by neural systems associated with anxiety disorders. Implementing the acoustic startle test in rodent models enables scrutinization of the relationship between early adverse experiences, pubertal development, and threat responsivity over the lifespan. The current study investigated the development of the startle response across the pubertal transition (postnatal days 25, 35, and 55) and assessed the impact of maternal separation (MS) on startle progression in males and females. Furthermore, we assessed the startle response after presentation of a social threat: a pre-recorded conspecific's ultrasonic vocalization alarm call. Similar to the potentiating effects on anxiety when humans are presented with a fearful face, the alarm call is a species-specific signal of potential danger in the environment that may differentially modulate the acoustic startle response. With evidence that MS-exposed females experience accelerated pubertal development and the notion that pubertal timing can impact mental health outcomes, we also investigated whether the timing of puberty was associated with startle amplitude. Understanding how the startle response develops across puberty will contribute to our understanding of anxiety-related disorders to identify opportunities for intervention during critical transitional windows.

Disclosures: L.E. Granata: None. **A.E.R. Parakoyi:** None. **H.C. Brenhouse:** None.

Poster

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Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.06

Topic: F.04. Stress and the Brain

Support: Baylor University

Title: Sex Effects of Early Corticosterone Exposure on LPS Later in Life

Authors: *H. RODGERS[1], K. GILLEY[2], P. SHARMA[3], E. CASTRO[3], D. COLE[3], E. G. VICHAYA[3]; [1]Baylor Univ. Grad. Psychology & Neurosci., Waco, TX; [2]Psychology, [3]Baylor Univ., Waco, TX

Abstract: Depression is a prevalent psychiatric disorder affecting over 200 million people worldwide. It is a complex and multifactorial disease involving many risk factors, including inflammation. There is now compelling evidence that chronic low-grade inflammation is associated with depressive symptoms. While depression and inflammation are more common in women, most animal models we use show male mice to be more susceptible. For example, in response to 0.5 mg/kg lipopolysaccharide (LPS) female mice show blunted sickness behavior and a reduced neuroinflammatory response as measured by qPCR. Our inability to replicate the sex-bias in pre-clinical depression models may be related to our failure to account for potential lifetime stress history. There is evidence that women experience a higher stress burden, which may impact the responsivity of their hypothalamic-pituitary-adrenal (HPA) axis and innate immune system. We sought to examine this possible relationship using a maternal corticosterone exposure model, in which 75 µg/mL of corticosterone is provided in the drinking water to dams from postnatal days 2-8 and is transferred from dam to pups via maternal milk. We hypothesized that maternal corticosterone would increase inflammation-induced depression-like behavior in early adulthood and female mice would

be more sensitive to these effects. We used a 2 (+/- early corticosterone) x 2 (+/- LPS). Maternally treated mice were treated with saline or 0.5 mg/kg LPS at 8-9 weeks of age. The next day we evaluated locomotor activity, forced swim (FST), tail suspension (TST), and spontaneous alterations in the Y-maze to explore depressive-like behavior and cognitive effects. We observed an interaction between corticosterone and sex, such that female mice exposed to corticosterone early in life showed mildly reduced immobility while male mice showed an elevation. This is potentially indicative of a protective effect in female mice. Murine models of early life stress have shown that sex, timing, and stressor severity play a role in determining whether the stress enhances depression risk or promotes resiliency. Further research is needed to confirm risk result and determine if there if a different manipulation that may improve our capacity to replicate the sex bias observed in human populations.

Disclosures: H. Rodgers: None. **K. Gilley:** None. **P. Sharma:** None. **E. Castro:** None. **D. Cole:** None. **E.G. Vichaya:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.07

Topic: F.04. Stress and the Brain

Support: Tata Institute of Fundamental Research (RTI4003)

Title: Chemogenetic activation of gi signalling within excitatory neurons of the forebrain in postnatal or juvenile windows of life does not influence the emergence of anxiety or despair like behaviour in adulthood

Authors: *P. TIWARI, D. KAPRI, A. PRADHAN, A. BALAKRISHNAN, P. CHAUDHARI, V. A. VAIDYA;
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Abstract: Early life experience plays an important role in shaping functional and behavioural responses. It is known that during this early window, serotonin (5HT) receptors, in particular the Gi-coupled 5HT1A and the Gq-coupled 5HT2A receptor function, play a crucial role in programming anxiety and depressive behavioural states in adulthood. Studies suggest that stimulation of Gi-coupled 5HT1A receptor in this window may serve to program a reduction in trait anxiety, and pharmacological blockade of 5HT1A receptor has been shown to evoke an anxiogenic phenotype in adulthood. To address the role of Gi signalling in this early life window we used a bigenic line in which hM4Di DREADD was expressed exclusively in CamKII-alpha positive excitatory neurons in the forebrain. Previous work done in the lab shows that increased Gq signalling in excitatory neurons in the forebrain in the early postnatal window (P2-P14) increases vulnerability to anxiety and despair-like behaviour in adulthood. The comparative question was to ask whether enhanced Gi signalling promotes the possibility of either resilience to adult onset stress or baseline changes in trait anxiety and despair. We carried out reflex behaviour in neonates that suggested no developmental defects. Anxiety and despair related tests carried out in adulthood also show no difference in behaviors in animals that were subjected to CNO administration in either postnatal

(P2-P14) or juvenile (P28-P40) windows of life, indicating that increasing Gi signalling in these windows may not be sufficient to modulate anxiety and despair like behaviors.

Disclosures: P. Tiwari: None. **D. Kapri:** None. **A. Pradhan:** None. **A. Balakrishnan:** None. **P. Chaudhari:** None. **V.A. Vaidya:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.08

Topic: F.04. Stress and the Brain

Support: This work was supported by National Fund for Scientific, Technological, and Technological Innovation Development) (FONDECYT) and Word Bank (BM) grant # 025-2019 Fondecyt-BM

Title: The Long-term impact of early-life stress on anxiety and depression-like behaviors and mRNA expression of CRH receptor 1 in the hippocampus of BALB/c and C57BL/6NCrl male and female mice

Authors: R. MONTOYA[1], F. DELGADO[1], C. BECERRA[2,1], A. ZEVALLOS[1], G. E. PARDO[1], J. M. IGLESIAS-PEDRAZ[1], L. F. PACHECO-OTALORA[1];
[1]Lab. de Investigacion de Neurociencias, Univ. Andina del Cusco, Cusco, Peru; [2]Univ. Nacional de San Antonio Abad del Cusco, Cusco, Peru

Abstract: Background: Several Preclinical and epidemiologic studies associate early-life stress (ELS) with emotional and cognitive disorders later in life. However, susceptibility to stress and the development of stress-related disorders differ substantially among individuals due to the influence of numerous endogenous and exogenous factors. The use of inbred mouse strain could provide a relatively stable and narrow range of genetic and environmental variability to unravel the gene-stress interactions. The neuropeptide corticotropin-releasing (CRH) system is crucial for neuroendocrine and behavioral responses to stress. The CRH plays a key role in the integration of neuroendocrine, autonomic, and behavioral responses to stress acting via corticotropin-releasing hormone receptor 1 (Crhr1). In the present study, we explore the potential behavioral differences in anxiety and depression and measured Crhr1 expression level in the hippocampus between BALB/c and C57BL/6NCrl strains mice after exposition to ELS. **Methods:** Litters from both strains were exposed to ELS by transferring dam and pups from their standard cage condition to a cage with a wire mesh floor and limited bedding and nesting material during postnatal days (PND) 2-9. On PND 10, litters were returned to their standard housing condition, where they remain until weaning at PND 23. Effects of ELS on anxiety and depressive-like behaviors were assessed during PND 73-76 using the elevated plus maze and forced swimming test, respectively. One day after the last behavioral test mice were decapitated and their hippocampi dissected for gene expression analysis of Crhr1. **Results:** Males and females of BALB/c presented higher basal anxiety and depression-like behaviors than males and females of C57BL/6NCrl strain. The ELS increased considerably basal anxiety profile in male BALB/c and reduced in males C57BL/6NCrl with no significant effects on depression-like behavior profile. Conversely, ELS increased markedly depression-

like behavior profile in females BALB/c with no changes in female C57BL/6NCrl and males from both strains. Our preliminary data show that the exposition to ELS also increased significantly the mRNA expression of Crhr1 in the hippocampi of male BALB/c compared to C57BL/6NCrl, with no changes in females from both strains. **Conclusion**: Our data suggest that early adverse experiences increase susceptibility to stress and development of anxiety and depression-like profiles in a stable phenotype animal with a preexisting genetic vulnerability to stress, anxiety, and depression. Furthermore, the development of an anxiety-like phenotype seems to be related to a long-term alteration in Crhr1.

Disclosures: R. Montoya: None. **F. Delgado:** None. **C. Becerra:** None. **A. Zevallos:** None. **G.E. Pardo:** None. **J.M. Iglesias-Pedraz:** None. **L.F. Pacheco-Otalora:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.09

Topic: F.04. Stress and the Brain

Support: NIH Z01 ES100221

Title: Hippocampal CA2 development under the influence of prenatal spironolactone

Authors: *S. J. SLEIMAN[1], K. E. MCCANN[1,2], S. A. FRY[1], E. K. SHAUGHNESSY[1,3], S. M. DUDEK[1];
[1]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]Emory Univ. Sch. of Med., Atlanta, GA; [3]Neurosci. Grad. Program, Georgia State Univ., Atlanta, GA

Abstract: Mineralocorticoid receptors (MRs; *Nr3c2*) are highly expressed in hippocampal area CA2, where they regulate CA2 gene expression and social memory. In addition, mutations in *Nr3c2* can cause a syndromic form of autism in humans. Previous work by our lab and others has shown that MR knockout (KO) in mice causes disruption of social recognition memory and increased responses to novelty and in addition, disrupts expression of CA2 'plasticity brake' genes resulting in an abnormal capacity for LTP in CA2. Although our previous studies using conditional MR KO mice provided valuable information relevant to genetic disruption of MRs, pharmacological blockade of MRs could provide a clinically and translationally relevant model of stress-related disorders, given that MRs bind corticosterone/cortisol. Thus, we set out to test our hypothesis that chronic, prenatal exposure to the MR antagonist spironolactone would disrupt CA2 gene expression and social behavior similar to what we observed using conditional MR KO mice. To do this, we implanted subcutaneous 21-day release pellets in two dam groups—Vehicle and Spironolactone—at approximately gestational day 12 (+/- 3 days), alongside a no-surgery Control dam group. Using immunofluorescence, we examined CA2 marker development in the resulting litters at postnatal days (PNDs) 12, 14, and 21. A separate set of pups was allowed to grow until adulthood (PND 60 or PND 170) to investigate the impact of prenatal MR blockade on behavior. We tested mice in the open field, novel object exposure, novel social interaction, and social discrimination. In both males and females, we found that prenatal MR antagonism with spironolactone did not cause overt effects on the development of CA2. However, prenatal spironolactone exposure did cause an increase in

anxiety-like behavior (F(1, 41)=6.104, p=0.0177) and increased reactivity to novel objects (F(1,41)=4.919, p=0.0322), comparable to that of the embryonic MR KO model, without detected disruptions in social memory. As spironolactone is currently used clinically, and there is some evidence that offspring become feminized (in rodents), future studies will be focused on behaviors with known sex differences, such as aggression.

Disclosures: S.J. Sleiman: None. **K.E. McCann:** None. **S.A. Fry:** None. **E.K. Shaughnessy:** None. **S.M. Dudek:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

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Topic: F.04. Stress and the Brain

Support: National Natural Science Foundation of China (NO. 81870935, JW)
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Wuhan University of Technology post-doctor fellowship award (NO. 3120621249, AZ)

Title: Prenatal Citalopram exposure induced anxiety and depression-like behavior with medial prefrontal cortex dysfunction during adolescence

Authors: L. DU[1], A. ZAHRA[2], Q. WANG[3], Y. WANG[5], ***J. WU**[4];
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Abstract: Depressive disorder is one of the most distressing disorders, affecting over 300 million people around the world. Numerous studies have been conducted in an attempt to identify the critical brain regions implicated in the major depressive disorder (MDD) etiology. However, the neurological underpinnings of these atypical behaviors remain unknown. Gestational stress has been shown to raise the probability of developing anxiety and depression in early adulthood. Antidepressant treatment during pregnancy has a significant effect on the offspring's neurobehavioral development. Currently, we examined modifications in physiological, morphological, and biochemical characteristics in mice offspring exposed to CTM during the third trimester of pregnancy. We studied behaviors such as depression, anxiety and locomotion deficits in CTM-exposed mouse offspring. We used Golgi-Cox staining to examine the neuronal structure of prefrontal neurons, and there was a substantial reduction in dendritic length and the number of dendritic branches in CTM-exposed mice following altered protein expression levels relative to controls. We found that maternal CTM exposure causes explicit changes in the brain, particularly those regions involved in cognition and drug reinforcement.These findings highlight further research to elucidate the essential pathways and translational potential of therapeutic significance of CTM during pregnancy.

Disclosures: L. Du: None. **A. Zahra:** None. **Q. Wang:** None. **Y. Wang:** None. **J. Wu:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.11

Topic: F.04. Stress and the Brain

Support: NIH R01ES032163

Title: Investigating prenatal exposure to an environmentally relevant phthalate mixture on the anxiety-like behavior in adult male and female mice

Authors: S. SORIANO[1], L. JONES[2], N. VALLURU[3], E. BREHM[3], H. GRITTON[3,4], ***M. MAHONEY**[4,3];
[2]Mol. and Cell. Biol., [3]Comparative Biosci., [4]Neurosci. Program, [1]Univ. of Illinois at Urbana Champaign, Urbana, IL

Abstract: Endocrine-disrupting chemicals (EDCs) are pervasive in the environment. These chemicals are known to interfere with hormone synthesis and metabolism although their effects on behavior are not well studied. Importantly, gonadal hormones are known to modulate emotional behaviors including anxiety and depression. To better understand how phthalate exposure during development impacts measures of anxiety-like behaviors we treated pregnant CD-1 dams with vehicle (tocopherol-stripped corn oil) or an environmentally relevant phthalate mixture (20, 200 μg/kg/day, and 200 mg/kg/day) daily from gestational day 10.5 to birth. The mixture was composed of 35% diethyl phthalate, 21% di(2-ethylhexyl) phthalate, 15% dibutyl phthalate, 15% diisononyl phthalate, 8% diisobutyl phthalate, and 5% benzylbutyl phthalate. Activity in adults was tested in the light-dark box, open field, elevated plus maze, and running wheels. Preliminary analyses reveal that prenatal exposure to phthalates significantly increased the number of transitions that adult mice exhibited between the illuminated and dark zones in the light-dark box test ($p=0.004$). More specifically, control animals had fewer transitions than 200 μg or 200 mg groups despite showing similar levels of time spent in the light or dark box areas. Interestingly, females showed more transitions at relatively lower phthalate doses compared to males suggesting higher levels of activity when exposed to a novel environment. When we examined the daily distribution of running wheel activity, we found phthalate exposed animals had more activity in the dark relative to the light period of the day compared to controls. Future analysis will examine gene expression in brain regions critical for anxiety-like behavior and hormone responsiveness. Collectively, our preliminary data suggest that prenatal exposure to an environmentally relevant phthalate mixture disrupts aspects of anxiety-like behavior and this effect is differentially impacted by sex.

Disclosures: S. Soriano: None. **L. Jones:** None. **N. Valluru:** None. **E. Brehm:** None. **H. Gritton:** None. **M. Mahoney:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.12

Topic: F.04. Stress and the Brain

Title: Modulation of depression-like behavior by FOXP3^{+} T cell: a causal link to Alzheimer's disease pathophysiology

Authors: *E. YANG, G. M. PASINETTI;
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Abstract: Alzheimer's disease (AD) is the most common form of dementia among the elderly and the number of individuals with AD continues to increase. Among the various causative factors, depression has emerged as a critical factor, increasing the risk of developing AD by 2 to 4-fold. Thus, mitigating depression-like behavior at early-life could lessen the risk of AD at later stages; and that elucidating underlying molecular mechanisms linking depression to AD would offer feasible target for preventing AD progression. We have recently reported the involvement of Forkhead box P3 (FOXP3), a transcription factor modulating the function of regulatory T cells (Tregs) in peripheral immune system, in inducing depression-like behavior in mice following chronic unpredictable stress. We have also identified peripheral FOXP3-Treg cascade as a molecular pathway regulating such behavior. However, it is not known if alleviating depression by modulating FOXP3 could reduce the risk of developing AD-like pathologies. In the present study, we utilized a FOXP3 conditional knockout mouse model [FOXP3-Diptheria Toxin (DT) Receptor] by treating with DT, which causes a reduction of FOXP3 expression. We have observed depression-like behavior following downregulation of FOXP3, accompanied by a significant reduction in Treg/Th17 ratio in the blood. To examine the relevance of this mechanism in AD, we generated a double transgenic mouse model by breeding FOXP3 conditional knockout mice with 5xFAD. We are investigating whether reduction of peripheral FOXP3 in AD model mice alters blood brain barrier (BBB) permeability leading to neuroinflammation, and thereby exacerbating brain cognitive behaviors. In conclusion, our data suggest FOXP3 as a causal link in the peripheral immune system mediating depression like behavior, leading to exacerbation of AD type brain cognitive deterioration.

Disclosures: E. Yang: None. **G.M. Pasinetti:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

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Topic: F.04. Stress and the Brain

Support: OIRE PIRE NSF Grant 1545803
RISE NIH Grant R25 GM061838
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NIMHD, NIH Grant S21 MD001830-04

Title: Exercise as an intervention to minimize the effects of social isolation on anxiety.

Authors: *A. K. RODRÍGUEZ-RIVERA[1], E. U. PÉREZ-CARDONA[2], W. R. FRONTERA-ROURA[3], A. C. SEGARRA-MARRERO[3];
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Abstract: Adolescence is an important period for brain maturation. Isolation during adolescence increases the incidence of mental disorders in adulthood. Anxiety, characterized by a state of hypervigilance and pacing is the most prevalent mental disorder. Exercise is used as a care strategy to treat several mental disorders. In this study we investigated the effects of exercise in mitigating anxiety produced by single housing in adolescent rats. After weaning (day 23), male and female rats were divided into one of the following groups: group-housed, single-housed, or single-housed with exercise. Exercise training started the day of single housing and consisted of running 30 minutes at speed up to 10 m/min on a treadmill once a day, five times a week until day 33. The rats were tested for anxiety-like behavior on day 34 in an Elevated Plus Maze test. Rats reared in isolation spent less time in the open arm than group-housed rats. However, single-housed rats that exercised spent the same time than group-house and made more entries into the open arms than the other two groups, regardless of the sex of the animals. In conclusion, the increased anxiety observed after 12 days of social isolation in single-housed animals was ameliorated in rats that exercised. These findings indicate that running exercise training is effective in diminishing the detrimental effects of social isolation on anxiety in males and females adolescent rats.

Disclosures: A.K. Rodríguez-Rivera: None. **E.U. Pérez-Cardona:** None. **W.R. Frontera-Roura:** None. **A.C. Segarra-Marrero:** None.

Poster

P604. Early-Life Stress: Effects on Anxiety and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P604.14

Topic: F.04. Stress and the Brain

Title: Microbiota transfer therapy causes a stable reversion of early life stress-induced behavioral and neuroendocrine alterations

Authors: *R. RUIZ, A. ROQUE, N. LAJUD;
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Abstract: Early life stress (ELS) disturbs microbiota composition and it has been shown that the use of probiotics and prebiotics can prevent some of ELS-induced behavioral and neuroendocrine alterations. However, the effect of reversing microbiota dysbiosis in animals that already present the alterations commonly associated to ELS has never been studied. In here, we evaluated whether microbiota transference from healthy animals restores the alterations caused by ELS in “dirty rats”. For this, control (CONT, n = 20) and maternally separated (MS, 3 h/day from postnatal day 1 to 14, n = 20) male Sprague Dawley rats were utilized. At 2 months of age, half of the individuals in each group were treated with oral

antibiotics for 30 days. Subsequently, microbiota transfer therapy was performed by housing receptor animals with intact donors for 60 days. Transference was interrupted and animals were allowed to recover from 30 days. Our results show that MS decreased the discrimination index in the in the object-location test; as well as a decrease in the struggling time and an increase in the immobility time of the forced swimming test, when compared to the CONT group. In the glucose tolerance test, we observed that MS caused an increase in glucose concentrations 30 and 120 min after administration of a glucose load. MS also increased plasma corticosterone concentrations when compared to controls. Furthermore, MS caused a decrease in hippocampal DCX+ cell number. One month after interrupting microbiota transference, all this ELS-induced alterations were reversed and MS group no longer differed from CONT. In conclusion, our results indicate that microbiota transfer therapy reverses behavioral and neuroendocrine ELS-induced alterations, this effect remains stable even one month after interrupting the transference. Our findings provide evidence of the importance of the intestinal microbiota in regulating the HPA axis in adult animals that already present ELS-induced behavioral and neuroendocrine alterations.

Disclosures: R. Ruiz: None. **A. Roque:** None. **N. Lajud:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Program #/Poster #: P626.01

Topic: F.07. Autonomic Regulation

Support: NIH HL132836 (EMH)
HL128454 (DDK)
American Autonomic Society-Lundbeck Fellowship (LLS)
AHA836140 (LLS)

Title: Cardiovascular Deconditioning Increases GABAergic Signaling in the Nucleus Tractus Solitarii

Authors: *L. LIMA-SILVEIRA, E. M. HASSER, D. D. KLINE;
Univ. of Missouri, Columbia, Columbia, MO

Abstract: Cardiovascular deconditioning increases GABAergic signaling in the nucleus tractus solitarii Ludmila Lima-Silveira, Eileen M Hasser, David D Kline.Dept. Biomedical Sciences and Dalton Cardiovascular Research Center, University of Missouri, Columbia MO 65211. Hindlimb Unloading (HU) in rats induces dysautonomia and cardiovascular deconditioning (CVD) similar to that seen in bedridden individuals. The autonomic alterations in CVD and HU are related to plasticity within the central nervous system. The nucleus tractus solitarii (nTS) is the major integrative brainstem region for autonomic modulation and processing of the cardiovascular reflex. GABA and Glutamate are the main inhibitory and excitatory neurotransmitters within this nucleus. HU increases nTS glutamatergic neurotransmission yet decreases neuronal excitability. In this study, we investigated the role for GABA in counter-balancing glutamatergic signaling in the nTS. We hypothesized that HU increases GABA synaptic modulation of nTS neurons, which contributes to impaired autonomic and cardiovascular control. HU was induced by placing stainless wire rings in the tail of male Sprague-Dawley rats (3 weeks

old), and after one week of recovery suspending rats at an angle of 30–35° for two weeks with free access to food and water. Control animals were maintained in normal postural conditions. After HU or the control period, coronal brainstem slices were generated and whole-cell patch clamp was performed to evaluate GABA neurotransmission and electrophysiological properties of nTS neurons. The magnitude of GABA release was evaluated via an intensity-based GABA sensing fluorescence reporter (iGABASnFR). Block of GABAA receptors (Gabazine, 20μM and Bicuculline, 20μM) depolarized membrane potential in HU but not in Control, suggesting greater tonic GABA inhibition in HU. In response to GABA interneuron stimulation the evoked IPSC amplitude and its area, as well as iGABASnFR fluorescence, was greater in HU than Control. HU also elevated the frequency of spontaneous miniature IPSCs but not their amplitude. Puffer application of GABA (100μM, 50ms) produced similar postsynaptic current response in nTS neurons of HU and Control. These results indicate that HU increases GABAergic signaling in the nTS likely via augmented release of GABA from presynaptic terminals. This synaptic plasticity may be part of the mechanisms underlying the autonomic and cardiovascular alterations following CVD. Financial support: NIH HL132836 (EMH) and HL128454 (DDK) & American Autonomic Society-Lundbeck Fellowship (LLS), AHA836140 (LLS).

Disclosures: L. Lima-Silveira: None. **E.M. Hasser:** None. **D.D. Kline:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.02

Topic: F.07. Autonomic Regulation

Support: NHLBI R15HL145645-01

Title: Role of the paraventricular hypothalamic nucleus in the cardiogenic sympathetic afferent reflex in spontaneously hypertensive rats

Authors: *M. R. ZAHNER[1], M. C. BROWN[2], M. J. CHANDLEY[1];
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Abstract: The Cardiogenic Sympathetic Afferent Reflex (CSAR) is a reflex characterized by increased sympathetic activity and blood pressure during myocardial ischemia. Metabolites such as bradykinin (BK), stimulate cardiac spinal sensory afferents causing chest pain and increase sympathetic activity in the CSAR. It has been shown that conditions that increase sympathetic-related cardiovascular activity can augment the CSAR and this is mediated in part by the paraventricular hypothalamic nucleus (PVN). Glutamatergic activation of the PVN in the spontaneously hypertensive rat (SHR) drives elevated sympathetic activity. We have previously shown that inhibition of the PVN attenuates the CSAR in normotensive rats. However, little is known regarding neurogenic hypertension in the CSAR. In this study, we tested the hypothesis that “the sympathetic response to epicardial BK is augmented in the SHR and that this is mediated by glutamatergic PVN neurons”. Renal sympathetic nerve activity (RSNA) and blood pressure was recorded in anesthetized Wistar Kyoto (WKY) and SHRs during epicardial application of BK (10 μg/ml) before and after bilateral microinjection of vehicle, muscimol (0.5 nmol in

50 nl), or kynurenic acid (50 nmol in 50 nl) into the PVN. Vehicle microinjection into the PVN of WKY (N=8) and SHRs (N=8) did not affect basal RSNA or blood pressure, and epicardial BK elicited a significant ($p < 0.05$) RSNA and blood pressure response. Microinjection of the $GABA_A$ receptor agonist muscimol in WKY rats significantly reduced basal blood pressure and the BK-induced RSNA and blood pressure responses ($p < 0.05$, N=10). Microinjection of muscimol in the SHRs significantly reduced basal RSNA and blood pressure and the BK-induced responses compared with controls ($p < 0.05$, N=8). Microinjection of ionotropic glutamate receptor antagonist kynurenic acid in WKY rats had no significant effect on basal RSNA or blood pressure ($p > 0.05$, N=10). However, the BK-induced blood pressure response in this group of rats was significantly reduced ($p < 0.05$) while the RSNA response was unaffected. In the SHRs, kynurenic acid microinjection significantly reduced basal blood pressure and attenuated the BK-induced response ($p < 0.05$, N=8). Neither the basal RSNA nor the RSNA response to BK was significantly reduced compared with controls. These data provide new evidence that the CSAR is augmented in the SHR and that the elevated hemodynamic response to epicardial BK is mediated in part by glutamatergic input in the PVN. GABAergic inhibition decreased basal and reflex responsiveness to epicardial BK demonstrating that the PVN activity plays an important role in the full manifestation of the CSAR in SHRs.

Disclosures: M.R. Zahner: None. **M.J. Chandley:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Program #/Poster #: P626.03

Topic: F.07. Autonomic Regulation

Support: NIH grant HL148004

Title: Activation of A5 noradrenergic neurons increases visceral sympathetic nerve activity and blood pressure in rats.

Authors: *S. B. G. ABBOTT, D. S. STORNETTA, R. L. STORNETTA, G. M. P. R. SOUZA;
Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: A5 noradrenergic neurons in the ventrolateral pons are the principal source of noradrenaline for preganglionic neurons in the spinal cord that regulate the peripheral sympathetic nervous system. A5 neurons are thought to contribute to the sympathetic response to stress, however the nature of A5's role in sympathetic regulation is not well understood. We examined the effects of chemogenetic activation of A5 neurons on cardiovascular function, breathing and metabolism in freely-behaving male and female rats. A5 neurons were targeted by local injection of AAV encoding Cre-dependent HM3Dq, a Designer Receptor Exclusively Activated by Designer Drug (DREADD), in 3 models including 1) transgenic Tyrosine Hydroxylase Cre (Th-Cre) rats, 2) in-bred Sprague Dawley rats with Cre targeted to A5 using a lentivirus that drives Cre expression from an artificial *Phox2b*-promoter, PRSX8, and 3) in-bred Sprague Dawley rats with Cre targeted to spinally projecting A5 neurons with injections of AAV-Cre with a retrograde serotype in the thoracic spinal cord. Data is presented as mean ± SEM. Intraperitoneal

injections of HM3Dq agonist clozapine-N-oxide (0.3 mg/kg, i.p.) increased blood pressure in rats in which A5 neurons expressed the HM3Dq (model 1- 15.5 ± 1.5 mmHg, N=9; model 2- 12.7 ± 2.0 mmHg, N=5; model 3- 18.0 ± 3.1 mmHg, N=7), whereas CNO had no effect on BP in HM3Dq-negative controls (0.4 ± 1.5 mmHg, N=9, P<0.0001 for control vs model 1, 2 & 3 by Dunnett's multiple comparison test following 1-way ANOVA). Stimulation of A5 neurons produced no change in locomotor activity, metabolism or breathing. In anesthetized Th-Cre rats, chemogenetic activation of A5 neurons increased greater splanchnic sympathetic nerve activity (SNA) (HM3Dq vs. control- 61.5 ± 7.1% vs. -7.3 ± 6.3%, N= 8 vs. 7, P<0.0001 by unpaired t-test) and had no effect on lumbar SNA (HM3Dq vs. control- 7.6 ± 5.6% vs. -6.6 ± 3.2%, N= 8 vs. 7, P=0.88 by unpaired t-test). Activation of A5 increased maximum splanchnic SNA during baroreceptor unloading with sodium nitroprusside (P=0.0016), but did not consistently increase the slope of baroreflex function curve (P=0.99). These results indicate A5 neurons promote visceral vasoconstriction while preserving the regulation of SNA by the arterial baroreflex. Hence, activation of A5 neurons may contribute to the redistribution of blood flow away from splanchnic beds to skeletal muscle, the brain and heart during stress.

Disclosures: S.B.G. Abbott: None. **D.S. Stornetta:** None. **R.L. Stornetta:** None. **G.M.P.R. Souza:** None.

Poster

P626. Cardiovascular Regulation: Central Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.04

Topic: F.07. Autonomic Regulation

Support: NRF-2019M3C7A1031278

Title: Investigation of cardiovascular response to trigeminal nerve electrical stimulation

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Abstract: Recently, the modulation of the autonomic nervous system, especially the parasympathetic nervous system, using non-invasive electrical stimulation has been investigated in various fields such as rehabilitation and treatment. The trigeminal nerve has been known as the cranial nerve that could regulate the activity of the parasympathetic nervous system with the connection to the vagus nerve through the brainstem. Although various studies reported the modulation in cardiovascular response according to trigeminal nerve stimulation, few studies showed cardiovascular physiological responses in the normal subject depending on the trigeminal electrical stimulation frequency. This study conducted the trigeminal stimulation experiments on four groups (sham, 2Hz, 20Hz, and 200Hz stimulation frequency groups) of 61 normal subjects with three consecutive 2 minutes on and off protocols. During the protocol, electrocardiography (ECG) from the chest and abdomen and photoplethysmography (PPG) from the left finger were obtained, and heart rate (HR) and pulse transit time (PTT) were calculated from them. As a

result, the HR and PTT significantly decreased in all three 2Hz, 20Hz, 200Hz groups except for the sham group ($P<0.001$). Among the three groups, the 200 Hz evoked the most significant change in the HR and PTT. One of the interesting points is that the decrease of HR and PTT just after stimulation got back to the normal state with different delay time (10 seconds and 15 seconds, respectively). These results indicated that the activity of the parasympathetic nervous system could be modulated through the trigeminal nerve, but the recovery time from changes could be different from physiological measurements. In conclusion, these studies demonstrated the possibility that the cardiovascular responses on the trigeminal nerve stimulation with 200Hz frequency could be utilized as validation tool for the autonomic nervous system.

Disclosures: C. Kim: None. **S. Lim:** None. **H. Kim:** None. **Y. Park:** None. **D. Kim:** None. **D. Jang:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Program #/Poster #: P626.05

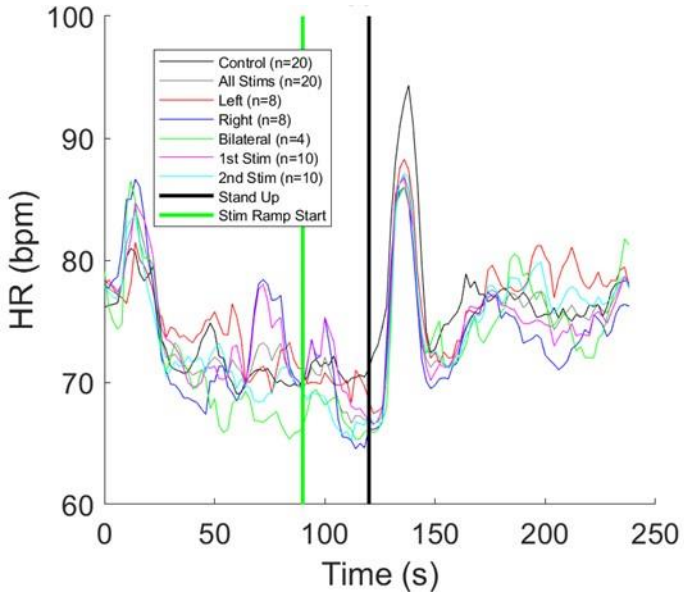
Topic: F.07. Autonomic Regulation

Title: Utilizing transcutaneous auricular neurostimulation to reduce heart rate

Authors: *M. DARROW[1], I. BAUMGART[1], D. GABRIELI[1], N. KHODAPARAST[2], A. COVALIN[2], S. WASHBURN[2], E. MEYERS[1], P. D. GANZER[1];
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Abstract: Every year, over 600,000 Americans die from heart disease, making it the leading cause of death in the United States. People living with cardiovascular disease can struggle with everyday activities as these can put too much load on their heart. Currently there is no well-established non-invasive method to reduce cardiac stress specifically during events that can require a higher cardiac load. However, recent evidence suggests that stimulation of cranial nerves (vagus and/or trigeminal) may reduce cardiac stress during these events. Battelle has developed a completely non-invasive system, the CardioHub™, to track many cardiovascular physiological signals to predict in real-time when elevated cardiac stress is about to occur. This triggers transcutaneous auricular neurostimulation (tAN) using the Spark Biomedical Sparrow™ device to reduce cardiac output. The CardioHub is designed to incorporate many wearable and non-invasive sensors to measure biosignals like electromyography (EMG), electrodermal activity (EDA), electrocardiogram (ECG), blood pressure, and more. The CardioHub, using machine learning (ML), extracts features from these biosignals and is able to make informed predictions about when elevated cardiac output is about to occur in order to trigger tAN. In order to test out the efficacy of tAN, we developed an experimental design where participants repeatedly perform the sit-to-stand (STS) maneuver. This causes an average heart rate elevation of ~50% for approximately 5-15 seconds and currently, we have observed an average reduction of heart rate of ~9% during the STS transition period. We have also observed a modest effect of reducing heart rate by ~4% (~3-6bpm) while the participant is sitting at rest. This data demonstrates a novel, completely non-invasive method, to reduce cardiac stress and improve the

everyday lives of people with cardiovascular disease. We are also further investigating the effects of tAN in other applications including reducing symptoms of psychological stress and opioid withdrawal.



Disclosures: M. Darrow: None. **I. Baumgart:** None. **D. Gabrieli:** None. **N. Khodaparast:** None. **A. Covalin:** None. **S. Washburn:** None. **E. Meyers:** None. **P.D. Ganzer:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.06

Topic: F.07. Autonomic Regulation

Title: The effect of three different pulse lengths (100 μs, 250 μs, 500 μs) and two different frequencies (10 Hz, 25 Hz) of taVNS on heart rate variability in healthy volunteers.

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Abstract: Transcutaneous electrostimulation of the auricular vagus nerve (taVNS) is gaining attention as a potential therapy for modulating the autonomic nervous system. Most commonly used parameters have been derived from experience with cervical vagus stimulation. Because the auricular and cervical vagus branches are morphologically and functionally distinct, optimal taVNS parameters are unknown. Heart rate variability (HRV) is an indirect metric of autonomic nervous system activity. In our study, we used HRV to compare the effectiveness of 6 different combinations of electrical pulse length and pulse frequency to modulate the vagus nerve activity. **Methods:** 35 healthy volunteers (mean age 35.5 years, 60% females) completed 7 visits, separated by at least 3 days. During each visit, they received one of 6 different taVNS parameters or sham treatment in a random order. During the visit participants were

placed in a semi supine position. Each visit consisted of an accommodation phase (5 min), a baseline rest phase (10 min), a stimulation phase (15 min), and a recovery phase (10 min), during which ECG data was acquired. TaVNS stimulation was applied at the cymba conchae of the left ear. Participants received monophasic stimulation with 3 different pulse lengths (100 μs, 250 μs, and 500 μs) and 2 different frequencies (10 Hz and 25 Hz), for a total of 6 combinations. RR intervals were recorded from ECG data, using the Ahlstrom and Tompkins algorithm. Last 5min windows of RR intervals from the baseline resting phase, the stimulation phase and the recovery phase were used to calculate rmSSD, SDNN, and HF HRV parameters. **Results:** Factorial rmANOVA showed no difference in the effect of different pulse lengths and frequencies (including sham) on the HRV parameters tested. There was a significant difference in the effect of phase of the experiment (baseline, stimulation, recovery) on HRV parameters. Pairwise post-hoc analysis revealed that SDNN was significantly different between all three phases ($p<0.05$), rmSSD was significantly different between baseline and stimulation phase ($p<0.05$), while HF was significantly different between baseline and recovery phase ($p<0.05$). These differences in HRV between phases of the experiment were not significantly different between stimulation groups (including sham). **Conclusions:** The results presented here suggest that taVNS does not have the ability to significantly alter HRV during or shortly after stimulation. This could be due to either a) a weak or absent effect of taVNS, b) the use of suboptimal stimulation parameters, c) HRV not being a sufficiently sensitive marker. A larger sample size is needed before any conclusions can be drawn.

Disclosures: P. Atanackov: None. **U. Kovačič:** None. **K. Elersič:** None. **F. Bajrović:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Program #/Poster #: P626.07

Topic: F.07. Autonomic Regulation

Support: NIH R01 HL116476

Title: Lesion of the OVLT impairs the development of hypertension and polydipsia in 2-kidney, 1-clip hypertensive rats

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Abstract: Hypertension (HTN) is a multifaceted condition that affects one-third of the population of western countries. It is well established that renal ischemia results in secondary renovascular HTN. Experimental renovascular HTN is induced in rats by creating stenosis of the left renal artery, thereby decreasing perfusion pressure of the clipped kidney (2K1C-HTN), leading to increased renin-angiotensin system activity which may act centrally to increase arterial pressure, sympathetic nerve activity, and water intake (Collister et al.,2018). The organum vasculosum of the lamina terminalis (OVLT) is a circumventricular organ which is responsive to blood borne substances such as angiotensin II, and has

been implicated in the regulation of arterial pressure, sympathetic activity and thirst. Previous studies have shown that OVLT lesion attenuates development of the DOCA-model of hypertension, but does not modify the water intake. In the present study we tested the hypothesis that the OVLT is required for the development of 2K1C-HTN as polydipsia is observed in this model. Male Sprague-Dawley rats (n=3-5/group) were randomly selected to receive either electrolytic lesion of the OVLT (OVLTx) or sham operation. After one week, they were instrumented with telemeters to measure mean arterial pressure (MAP). Two weeks after OVLTx, the left renal artery was stenosed by application of a silver clip. MAP was measured continuously for 6 weeks and, once a week, rats were housed in metabolic cages for 24 hours to measure water intake and urine volume. At the end of the protocol, MAP was significantly ($p<0.001$) lower in OVLTx-2K1C (134 ± 8 mmHg) compared to sham lesion-2K1C (163 ± 6 mmHg) rats. In addition, water intake was significantly ($p<0.001$) lower in OVLTx-2K1C (42 ± 2 ml/day) compared to sham lesion-2K1C (73 ± 2 ml/day) rats. Similarly, urinary volume excretion was reduced in OVLTx-2K1C (25 ± 2 ml/day) compared to sham lesion-2K1C (52 ± 5 ml/day) rats. We conclude that the integrity of OVLT is required for the development of 2K1C hypertension as well the polydipsia observed following renal artery stenosis.

Disclosures: M.R. Lauar: None. **N. Pestana-Oliveira:** None. **D. Van Helden:** None. **J.P. Collister:** None. **J.W. Osborn:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.08

Topic: F.07. Autonomic Regulation

Support: International Foundation for Research in Paraplegia Grant P176

Title: Cardio-vascular modulation by muscarinic antagonists in spinal cord injured rats

Authors: *T. MILLE[1], A. BONILLA[1], C. MENUET[2], S. S. BERTRAND[1], J.-R. CAZALETS[1];
[1]INCIA - CNRS UMR 5287, Bordeaux, France; [2]INMED - INSERM UMR 1249, Marseille, France

Abstract: Spinal cord injury (SCI) is one of the most impairing health problems worldwide. Besides its sensory-motor consequences, SCI induces a hemodynamic instability by interrupting supraspinal regulation of vascular tone, inducing life threatening conditions such as autonomic dysreflexia. Sympathetic preganglionic neurons (SPNs), located in the thoracolumbar segments, are cholinergic neurons controlled by supraspinal structures. SPNs generate slow (2.5s period in rats) oscillations in blood pressure known as Mayer Waves, which are generally used as a marker of sympathetic vasomotor activity. Mayer waves are strongly disturbed after SCI, reflecting the impaired sympathetic vasomotor control, yet their physiological function remains elusive.
To determine if some level of vasomotor sympathetic control of blood pressure persists after high thoracic SCI in rats, we silenced the antagonistic action of parasympathetic cardiovascular regulation. We used methyl-scopolamine (MS), a muscarinic antagonist unable to cross the blood brain barrier. Adult female Sprague-Dawley rats were implanted with a telemetric probe to record cardiovascular parameters. Mean,

systolic and diastolic blood pressure, as well as heart rate, were continuously monitored before, during and after injection of MS or saline. The same recordings and injection procedures were repeated after complete T3 spinal cord transection. A frequency domain analysis (Fast Fourier Transform) of systolic blood pressure and inter-beat interval were used to assess sympathetic/parasympathetic regulation of blood pressure and heart rate, respectively, with a focus on Mayer waves. Correlations between Mayer wave peak and the other physiological variables were computed.
Our preliminary data show that injection of MS after SCI increases the low frequency component (0.3-0.6Hz) of systolic blood pressure, indicative of increased Mayer waves. These preliminary data suggest that in the absence of supraspinal influences, sympathetic regulation can be revealed by peripheral inhibition of muscarinic receptors.

Disclosures: T. Mille: None. **A. Bonilla:** None. **C. Menuet:** None. **S.S. Bertrand:** None. **J. Cazalets:** None.

Poster

P626. Cardiovascular Regulation: Central Control

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.09

Topic: F.07. Autonomic Regulation

Support: Midwestern University Intramural

Title: Trigeminal medullary dorsal horn neurons activated during voluntary diving in rats express AMPA glutamate receptors

Authors: *P. MCCULLOCH, K. M. DINOVO;
Midwestern Univ., Downers Grove, IL

Abstract: The diving response is an autonomic reflex characterized by apnea, bradycardia and increased peripheral vascular resistance initiated when animals submerge underwater. Afferent stimulation initiating this response projects from the nasal mucosa via the anterior ethmoidal nerve (AEN) to second-order afferent neurons located within the trigeminal medullary dorsal horn (MDH). The present study investigated the synapse between the AEN and MDH neurons, specifically what glutamatergic receptors are expressed by MDH neurons activated during voluntary diving. In male Sprague-Dawley rats, Fos immunohistochemisty identified MDH neurons activated by repetitive diving through an underwater maze. Further immunohistochemistry identified AMPA receptors subunits expressed by these trigeminal neurons. Within the superficial MDH (laminae I and II), deep MDH (laminae III-V), and Paratrigeminal Nucleus within the spinal trigeminal tract, 26.0%, 68.7%, and 21.2% of Fos-positive neurons, respectively, expressed the GluR 1 subunit; 7.0%, 39.4%, and 19.4% of Fos-positive neurons, respectively, expressed the GluR 2/3 subunit; and 20.8%, 30.07%, and 16.5% of Fos-positive neurons, respectively, expressed the GluR 4 subunit. We conclude the AEN releases glutamate as a neurotransmitter that activates AMPA receptors on second-order MDH neurons during voluntary diving in rats.

Disclosures: P. McCulloch: None. **K.M. DiNovo:** None.

Poster

P626. Cardiovascular Regulation: Central Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.10

Topic: F.07. Autonomic Regulation

Support: NIH SPARC OT2OD024909

Title: Sparc-optical nanosensors detect neurotransmitter release in the peripheral nervous system

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Abstract: Developing methods to monitor the release of neurotransmitters during synaptic transmission would have a significant impact on the diagnosis and the treatment of various neurological diseases. Previously, we have reported a novel DNA-based enzymatic nanosensor capable of detecting acetylcholine (ACh) in the submandibular ganglion (SMG) of living mice with high sensitivity, in vivo reversibility, and dose-dependent response. Equipped with an advanced imaging processing tool, we measured spatially-resolved ACh signal propagation on the tissue level. The ACh nanosensor is based on a bottom-up modular design and assembly process, consisting of DNA as the scaffold, acetylcholinesterase as the recognition component, pH-sensitive fluorophores as the reporters, and α-bungarotoxin as the targeting ligand. The modular design of the ACh nanosensor imparts versatility, enabling easy repurposing for other applications or imaging in different regions of the body. The sino-atrial node (SAN), the pacemaker of the heart, controls the autonomic nervous system in mammals. However, the relationship of SAN with the pathogenesis of cardiovascular disorders is poorly understood due to lack of tools to perform these investigations. Here, we demonstrate the transformation of our nanosensor platform for imaging ACh and norepinephrine (NE) in SAN. For imaging ACh in SAN, we switch the targeting ligand to be the pirenzepine analogue with high affinity to the muscarinic receptors that are highly expressed in the SA node. Our preliminary data illustrate that the new ACh nanosensor can efficiently label the SA node in a living mouse, and rapidly respond to vagus nerve stimulation as confirmed by electrocardiogram. We then redesigned the nanosensor to respond to norepinephrine (NE) by replacing the recognition-reporter pair with tyrosinase and Pt-coproporphyrin, respectively, and the targeting ligand with propranolol analogues. We confirmed successful assembly of the NE nanosensors with UV-Vis spectrophotometry and size exclusion HPLC and the targeting affinity of propranolol-modified DNA scaffold to β1 adrenoreceptors in transfected CHO cells. The NE sensor was designed to emit fluorescence at λem=650 nm, distinct from our ACh nanosensor λem=560 nm, thus facilitating dual imaging of two neurotransmitters in a single organ. We envision such a sensor platform could be compatible with two-photon microscopy and further extend to other organs in the peripheral nervous system with efficient reduction of background noise and a great enhancement in spatial and temporal resolution.

Disclosures: H. Yang: None. **N. Micovic:** None. **J.R. Monaghan:** None. **H.A. Clark:** None.

Poster

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Program #/Poster #: P626.11

Topic: F.07. Autonomic Regulation

Support: NIH 1R21NS116647-01A1

Title: Compromised reactive oxygen species scavenging in Scn1b$^{-/-}$mice, implications for SUDEP.

Authors: J. MURPHY, E. ALEXANDER, ***C. FRASIER**;
Biomed. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: Sudden Unexpected Death in Epilepsy (SUDEP) is one of the most common causes of death in individuals with epilepsy. The exact mechanisms surrounding SUDEP are poorly understood, although cardiac arrhythmias have been implicated. In this exploratory study we used the *Scn1b*$^{-/-}$ mouse model of Dravet syndrome, a severe pediatric epilepsy, to determine how reactive oxygen species (ROS) scavenging is altered during a prolonged oxidative challenge. In heart, ROS balance is largely managed by the glutathione redox couple. During prolonged oxidative stress the ROS scavenging capacity can be overwhelmed, leading to an instability in mitochondrial membrane potential, which may underlie changes to cellular excitability. Our previous work suggests under prolonged oxidative stress induced by diamide, compromises ROS scavenging, can lead to instability in mitochondrial energetics, and cardiac arrhythmias. We hypothesized the Scn1b-/- mice have a decreased ability to buffer increased ROS production during times of stress, making them more susceptible to cardiac arrhythmias. We first isolated primary ventricular cardiomyocytes from *Scn1b*$^{+/+}$ (WT; N=7) and *Scn1b*$^{-/-}$ (KO; N= 8) mice between P15 and P20, loaded them with DCF to detect ROS production, and performed fluorescence microscopy in cells following addition of 80 µM diamide. Diamide oxidizes thiols, depleting the glutathione pool within the cell, ultimately decreasing a major antioxidant pathway in the heart. Our results indicate that cells isolated from KO mice (n=28) have a reduced ability to buffer changes in ROS and die significantly faster than those from WT (n=29). The average time to death was significantly lower in KO cells by 4.25 minutes ($p = 0.03$), with the first cell death occurring within 1 minute of diamide addition in KO cells compared to 5.5 minutes in WT. This was paralleled with a decreased time of onset for increases in the DCF signal, demonstrating that ROS production precedes cell death. Since there were deficits in the ability of KO myocytes to balance increasing oxidative stress, we next performed qPCR on P17 hearts to determine if there were differences in antioxidant gene expression. There was a decrease in the expression of *Sod1* (Cu/ZnSOD, 0.52-fold; $p = 0.03$), but no difference in *Sod2* (MnSOD). In addition, there was a decrease in *Gpx* (glutathione peroxidase) expression in KO mice (0.27-fold; $p = 0.03$), but there were no differences in expression of *Gsr* (glutathione reductase). Taken together our results suggest that cardiac tissue from Scn1b-/- mice have decreased ability to handle prolonged bouts of oxidative stress. This is likely due to a decrease in the availability of the glutathione system.

Disclosures: J. Murphy: None. **E. Alexander:** None. **C. Frasier:** None.

Poster

P626. Cardiovascular Regulation: Central Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.12

Topic: F.09. Food and Water Intake and Energy Balance

Title: Stem cell proliferation in the sensory circumventricular organs of adult rats is modified by salt loading

Authors: *S. ZHOU, M. PRAGER-KHOUTORSKY;
Dept. of Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Circumventricular organs (CVOs) are specialized brain regions characterized by a high density of fenestrated blood vessels, thus lacking a complete blood-brain barrier. The organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO) are sensory CVOs involved in the regulation of body fluid homeostasis and cardiac function. Recent studies reveal that secretory CVOs (the median eminence and the adjacent arcuate nucleus) harbor neural stem cells in the adult rodent brain. However, it remains unknown if sensory CVOs such as the OVLT and SFO also contain neural stem cells. To study if cells in the OVLT and SFO undergo constant proliferation in the adult brain, we intraperitoneally injected Wistar rats with a mitotic marker bromodeoxyuridine (BrdU) and used immunohistochemistry to visualize new-born cells. We have identified that NG2 glia, tanycytes, pericytes and microglia undergo constant proliferation in the adult rat OVLT and SFO. Moreover, a small fraction of BrdU-positive cells expresses a neuronal fate marker, doublecortin. To examine if cell proliferation is attenuated in conditions associated with abnormal fluid balance, we subjected rats to a model of salt-dependent hypertension. Rats were exposed to salt-loading protocol by replacing the drinking water with 2% NaCl for 7 days, leading to an increase in blood pressure. We found increased number of BrdU-positive cells in the OVLT and SFO of rats exposed to 7 days of salt-loading. Our data suggest that OVLT and SFO contain stem cells that undergo constant cell proliferation and might represent an additional neurogenic niche in the adult rat brain; and hypothalamic stem cell proliferation can be modified in response to fluid balance perturbation.

Disclosures: S. Zhou: None. **M. Prager-Khoutorsky:** None.

Poster

P626. Cardiovascular Regulation: Central Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.13

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL146833

Title: Morphology of subpopulations of stellate sympathetic ganglion neurons in mouse

Authors: M. S. BARRETT, D. M. HEGARTY, B. A. HABECKER, *S. A. AICHER;
Chem. Physiol. & Biochem., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Sympathetic nerves innervate the heart, and changes in sympathetic efferent activity can modulate cardiac function. The post-ganglionic sympathetic neurons that innervate the heart are located primarily in the stellate ganglion (SG), which also contains neurons that project to brown adipose tissue (BAT) and other target tissues. We aim to examine morphological changes in SG neurons after myocardial infarction, and characterize the specificity of neural plasticity within the ganglion. To interpret morphological changes induced by cardiac injury, we must first fully understand the normal morphology of distinct groups of SG neurons. To that end, we examined SG neurons following injections of retrograde tracers into cardiac tissue and/or intrascapular brown adipose tissue (iBAT) in adult male and female C57BL/6J mice (ages 23-32 weeks, weighing 24-39 g; The Jackson Laboratory). We examined the number, distribution, and morphology of retrogradely labeled SG neurons using cholera toxin B (CTb) (1 mg/mL in 0.1 M PBS) conjugated to two different fluorophores (Alexa Fluor 488 and AF-555) and we also examined iBAT SG neurons at different times after retrograde tracer injections (n=2 per time point). iBAT-projecting SG neurons were successfully detected 7, 14 and 28 days after injections and could be visualized directly or with antibodies against CTb. iBAT-projecting neurons were located in both left and right SG, predominately ipsilateral to the injection site and were widely dispersed. In contrast, cardiac-projecting SG neurons were more localized near the base of the inferior cardiac nerve within the stellate ganglion and were asymmetrically distributed between left and right SG. In dually injected animals (iBAT + cardiac; n=5), we found that SG neurons were not dual-labeled - supporting the notion that sympathetic innervation to target tissues is specific. We also compared other characteristics of tracer-labeled cardiac and iBAT SG neurons including dispersion, cell count, and soma size within the mouse SG. Our long-term goal is to understand the neural plasticity within post-ganglionic sympathetic neurons that can lead to sympathetic dysregulation after myocardial infarction or heart disease.

Disclosures: M.S. Barrett: None. **D.M. Hegarty:** None. **B.A. Habecker:** None. **S.A. Aicher:** None.

Poster

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P626.14

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL146833

Title: Evidence for cholinergic collateral projections between sympathetic neurons in the murine stellate ganglion

Authors: *C. CLYBURN[1], S. L. INGRAM[2], M. C. ANDRESEN[1], B. A. HABECKER[1];
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Abstract: Cardiac-projecting stellate ganglion (SG) neurons integrate cholinergic signals from preganglionic neurons via T-2 and send noradrenergic projections to the heart to regulate cardiac function. While SG neurons are thought to receive only monosynaptic inputs, early studies hinted at the presence of cholinergic collateral projections between SG neurons. Interestingly, cultured SG neurons use both cholinergic and noradrenergic transmission and can form cholinergic synaptic connections between

one other. The purpose of this study is to test the hypothesis cholinergic collateral projections are present between sympathetic neurons of intact SG in mice.Whole-cell patch clamp recordings were made of intact SG neurons from male and female C57BL/6J mice. $ChAT^{TH\text{-}CreERT2/lox}$ mice allowed for the conditional knockout (KO) of choline acetyltransferase (ChAT) in tyrosine hydroxylase positive (TH+; i.e. noradrenergic) cells. T-2 was electrically stimulated to evoke excitatory postsynaptic currents (eEPSCs) at various stimulation intensities. The jitter (i.e. variability in latency) and amplitude of eEPSCs were assessed in control and ChAT KO mice. The amplitude and frequency of spontaneous EPSCs (sEPSCs) were also examined. Initial studies found that sEPSCs in ChAT KO neurons were lower in frequency compared to controls (0.10±0.03 events/s vs. 1.19±0.24 events/s, respectively, N=5, $P<0.05$), but had similar amplitudes (23.8±2.3pA vs. 31.4±3.1pA, N=5, $P>0.05$), suggesting the loss of presynaptic cholinergic inputs from adrenergic, presumably SG, cells. Preliminary studies also found low and high jitter all-or-none eEPSCs in control ganglia (107.8±3.7μs and 211.6±8.0μs, N=4), but only low jitter eEPSCs in ChAT KO neurons (119.7±6.0μs, N=3), suggesting the loss of polysynaptic inputs in ChAT KO mice. Low jitter eEPSCs in control neurons also had a larger amplitude than high jitter eEPSCs (1445.9±369.5pA vs. 485.9±101.5pA, N=3-4, $P<0.05$). Although preliminary, our results are consistent with the presence of cholinergic collateral connections between postganglionic adrenergic SG neurons. Understanding SG neurocircuitry is critical in deciphering the changes that are observed in cardiac sympathetic neurons and sympathetic activity following myocardial infarction and in heart failure.

Disclosures: C. Clyburn: None. **S.L. Ingram:** None. **M.C. Andresen:** None. **B.A. Habecker:** None.

Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P631.01

Topic: F.08. Biological Rhythms and Sleep

Support: CSIC, Universidad de la República, Uruguay, Programa Grupos I+D - 2018 # 92

Title: The determinants of human circadian phase in two real-life situations

Authors: *A. SILVA[1,2], N. COIROLO[2], J. CASTILLO[2], B. TASSINO[1,2];
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Abstract: Dim light melatonin onset (DLMO) is the most reliable measure of human central circadian timing. The circadian phase, which ultimately depends on the expression of clock genes, is also extremely plastic. Light is the major and best-known circadian zeitgeber, while other non-photic factors such as chronotype, sleep and feeding habits, exercise, and social pressures can also be relevant. Only a few studies have previously addressed the modulation of the circadian phase in non-experimental conditions. In Uruguayan college students (18-30 years old), we evaluated the impact of photic and non-photic factors on the circadian phase estimated by DLMO in two natural scenarios using self-reported data (MCTQ, MEQ) and objective activity and light measurements (actigraphy, GENEactive). First, we evaluated DLMO changes in university students (n=11) between the Antarctic summer (10 days) and the

autumn equinox in Montevideo, Uruguay (10 days). Individual changes in DLMO between both conditions were associated with the change in light exposure in both the morning and the evening, suggesting that those with more light in Antarctica in the morning advanced their circadian phase (R=-0.800, p=0.003), and those with more light in the evening delayed their phase (R=0.747, p=0.008). The change in DLMO also correlated with participants' circadian preferences (R=0.663, p=0.026), and with changes in sleep timing (estimated by the midpoint of the least active 5h period in actigraphy recordings, R=0.693, p=0.018). Second, we evaluated DLMO changes in dance students being trained in two different shifts, morning (8:30 to 12:30, n=7), and night (20:00 to 24:00, n=11) at the National School of Dance in Uruguay. The DLMO of night-shift dancers was later than in morning-shift ones (21:42 ± 0:53 vs 20:32 ± 0:34, p=0.009) and correlated with participants' chronotype (R=0.778, p=0.005) and sleep timing (R=0.563, p=0.072). Interestingly, evening exercise (but not light exposure) delayed the DLMO (R=0.573, p=0.02). Overall, this study contributes real-life examples of the complex integration of photic and non-photic pressures in shaping the plasticity of the human circadian phase.

Disclosures: A. Silva: None. **N. Coirolo:** None. **J. Castillo:** None. **B. Tassino:** None.

Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P631.02

Topic: F.08. Biological Rhythms and Sleep

Support: NIH P50 DA046346

Title: Natural variations in sleep and circadian rhythm phenotypes, sleep fragmentation, and circadian phase shifts leads to alterations of gene and protein expression in rats

Authors: *A. J. CERWENSKY, S. MOON-KIM, A. M. EGAZARIAN, M. WRIGHT, J. ZEAK, I. H. MIGIAS, M. TORREGROSSA, C. MCCLUNG;
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Abstract: Studies show that adolescents are particularly at risk for substance use disorders (SUDs) because they are generally more reward driven, impulsive, and sensation seeking than adults or younger children. Furthermore, genetic, social, and environmental factors can also lead to sleep loss and circadian rhythm misalignment in this population. The Center for Adolescent Reward, Rhythms, and Sleep's (CARRS) general aim is to understand how sleep and circadian rhythm traits and environmental disruptions during adolescence lead to increased vulnerability for substance abuse. In our particular study we aim to determine how natural variations in sleep and circadian rhythm phenotypes, sleep fragmentation, and circadian phase shifts are associated with molecular measures of gene and protein expression in adolescent rats. To approach this, we use Heterogenous Stock (HS) outbred rats obtained from Wake Forest and bred in-facility that are suitable for researching complex traits such as SU-related behaviors both genetically and molecularly. To perform acute sleep restriction, we gently handle adolescent rats for 6 hours starting at Zeitgeiber Time (ZT) 0, the onset of the light phase. For a more mild sleep restriction paradigm, we also restrict the rats by ~40% for 5 days with a 2 day recovery period

for 2-3 cycles. Lastly, to perform circadian rhythm misalignment, we implement a 12 hour light advance every 3 days. Following each of these manipulations, rats are sacrificed at both ZT 2-4 (light cycle) and ZT 14-16 (dark cycle) for tissue analysis. A group of control rats kept on a normal light/dark cycle are also used and sacrificed at the same time points for comparison. Brains are collected and flash frozen to obtain the PFC and NAc for RNA sequencing and differential expression analysis. Based on our pilot data, we expect to find changes in genes involved in neuronal activity (i.e. ion channels) and inflammation in the PFC. We also expect to find changes in genes involved in dopaminergic signalling and MSN activity in the NAc. Overall, the goal of this study is to identify alterations in gene expression as a result of circadian misalignment and sleep restriction in order to further dissect the effects of these specific manipulations and provide a better understanding of how circadian disruption may lead to addiction-like behavior.

Disclosures: A.J. Cerwensky: A. Employment/Salary (full or part-time):; Full Time Lab Manager. **S. Moon-Kim:** None. **A.M. Egazarian:** None. **M. Wright:** None. **J. Zeak:** None. **I.H. Migias:** None. **M. Torregrossa:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI. **C. McClung:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI.

Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P631.03

Topic: F.08. Biological Rhythms and Sleep

Support: DGAPA IG-201321
CONACyT Frontera 2017-1802
CONACyT QUEBEC 279293

Title: Skeleton photoperiod induces glucose intolerance, not associated with food intake during the rest phase

Authors: *R. MÉNDEZ-HERNÁNDEZ[1], V. RUMANOVÁ[2], M. A. GUZMÁN-RUIZ[3], E. FOPPEN[4,5], G. HURTADO-ALVARADO[1], R. MORENO-MORTON[6], C. ESCOBAR-BRIONES[7], A. KALSBEEK[4,8], R. BUIJS[1];
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Abstract: Eating during the resting phase (reverse feeding) is strongly associated with obesity and metabolic syndrome. In the last decade, chronobiologists have generated several hypotheses regarding the mechanisms that underlie this association. One generally accepted view is that reverse feeding involves an internal conflict between food consumption and the energy-saving state imposed by the endogenous circadian system. However, in rodents, reverse feeding also implies food intake during the light period, which is known to exert metabolic changes as well. This suggests that the metabolic impairments derived from reverse feeding could be influenced by the effects of light on the circadian system. To investigate the conflict between food and the endogenous circadian system without the interference of light, we designed an experiment in which light was absent for most part of the day, but rats were entrained to a 12:12 cycle. For this, we adopted the skeleton photoperiod (SK) in which two light pulses indicated the beginning and end of the subjective day. Under SK conditions, we restricted food intake to either the subjective day or night, carefully assuring that light and food were not available at the same time. After 5 weeks under this protocol, we observed that glucose intolerance was induced by reversed feeding even when animals were not exposed to light. In addition, animals subjected to SK displayed glucose intolerance and increased adiposity regardless of the moment of their food intake. These changes were accompanied by alterations in their daily rhythms of temperature, locomotor activity, energy expenditure, and lipid oxidation, suggesting that the lack of an extended period of light during the daytime deeply alters metabolic rhythms. These data suggest that prolonged daytime light exposure and correct timing of food intake are both essential to maintain metabolic health.

Disclosures: R. Méndez-Hernández: None. **V. Rumanová:** None. **M.A. Guzmán-Ruiz:** None. **E. Foppen:** None. **G. Hurtado-Alvarado:** None. **R. Moreno-Morton:** None. **C. Escobar-Briones:** None. **A. Kalsbeek:** None. **R. Buijs:** None.

Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P631.04

Topic: F.08. Biological Rhythms and Sleep

Support: Marquette University

Title: The timing of food intake differentially alters daily rhythms in metabolic rate and ventilation in mice

Authors: *A. A. JONES, K. PROPSOM, L. R. NELSON, D. M. ARBLE;
Biol. Sci., Marquette Univ., Milwaukee, WI

Abstract: To efficiently deal with changes in nutrient availability across the 24-hr day, animals have evolved daily rhythms in energy metabolism and, consequently, a daily rhythm in breathing to mediate metabolic gas exchange. The daily rhythm in minute ventilation, for example, is controlled by the suprachiasmatic nucleus (SCN). However, it is unclear if this ventilatory rhythm is secondary to the SCN-imposed rhythms of metabolic rate or feeding-fasting. Here, we use a desynchronized feeding protocol to determine the extent to which ventilation rhythms are driven by the circadian clock or secondary to

metabolic rate or feeding-fasting. Metabolic rate and feeding patterns were assessed using indirect calorimetry cages and ventilatory function was determined using whole-body plethysmography. As expected, we found that under *ad libitum* and night-time feeding conditions, the daily rhythms in food intake, carbon dioxide production, oxygen consumption, and minute ventilation remained tightly aligned to the dark phase and SCN timing. However, under exclusive day-time feeding, carbon dioxide production shifted to align with food intake while oxygen consumption and ventilation remained coupled to the circadian clock. These results indicate that the daily rhythm in minute ventilation is not primarily mediated by food intake or carbon dioxide production, but instead more strongly linked to oxygen cycles and/or SCN activity.

Disclosures: A.A. Jones: None. **K. Propsom:** None. **L.R. Nelson:** None. **D.M. Arble:** None.

Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P631.05

Topic: F.08. Biological Rhythms and Sleep

Title: Using circular statistics to measure degree ofsynchronization of circadian locomotor activity in spiders with two different evolutionary behavioral strategies

Authors: *Y. WU[1], D. MOORE[2], T. C. JONES[2], N. TOPORIKOVA[3];
[1]Div. of Natural and Applied Sci., Duke Kunshan Univ., Jiangsu, China; [2]Dept. of Biol. Sci., East Tennessee St Univ., Johnson City, TN; [3]BIology, Washington and Lee Univ., Lexington, VA

Abstract: Although locomotor activity often is measured as an output of the circadian clock, the mechanism of coordination between the clock and locomotor activity is not fully understood. The phasing of locomotor activity in nature is expressed as the organism's chronotype (for example, anticipation of sunrise, sunset, food availability, predictable presence or absence of predators, etc.) and is assumed to be under selective pressure. For most spiders, there is an optimal time to collect prey from the web but this behavior also must be balanced against predator avoidance. In this work, we analyzed locomotor activity of two spider species, the common house spider *Parasteatoda tepidariorum* and the southern black widow *Latrodectus mactans*. In nature, both species are opportunistic, and capture both diurnal and nocturnal prey. Both species occupy often-shaded rocky crevices or outcrops and are thus subject to variations in onset of local darkness which enables prey capture during daylight hours while providing some protection from visual predators. However, our previous work discovered that both species experience negative masking during the photophase of light/dark (LD) cycles. The inhibited (masked) phase extends through virtually all of the photophase in *L. mactans* but is restricted to late photophase in *P. tepidariorum*. These findings suggest that *P. tepidariorum* is more neurologically primed for attacking prey during the late photophase whereas such neurological arousal in *L. mactans* spans the entire circadian cycle. Using circular statistics, our analyses revealed that *P. tepidariorum* has a higher degree of synchrony between LD cycles and locomotor activity than *L. mactans*. We then measured the distribution of locomotor activity in constant darkness for the same two species. We found that the distribution of mean vectors, indicating the preferred phase of locomotor activity, is highly concentrated for *P.*

tepidariorum. In contrast, mean vectors in *L. mactans* were uniformly distributed throughout the circadian cycle. Thus, our findings suggest that the distribution of locomotor activity throughout the circadian day may correspond to different behavioral strategies in nature.

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Poster

P631. Sleep: Perturbations and Rhythms I

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Title: The Effects of Gut Microbiota on the Developmental Circadian Rhythm in Honey Bees

Authors: *Y. B. KORU[1], Y. ORTIZ-ALVARADO[1], A. A. RUGGIERI[1], E. J. AVILÉS[1], N. RODRIGUEZ[1], R. GIORDANO[2], R. K. DONTHU[3], J. R. LEON[1], T. GIRAY[1], J. L. AGOSTO-RIVERA[1];
[1]Dept. of Biol., Univ. of Puerto Rico, San Juan, PR; [2]Ctr. for Envrn. Sci., Florida Intl. Univ., Miami, FL; [3]Know Your Bee, San Juan, PR

Abstract: Circadian rhythms in honey bees are included in numerous biological processes that influence colony survival and honey bee behavior, such as division of labor. The nurse bees, which show an arrhythmic circadian pattern, take care of brood from 4 to 12 days of age, while forager bees collect resources for the colony from 21 days of age until they die. The gut microbiota of the honey bees is composed of limited number of bacteria species that affect metabolism, physiology, and neurobiological processes. Previous studies show that the honey bee's gut microbiota affects the immune system, learning, and memory. However, postembryonic development of circadian rhythm on honey bees related to changing gut microbiota has not been completely elucidated. This study examines the effects of gut microbiota on the ontogeny of circadian rhythm of young workers under laboratory conditions by using locomotor activity monitor to measure rhythmicity. We hypothesized that changes in gut microbiota are vital to the development of circadian rhythmicity in young workers. We set two groups, consisting of control and antibiotic treatment. We used 50 µg of Tylosin Tartrate inside sugar candy while the honey bees in the control group were fed with only sugar candy. The honey bees were kept at 35 ºC and constant-dark conditions for 13 days inside an incubator. In addition, we used the RNA-Seq technique to investigate the effects of changes in gut flora on expressed genes in the brain by dissecting the brain and gut. Our results show that the honey bees in control reached rhythmicity faster and in greater proportion

than bees in antibiotic treatment. This study presents that the gut microbiota might be an essential factor influencing the ontogeny of circadian rhythm on honey bees. Moreover, honey bees can be used as model organisms on gut-brain axis studies, given their limited number of microorganisms living in their gut. Future studies will examine specific signaling molecules behind the process of ontogeny of circadian rhythm.

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Poster

P631. Sleep: Perturbations and Rhythms I

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Program #/Poster #: P631.07

Topic: F.08. Biological Rhythms and Sleep

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NIH Grant F99NS11874301

Title: The circadian modulation of cognition is disrupted in the 5XFAD mouse model of Alzheimer's disease

Authors: *A. KALIDINDI, K. HOYT, K. OBRIETAN;
Ohio State Univ., Columbus, OH

Abstract: Alzheimer’s disease (AD) is characterized by neurodegeneration and progressive deterioration of memory. AD patients also experience circadian timing system disruptions, with alterations in sleep cycle, core body temperature, activity rhythms, and the phasing of the melatonin rhythm. Recent work has raised the prospect that this circadian timing system disruption could also contribute to the cognitive decline observed in AD. AD pathogenesis has been linked to elevated levels of Aβ peptide, and here we tested whether Aβ disrupts circadian-gated cognition. Further, given that circadian timing is a distributed process, where the master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus functions in coordination with peripheral oscillator populations in the cortex and limbic system that underlie learning and memory, we examined whether Aβ affects clock timing in both the SCN and in cortico-limbic circuits. We used running wheel activity as a readout of SCN timekeeping in the 5XFAD mouse model of accelerated Aβ accumulation at 3-5 months of age (with mild cognitive decline and limited amyloid plaque formation), and at 8-9 months of age (characterized by marked cognitive decline along with amyloid plaque formation). We found no significant difference between 5XFAD mice and WT littermates in their circadian-gated running parameters (e.g., free running rhythms and light-mediated clock entrainment), at any point during the disease process, indicating that key functional properties of SCN clock timing and entrainment are intact in the 5XFAD mouse line. Next, we assessed whether circadian

clock-gated cognitive capacity was altered in the 5XFAD line. Consistent with previous studies, we found that overall cognitive capacity (working memory via the t-maze task, intermediate term memory via the novel object location test and long-term memory via contextual fear conditioning) of 5XFAD mice declined as a function of age. This cognitive decline was observed during both the circadian day and the circadian night. Interestingly, time-of-day analysis revealed that the daily rhythm in the relative efficacy of memory retrieval was significantly diminished in the 5XFAD mice; notably, damping of clock-gated cognitive output was detected early in the AD-like disease process (i.e., 4 months of age). Together, these data raise the prospect that elevated levels of Aβ disrupt cellular timing within forebrain circuits, and that this disruption manifests as a damped daily rhythm in cognition. Current work is focused on an examination of whether Aβ accumulation affects cellular clock timing properties within cortico-limbic circuits that underlie cognition.

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Poster

P631. Sleep: Perturbations and Rhythms I

Location: Virtual Only

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Program #/Poster #: P631.08

Topic: F.08. Biological Rhythms and Sleep

Support: T32 Fellowship, 5T32GM008151-35

Title: Examining Central Circadian Clock Regulation of Extra-SCN Inflammation and Neurodegeneration

Authors: *M. KING[1], E. S. MUSIEK[2];
[1]Neurol., Washington Univ. in St. Louis Neurosci. PhD Program, St. Louis, MO; [2]Neurol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Circadian rhythms align cellular and systemic function according to a 24-hour cycle. The central, light-sensitive circadian clock is located within the suprachiasmatic nucleus (SCN) of the hypothalamus, which synchronizes cellular clocks in peripheral tissues by a combination of electrical and humoral cues. Despite the accepted importance of circadian function on neurological health, the mechanisms involved remain an open question. Historically, we and others have examined circadian function by using knockouts of the master circadian protein Bmal1, and our group has shown that Bmal1 deletion has profound effects on glial activation, oxidative stress, and protein aggregation in the brain. However, knockout of Bmal1 both abrogates clock function and causes non-circadian changes in gene expression. A crucial question is which of the effects of Bmal1 deletion in the brain are due to disrupted central circadian rhythms, and which are due to loss of Bmal1 function in a given cell type. Decoupling these two effects will give us a better understanding of how exactly modern circadian disruptions such as jet lag, artificial lighting, and shift work regulate overall brain health and contribute to the pathology of neurological disorders, many of which have a circadian component.
We will address this question using a SCN-specific Bmal1-knockout mouse, which uses the Neuromedin-S promoter (NMS-Cre) to drive expression of Cre recombinase specifically in SCN neurons, disrupting

the central circadian clock without altering Bmal1 expression in cellular clocks elsewhere in the brain. We have confirmed strong Cre expression in the SCN, and negligible expression in other regions such as the cortex and hippocampus. Our actigraphy experiments demonstrate disrupted activity rhythms in NMS-Cre mice in constant darkness, which are exacerbated when subjected to altered light:dark cycles, such as 10h:10h light:dark. We will compare this NMS-Cre mouse with global Bmal1 KO mouse, in which Bmal1 is deleted in both central and peripheral clocks. Ongoing studies involve immunohistochemistry and transcriptomics to characterize the cellular responses to circadian impairment and peripheral inflammation. Finally, disease modeling is underway to understand how these disruptions contribute to the various hallmark pathologies (protein aggregation, oxidative stress, gliosis) of neurological disorders.

Disclosures: M. King: None. **E.S. Musiek:** None.

Poster

P653. Threat/Fear: Neural Circuits I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P653.01

Topic: G.01. Fear and Aversive Learning and Memory

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Brain Science Research Program (NRF-2015M3C7A1028392)
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Title: Neural correlates of risky decision-making in the periaqueductal gray-amygdala circuit

Authors: E. KIM[1], S. PARK[2], J. CHO[3], *J. J. KIM[1];
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Abstract: The dorsolateral/lateral divisions of periaqueductal gray (dl/lPAG) and the amygdala (AMYG) are implicated in defensive behaviors. We previously reported that electrical stimulation of the dl/lPAG caused naïve rats foraging for food in a large arena to flee to the nest sans external threats (Kim et al., 2013). This flight behavior was blocked by lesioning/inactivating the AMYG, suggesting the necessity of PAG-->AMYG information flow during escape behavior. We also found that optogenetic stimulation of dl/lPAG cells increased spiking activity of basolateral/central AMYG (BLA/CeA) cells that also responded to the robot predator. This study characterized dl/PAG and AMYG cells involved in antipredatory functions and then examined whether dl/lPAG stimulation altered the firing rates and synchronous firings of AMYG cell pairs. To do so, Long-Evans rats were implanted with tetrodes into the BLA and CeA and injected with AAV-CaMKIIα-hChR2-EYFP (AAV) into the dl/lPAG. After recovery, rats underwent habituation, baseline foraging, optogenetic dl/lPAG stimulation, and robot testing sessions while recording BLA/CeA units. We found distinct types of neurons in both dl/lPAG and BLA/CeA that increased activity to (i) robot activation, (ii) flight onset, (iii) pellet procurement, or (iv) multiple events.

Also, optical stimulation of dl/lPAG cells elicited both escape and neural activity in robot-responsive BLA/CeA cells, not the other cells. We then generated cross-correlograms (CCs) between simultaneously recorded AMYG cell pairs to test whether dl/lPAG stimulation-responsive AMYG cells exhibited synchronous activities during the predator surges. Among the AMYG cell pairs that showed spike synchrony during the robot-surge epochs, stimulation-responsive cell pairs showed higher CC peaks during the robot-surge epochs than the pellet procurement or stimulation epochs. However, there were no reliable CC peak differences across the epochs in the stimulation non-responsive cell pairs. We confirmed strong terminal expressions in the midline thalamic areas (Cameron et al., 1995; Krout & Loewy, 2000) following AAV injection into the dl/lPAG, and found increased fos+ cells in the paraventricular nucleus (PVT) in rats that encountered the robot predator compared to the foraging only controls. Subpopulations of the PVT fos+ cells also expressed Cholera toxin subunit B injected in the BLA or CeA, suggesting the PVT as a potential mediator of dl/lPAG-->amygdala neurotransmission. Taken together, these results suggest that functional interactions between the dl/lPAG and the amygdala neurons, possibly via the PVT, subserve antipredatory defensive mechanisms.

Disclosures: E. Kim: None. **S. Park:** None. **J. Cho:** None. **J.J. Kim:** None.

Poster

P653. Threat/Fear: Neural Circuits I

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P653.02

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant 2R01MH099073

Title: Naturalistic model of posttraumatic stress disorder in rats: effects of active predator assault

Authors: *P. R. ZAMBETTI, J. J. KIM;
Univ. of Washington, Seattle, WA

Abstract: Posttraumatic stress disorder (PTSD) is a devastating psychopathology affecting 8 million people in the US each year, with the incidence rate in women two times higher than in men. PTSD symptoms are multifaceted, including anxiety, avoidance, hyperarousal, and vivid flashbacks. Typically, PTSD develops in individuals after a traumatic event, such as child abuse, domestic violence, sexual assault, combat violence, where there are generally explicit threatening agents (e.g., assailants and enemy combatants). However, most preclinical PTSD research fails to incorporate external agents into animal and human models and focus on limited dependent variables (e.g., freezing in rodents, GSR in humans). To expand the translational relevance of basic PTSD research and provide a paradigm more akin to real-life traumas, we created a single-session inescapable predator-attack encounter in rats. Specifically, hunger-motivated male and female rats implanted subcutaneously with wires at the neck/back region were trained to leave the nest (via a gateway) to forage for a food pellet in a large arena (a purposive behavior) and return to the nest area for consumption (baseline sessions). On the predatory assault encounter session, as the animal approached the food pellet, the nest gateway automatically closed (preventing escape), and a remote-controlled robot surged towards the rat followed by a shock (1 sec, 2.5 mA) to the

animal's neck/back region via a tether cable. This robot+shock attack transpired every minute for 10 minutes. After the last robot surge-shock episode, the gateway opened, and the animal escaped into the nest. Control animals encountered the same surging robot (without shock) in the foraging arena every minute for 10 minutes. On subsequent days, the animals were placed back in the nest and, upon opening the gate, were given 10 minutes to retrieve a food pellet from the foraging area. On the first testing day, robot+shock rats had significantly longer latencies (increased avoidance) to procure the food pellet than those rats exposed to the robot only. Across subsequent testing days, the avoidance behavior of robot+shock males waned at a significantly faster rate compared to robot+shock females. Afterwards, rats underwent Pavlovian contextual fear conditioning (3 footshocks: 1 sec, 1 mA, 1 min apart) to assess fear generalization to a different context. The robot+shock females, but not robot+shock males, displayed heightened contextual freezing during the retention test. This study shows that mimicking real-life uncontrollable traumatic events (i.e., inescapable assault) leads to intensified and generalized fear, particularly in female rats.

Disclosures: P.R. Zambetti: None. **J.J. Kim:** None.

Poster

P653. Threat/Fear: Neural Circuits I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P653.03

Topic: G.01. Fear and Aversive Learning and Memory

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McKnight Memory and Cognitive Disorders Award to DJC
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NARSAD Young Investigator Award to DJC
The Botanical Center Pilot Award to DJC
One Mind Otsuka Rising Star Award to DJC

Title: Amygdalar protein synthesis supports persistent trauma-induced shifts in perceived negative valence

Authors: *Z. T. PENNINGTON[1], A. R. LABANCA[2], T. R. FRANCISCO[2], D. J. CAI[1];
[1]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, New York, CA

Abstract: In addition to traumatic stress producing robust associative memories about the traumatic experience, trauma leaves individuals more vulnerable to future stressors. This vulnerability is thought to emerge in part via trauma's capacity to augment subsequent learning about aversive events. However, while much is known about the biology of aversive learning, little is known about how aversive learning is modified by prior traumatic experience. Defining the mechanism through which this change occurs may shed light on new treatment avenues for conditions like post-traumatic stress disorder, which are often predated by a history of traumatic experience. Using a model in which animals are initially given a

strong ‘trauma’, we find that subsequent learning about a second aversive experience is enhanced relative to trauma-naïve animals. Moreover, analysis of the learning curves of the second aversive experience indicates that trauma heightens the perceived valence of aversive stimuli, rather than the speed at which learning occurs, and is independent of peripheral sensitivity to aversive stimuli. Defining the locus of plasticity giving rise to this change in perceived valence, we find that protein synthesis within the basolateral amygdala immediately after trauma is necessary for subsequent enhancements in negative valence. Current work is ongoing to determine how this augmented valence is encoded within the amygdala, using a combination of *in vivo* calcium imaging and immediate early-gene tagging. By dissecting both the psychological process (i.e. enhanced valence), and amygdala activity correlates of trauma-induced changes in aversive learning, this work will hopefully render insights into why some are more vulnerable to trauma than others.

Disclosures: Z.T. Pennington: None. **A.R. LaBanca:** None. **T.R. Francisco:** None. **D.J. Cai:** None.

Poster

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Program #/Poster #: P653.04

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH 1F31MH126543-01
NIH 5R01MH120162-02
NIH 3DP2MH122399-01S1
Friedman Scholar Award
NARSAD Young Investigator Award
Brain Research Foundation Award
Klingenstein-Simons Fellowship

Title: Ensemble reactivation during an offline period links recent experience with past memories

Authors: *Y. ZAKI[1], Z. T. PENNINGTON[1], A. LABANCA[2], Z. DONG[3], K. RAJAN[2], D. J. CAI[1]; [1]Neurosci., [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: The compilation of memories, aggregated across a lifetime, defines our human experience. How are memories dynamically updated and integrated across time and experience? Using in vivo calcium imaging (with open-source Miniscopes in freely behaving mice), an activity-dependent cell tagging system, chemogenetics, and novel behavioral designs, we tested how hippocampal networks temporally link memories separated across days. We previously found that contextual memories encoded close in time are linked by directing storage into overlapping hippocampal ensembles, such that the recall of one memory can trigger the recall of another temporally-related memory - termed memory-linking. Here, we first asked whether the strength of an aversive experience affects memory-linking, and found that increasing the negative valence of a memory increases the likelihood of memory-linking. Past literature has shown that hippocampal activity patterns present during learning are reactivated in the hours

following learning, and this has been suggested as a mechanism for memory consolidation. Based on this work, we hypothesized that memory-linking may be driven by the simultaneous reactivation, or co-reactivation, of ensembles representing two experiences. We recorded neuronal activity from the CA1 of hippocampus using Miniscopes during learning of a neutral context, of an aversive context two days later, and during the hour following aversive learning. We found that in the hour after aversive learning, mice that received a weak shock—and didn't display memory-linking—had heightened reactivation of the aversive ensemble, but not of the neutral ensemble from days prior. In contrast, mice that received a strong shock displayed heightened reactivation of both the aversive ensemble and the neutral ensemble following aversive learning, suggesting that this ensemble co-reactivation may underlie memory-linking. Finally, we demonstrate that this transfer of fear from an aversive memory to a previously formed neutral memory can be abolished by inhibiting the reactivation of the ensemble of the neutral memory during the consolidation of the aversive memory. These results collectively suggest that memory-linking is driven by the "co-reactivation" during an offline period of ensembles representing two experiences. Current work is focused on uncovering the specific brain states during which ensemble co-reactivation occurs. These results shed light on the neural substrates underlying how memories are integrated and segregated in the brain.

Disclosures: Y. Zaki: None. **Z.T. Pennington:** None. **A. LaBanca:** None. **Z. Dong:** None. **K. Rajan:** None. **D.J. Cai:** None.

Poster

P653. Threat/Fear: Neural Circuits I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P653.05

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01MH117852

Title: The nucleus reuniens of the thalamus is necessary for both the retrieval of recent extinction memories and prefrontal-hippocampal theta synchrony

Authors: *M. S. TOTTY, K. R. RAMANATHAN, S. MAREN;
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Abstract: The nucleus reuniens of the thalamus (RE) is a small midline structure interconnecting the medial prefrontal cortex (mPFC) and hippocampus (HPC) that has been proposed to coordinate the precise retrieval of specific memories, such as fear extinction. One mechanism by which the RE may facilitate mPFC-HPC communication is by the coordination of theta oscillations. Previous work has revealed that pharmacological inactivation of the RE inhibits extinction recall, and RE inactivation impairs mPFC-HPC theta synchrony during work memory tasks. However, it is still unknown if the RE is critical for mPFC-HPC theta dynamics associated with extinction recall. Using auditory fear conditioning and extinction, we extend previous pharmacological findings by showing that optogenetic silencing of the RE using a red-shifted opsin (Jaws) impairs extinction retrieval 24 hours after extinction training. Importantly, we demonstrate that increased freezing due to RE inactivation is not non-specific as

inhibiting the RE in animals that were never conditioned had no effect of freezing behavior. In an additional experiment, we show that RE inactivation also impairs mPFC-HPC theta synchrony during extinction recall. These data extend our current understanding of the role of the RE in the retrieval of fear extinction memories and coordinating mPFC-HPC theta synchrony.

Disclosures: M.S. Totty: None. **K.R. Ramanathan:** None. **S. Maren:** None.

Poster

P653. Threat/Fear: Neural Circuits I

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Program #/Poster #: P653.06

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH R01MH117852
NIH R01MH117852S01

Title: Chemogenetic activation of the locus coeruleus modulates neuronal activity in the medial prefrontal cortex of rats

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Abstract: The locus coeruleus (LC) is a stress-sensitive brain region that provides noradrenergic input to key nodes in the fear extinction circuit, including the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA). Previous work from our lab has shown that systemic noradrenergic blockade prevents stress-induced deficits in fear extinction memory and stabilizes mPFC firing after acute stress. Additionally, chemogenetic LC activation can drive stress-induced impairments in fear extinction, which are blocked by intra-BLA, but not intra-mPFC, noradrenergic blockade. Based on these data, we hypothesize that stress-induced LC activation dampens mPFC activity via an inhibitory BLA-mPFC circuit to ultimately disrupt fear extinction memory. As a first step toward testing this hypothesis, we examined the effect of chemogenetic LC activation on mPFC calcium dynamics. Long-Evans rats received viral infusions to express excitatory DREADDs in the LC (AAV-PRSX8-hM3Dq-HA) and a CaMKII-driven calcium indicator (AAV-CaMKII-GCamP6m) in the mPFC. A gradient refractive index (GRIN) lens was implanted into the mPFC and a head-mounted miniscope was used to detect mPFC calcium transients. Each session consisted of a 10-min baseline recording followed by injection of vehicle or CNO (3 mg/kg, i.p.) to activate the LC; recording resumed during the 15- to 30-min post-injection time period. Putative neurons and their fluorescent traces were identified with CNMF-E and were matched across sessions using longitudinal registration. Contrary to our hypothesis, CNO treatment increased the calcium event rate in mPFC neurons relative to vehicle treatment. These results suggest that increased LC tonic activity is associated with increased mPFC principal neuron activity in awake and freely moving rats. Future experiments will examine the mechanisms underlying LC-induced modulation of mPFC activity and fear extinction memory.

Disclosures: A.N. Binette: None. **S. Maren:** None.

Poster

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Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01MH065961

Title: Relapse of Extinguished Fear After Chemogenetic Reactivation of Hippocampal Fear Ensembles in Rats

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Abstract: Recent work in mice has suggested that distinct ensembles of dorsal hippocampal (DH) neurons represent memories of fear and safety after contextual fear conditioning and extinction, respectively (Lacagnina et al. 2019). It is unknown, however, whether similar representations are formed by auditory fear conditioning and whether these representations modulate responding to extinguished conditioned stimuli (CSs). Here, we used an activity-dependent Tet-OFF tagging system ("TetTag") to express an excitatory DREADD (AAV.cfos.tTA9.bGH, AAV.TRE.hM3Dq.mcherry.rBG) in DH neurons active during auditory fear conditioning in rats. Male and female Long-Evans rats were put on doxycycline (DOX) diet prior to infusion of the TetTag AAVs into the DH. Three weeks later, rats were removed from DOX, and the following day were placed in a novel context and presented with 5 tone-shock pairings (n=24) or 5 tone-only presentations (n=8) before being put back on DOX and returning to their homecage. Forty-eight hours later, all animals underwent fear extinction (45 tone-only trials or until fear response sufficiently diminished). Rats then underwent two counterbalanced extinction retrieval tests on subsequent days, in which either clozapine-N-oxide (CNO) or vehicle (VEH) was systemically administered. Freezing was used as an index of fear. During the retrieval tests, CNO administration increased conditioned freezing to the extinguished CS relative to VEH-treated rats or rats that received CNO but were not conditioned. Interestingly, CNO administration did not increase pre-CS freezing to the test context, suggesting that reactivating DH conditioning ensembles did not increase CS freezing by increasing fear to the test context. Rather, chemogenetic reactivation of DH ensembles tagged during auditory conditioning caused a relapse of extinguished fear to an auditory CS. These results imply that contextual representations formed in the DH during auditory fear conditioning can serve to modulate expression of conditioned fear to an extinguished CS.

Disclosures: K. Vasudevan: None. **R. Ressler:** None. **S. Maren:** None.

Poster

P653. Threat/Fear: Neural Circuits I

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Program #/Poster #: P653.08

Topic: G.01. Fear and Aversive Learning and Memory

Support: MOST 110-2326-B-007-001-MY3

Title: Differential Contribution of Nucleus Reuniens and Perirhinal Cortex in Pavlovian Trace Fear Conditioning

Authors: *Y.-C. JHUANG, C.-H. CHANG;
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Abstract: Pavlovian fear conditioning is a widely used method to study the regulation of fear memory. By repeatedly presenting a conditioned stimulus (CS), such as a tone, with an unconditioned stimulus (US), such as a footshock, animals learn the association between the two events. In trace fear conditioning, the CS and the US are separated by a stimulus-free trace interval. Several studies have shown that the hippocampus (HPC) and the medial prefrontal cortex (mPFC) are both required to encode the association between the CS and the US in trace fear conditioning. Anatomically, the mPFC does not directly project to the HPC, but it can indirectly project to the HPC through the nucleus reuniens (RE) or the perirhinal cortex (PRC). Moreover, these two relay stations reciprocally connect to each other, increasing the complexity of the HPC-mPFC circuitry. Previous studies have shown that the RE and the PRC are both involved in trace fear conditioning; however, the detailed contribution of the two brain regions is still unclear. In this study, we sought to compare the roles of the two areas by pharmacologically inactivating the RE, the PRC, or both, in Long-Evans rats during the acquisition of trace fear memory. Our data suggested that animals could still encode certain level of trace fear under pre-conditioning inactivation of either the RE or the PRC. However, inactivation of both the areas completely abolished the acquisition of trace fear that these animals behaved similarly as the controls that never received footshock during training. Interestingly, we found that RE inactivation resulted in impairment during early retrieval trials, while PRC inactivation led to impairment during latter trials, suggesting their differential importance temporally. Currently, we are examining the effect of PRC activation under RE inactivation and vice versa to investigate whether the impaired acquisition due to loss of function in one relay station could be rescued by enhancing the activities of the other. Our preliminary data suggested that PRC activation did not rescue the impairment produced by RE inactivation. Together, our studies revealed the differential roles of the RE and the PRC in trace fear conditioning.

Disclosures: Y. Jhuang: None. **C. Chang:** None.

Poster

P653. Threat/Fear: Neural Circuits I

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Program #/Poster #: P653.09

Topic: G.01. Fear and Aversive Learning and Memory

Support: MOST 110-2326-B-007-001-MY3

Title: Differential Delays in between Conditional and Unconditional Stimulus Affect the Associative Strength of Trace Fear Conditioning

Authors: *Y.-J. CHIOU, C.-H. CHANG;
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Abstract: In classical fear conditioning, two stimuli are presented: the conditional stimulus (CS), such as a tone, and the unconditional stimulus (US), such as a foot-shock. Different from delay conditioning, in which the US is presented after the CS onset and the two stimuli overlap with each other, in trace conditioning, the CS and the US are separated by a stimulus-free temporal gap called "trace interval". Previously, we found that for long trace interval group (trace interval of 120 s), rats showed divergent fear response of either high or low freezing to the tones. In this study, we aimed to examine the hypothesis that as the trace intervals become longer, the association between the CS and the US become weaker. Alternatively, we hypothesized the rats would treat the CS as a safety signal that when the CS is presented, no US follows, and the high fear would peak around the time window when the US should have occurred. On Day 1, the rats received 10 tone (20 s, 85dB, 2kHZ)-foot-shock (2 s, 1.0mA) pairings with an inter-trial interval (ITI) of 240 s. On Day 2, the rats were tested with 10 tones alone (ITI of 240 s). Our results showed that in all experimental groups (DELAY controls and trace intervals of 30 s, 60 s and 120 s), the highest freezing occurred at the time the CS was presented, and the fear level became lower as the trace interval became longer. Because freezing behavior is detected as immobility and animals may decrease their active exploration due to prolonged session time, we next implemented bar pressing for food reward to maintain baseline activities on top of trace fear conditioning. Freezing and bar pressing suppression ratio (SR) were both assessed to measure the fear level. Our result showed the rats showed lower SR as the trace interval became longer, and the highest fear still occurred at the time when the CS was presented. Together, our results suggested that the low fear response to the CS in longer trace interval group is more likely a result of the weaker CS-US association, and we did not find supporting evidence that the animals encode the temporal relationship in between the CS and the US. We are now examining whether the activation level of the fear circuitry would negatively correlate with longer delays of trace intervals.

Disclosures: Y. Chiou: None. **C. Chang:** None.

Poster

P681. Cortical Neurocircuitry of Motivational Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P681.01

Topic: G.03. Motivation

Support: HBP SGA2 785907
HBP SGA3 945539

Title: Borders for Brodmann area 23 determined by quantitative cytoarchitectonic analysis

Authors: K. NWANKPA[1], S. YATES[1], A. RICHARDSEN[1], J. PETLEY[1], S. MARKLAND[1], A. KOSTRYK[1], C. T. CERATO[1], E. ARMSTRONG[1], ***N. PALOMERO-GALLAGHER**[2];
[1]Lake Erie Col. of Osteo. Med., Greensburg, PA; [2]Res. Ctr. Juelich, INM-1, Juelich, Germany

Abstract: The human posterior cingulate cortex (PCC) is of renewed interest stemming from its being an important node in long, intrinsic circuits, such as the default mode network and fronto-parietal control network, as well as local circuits within the cingulate and retrosplenial cortices. With these connections it is no surprise that this region makes important, if as yet poorly understood, contributions to pathologies including but not restricted to Alzheimer's disease, Parkinsonism, depression, schizophrenia, and autism. To better appreciate how molecular characteristics, especially those of receptors and transmitters, relate to more macro observed pathologies, scientists have used architectural maps of cell structures for reference; most commonly those created by Brodmann more than a century ago. We present here the results of using a quantitative and statistically testable cytoarchitectonic mapping protocol, which uses 10 features of cortical laminae to group and subdivide cortex. This study reports on divisions within the PCC between the retrosplenial and 'association' cortices, typically called in the Brodmann nomenclature, Area 23. Both hemispheres of five human brains were coronally sectioned. Sections were silver stained for neuronal perikarya, glial cells, and occasional endothelial nuclei (similar to Nissl stains), digitized, and mapped. Four regions corresponding to areas 23a, b, c and d were identified and segregated by this approach. Qualitatively the PCC has a very heterogeneous structure both in terms of cellular architecture and patterns of connections. The cytoarchitecturally defined subregions have defined topographic placements and both sets of qualitative observations, cytology and topography, were used to validate borders defined by the probabilistic protocol. Caudally Brodmann 23a (BA23a) abuts the retrosplenial area BA30m at or slightly distal to the cusp of the callosal sulcus; rostrally it borders BA23d (23dysgranular). BA23a is inferior to BA23b and both span the same rostrocaudal length. The transition between 23a and 23b is usually close to a dimple found midway along the dorsoventral height of the cingulate gyrus. Superiorly and laterally in the inferior lip of the cingulate sulcus, BA23b borders BA31. BA23d is the rostral-most part of PCC, abutting BA24d and also extending into the superior lip of the cingulate sulcus. Laterally in the cingulate sulcus BA24d borders BA23c, another dysgranular cortex. Given the validation with classic observations, there is now a reproducible way to reference and quantify normal and pathological variants.

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Poster

P681. Cortical Neurocircuitry of Motivational Processes

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Program #/Poster #: P681.02

Topic: G.03. Motivation

Support: NIH Grant 1R01AA025652
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Title: Impact of reinforcer type on the reversal learning deficits following developmental insult in mice.

Authors: B. Y. JACQUEZ, J. CHANDRASEKARAN, *J. BRIGMAN;
Neurosciences, Univ. of New Mexico SOM, Albuquerque, NM

Abstract: Behavioral flexibility, one of the core dimensions of executive functioning, which is critical for one's survival, allows for the individual to adapt to the everchanging environment. It is impaired in several neuropsychiatric and neurodevelopmental disorders including prenatal alcohol exposure. Touchscreen based discrimination and reversal tasks have been a reliable method across species to test the flexible behavior. Pre-clinical studies employing animal models use reinforcers following correct choice to motivate the animals to learn and perform the task. While there are several reinforcers available, most employed reinforcers are solid reward (food pellets) and liquid reward (strawberry milkshake). Performance on operant task is highly sensitive to reinforcer type. Previous studies have examined the effects of different solid reward or liquid dietary content on learning in instrumental responding and found that rodents on liquid reward with higher caloric content performed better with increased response and task acquisition rates. But the influence of reinforcer type on reversal learning has not been explored. Here, we aimed to test whether reinforcer type during learning or reversal would impact a previously replicated deficit seen in mice exposed to alcohol during gestation. To test this, we used male and female C57BL/6J mice (n=10/sex/ group) exposed to moderate prenatal alcohol exposure (PAE) via a drinking in the dark paradigm (10% EtOH available 4 hours/day throughout gestation; BAC: ~90mg/dL; SAC: saccharine controls). Mice were trained on a visual touchscreen-based discrimination and reversal task using flavorless dustless 14mg pellets or 30 ul strawberry Nesquik as reinforcers. Total number of correction trials when the mice perform under 50% correct, has shown to be a reliable measure of perseveration during early reversal. Our results show that the type of reinforcer predicted perseverative responses in PAE mice. Both male and female mice trained on liquid reward showed reduction in the total perseverative errors during early reversal compared to mice trained on solid reward. Although there were no significant differences in reaction time between the groups, there was a reduction in magazine latency among the liquid reward mice. Interestingly, mice trained on liquid discrimination and switched to pellets on reversal showed increase in the perseverative trials, compared to mice trained on liquid throughout. This data suggest that reinforce type can have a major impact on motivation, and therefore performance, during reversal learning. Highly motivating rewards may mask behavioral deficits seen with more moderately sought rewards.

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Poster

P681. Cortical Neurocircuitry of Motivational Processes

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Program #/Poster #: P681.03

Topic: G.03. Motivation

Title: Winning gains importance from repeated losing: Interpersonal competition, neural reward-processing, and intrinsic motivation.

Authors: *J. C. BARCH, J. M. CARLSON, E. NIEMAN, H. GABOURY, R. MILLER, J. FOLEY, N. MARION;
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Abstract: Self-determination theory postulates autonomy, competence, and relatedness are basic psychological needs for all humans. Decades of research demonstrates that supporting or thwarting one's perception of need fulfillment enhances or impairs intrinsic motivation, respectively. Less clear however, are the neurological processes underlying these effects. A small number of recent EEG studies have assessed how manipulating autonomy to decrease intrinsic motivation influences the feedback-related negativity difference wave (d-FRN), which represents a difference in participants' neuro-cognitive response to win and loss feedback. While we know that thwarting perceptions of competence in participants by way of rigged losses in competitive situations decreases intrinsic motivation, how these perceptions of competence are linked to electrocortical brain activity are less clear. The study aimed to link perceptions of competence to electrocortical measures of feedback processing. Participants (N = 52) were randomly assigned to either a competence-supporting (n = 23) or competence-thwarting (n = 29) condition in which they either won or lost 75% of trials in a reaction time competition task. During competitive trials, the target time was masked after four seconds, and feedback was a predetermined bright green 'WIN' or a bright red 'LOSE' by condition; but, ostensibly it indicated if they were closer to 5 seconds than their opponent. After the EEG session, participants completed a measure of psychological need satisfaction and self-reported intrinsic motivation. Data suggests effective manipulation of competence perceptions, which predict self-reported interest and enjoyment as expected. Participants experiencing thwarted competence displayed an enhanced d-FRN (as well as other feedback related ERPs) relative to the competence-supporting group. In other words, results suggest that repeatedly losing in a competitive situation enhances the reward-processing system while engaged in the competitive trials.

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Poster

P681. Cortical Neurocircuitry of Motivational Processes

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Program #/Poster #: P681.04

Topic: G.03. Motivation

Support: MH126285

Title: The anterior cingulate cortex is important in mediating motivated behavior based on reward-expectancy and satiety

Authors: *K. K. BODINAYAKE[1], B. HALBOUT[2], C. R. HUTSON[2], K. M. WASSUM[3], S. B. OSTLUND[4];
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Abstract: The anterior cingulate cortex (ACC) is thought to mediate the ability to exert cognitive control over decision making when faced with conflicting response tendencies. Importantly, the degree of conflict between reward-seeking actions is not fixed, but tends to vary over time based on factors such as reward availability and value. Our lab recently developed a probabilistic Pavlovian-instrumental transfer (pPIT) task to parse the motivational and predictive properties of reward-paired cues. Rats display a general increase in exploratory instrumental reward seeking when presented with a cue that signals a low-probability (30%) of reward but inhibit this behavior to focus their search at the food-delivery port when presented with a high-probability (100%) cue. We hypothesized that the ACC mediates the ability to use reward expectations to adaptively regulate conflict between generalized reward-seeking (motivational response) and food-port search behavior (prediction response). To test this hypothesis, we virally expressed the inhibitory DREADD hM4Di in the ACC of male Long-Evans rats (n = 14) before training them on the pPIT task. At test, we found that inhibiting ACC function with the DREADD agonist CNO disrupted the cue-specificity of pPIT performance, such that press rates were reduced during the 30% cue but elevated during the 100% cue. To further explore this apparent motivational deficit, rats were then tested on a task in which they could choose between performing an effortful lever-press response for a highly palatable sucrose reward or freely consume lab chow from a dish. Choice between these two options is strongly biased toward the high-effort/high-value reward when rats are fully satiated on home chow (as during training), but becomes more even when they are tested in a food-deprived state. We found that inhibiting the ACC had no effect on task performance when rats were sated prior to testing but decreased pursuit and consumption of both foods when tested hungry. These findings reveal that the ACC plays an important role in regulating motivated behavior based on changes in reward expectancy and physiological need states.

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Poster

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Program #/Poster #: P681.05

Topic: G.03. Motivation

Title: Anterior cingulate cortex functional connectivity is associated with tolerance to distress

Authors: *O. DEZACHYO[1], S. KOZAK[1], Y. BAR-HAIM[1], N. CENSOR[1], E. DAYAN[2];
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Abstract: Psychological resilience, defined as the ability to adapt under significant adversity, is instrumental in preventing stress-related disorders. An important aspect of resilience is distress tolerance, the capacity to endure affective distress when in pursuit of goals. However, evidence that links intrinsic baseline interactions within large-scale functional networks with performance under distress remains missing. We hypothesized that the anterior cingulate cortex (ACC) may engage in distress tolerance due to its involvement in attention and emotion regulation. Accordingly, we tested whether behavioral

performance under distress is associated with baseline resting-state ACC functional connectivity (FC). Distress tolerance was measured in 97 healthy participants using the behavioral indicator of resiliency to distress (BIRD) task. Analyses contrasted participants who quit the task before its designated termination (n=51) with those who persisted throughout it (n=46). Seed-based FC analysis indicated greater connectivity between the ACC and dorsolateral prefrontal cortex in subjects who persisted throughout the task, along with greater FC between the ACC and the precentral gyrus in those who quit before its termination. Differences in FC between the groups were specific to the ACC, and were absent in the medial prefrontal cortex (mPFC), a neighboring non-overlapping region used here as control for spatial specificity. The results shed light on the mechanisms underlying interindividual differences in the ability to handle distress.

Disclosures: O. Dezachyo: None. **S. Kozak:** None. **Y. Bar-Haim:** None. **N. Censor:** None. **E. Dayan:** None.

Poster

P681. Cortical Neurocircuitry of Motivational Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P681.06

Topic: G.03. Motivation

Support: NIH Grant P20GM109089

Title: The Cost of Flexible Decision Making and Apathy in Traumatic Brain Injury

Authors: *J. HOGEVEEN[1], D. F. ARAGON[1], E. M. CAMPBELL[1], J. ROMERO[1], E. D. PEARSON[1], C. W. SHUTTLEWORTH[2], R. A. CAMPBELL[3], D. GILL[3], M. HUSAIN[5], V. D. COSTA[6], S. PIRIO-RICHARDSON[4], A. R. MAYER[7];
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Abstract: The motivation to initiate action is central to adaptive functioning, but is impaired in a variety of neurological and psychiatric disorders. In particular, a significant number of patients with traumatic brain injury (TBI) demonstrate clinically-significant apathy—i.e., a negative change in goal-directed actions—which can significantly impact patients' lives and persist long after the injury event. Yet, the neurocomputational deficits causing chronic apathy in TBI remain underspecified. In normative decision making, an agent flexibly chooses between novel and familiar goals, which are expected to be valuable enough to justify their associated action costs or effort. Here, we merged computational modelling of 'explore-exploit' decision making (i.e., flexibly deciding whether to explore a novel option versus exploiting a familiar one) and effort-based decision making during fMRI in patients with TBI and low- to high-apathy problems in their everyday lives. Behavioral results indicated that TBI patients with elevated apathy demonstrate reduced exploration of novel choice options, and greater effort-based discounting of rewards, suggesting that the anticipated costs associated with flexible decision making may interact to shape apathy in TBI. fMRI analyses are ongoing, but will test the hypotheses that neural computations

critical for explore-exploit decision flexibility and effort estimation are both disrupted in individuals with TBI and increased levels of apathy. A greater understanding of the neurocomputational bases of apathy in TBI could shape the design of more effective brain-based interventions for normalizing goal-directed behavior in patients.

Disclosures: J. Hogeveen: None. **D.F. Aragon:** None. **E.M. Campbell:** None. **J. Romero:** None. **E.D. Pearson:** None. **C.W. Shuttleworth:** None. **R.A. Campbell:** None. **D. Gill:** None. **M. Husain:** None. **V.D. Costa:** None. **S. Pirio-Richardson:** None. **A.R. Mayer:** None.

Poster

P681. Cortical Neurocircuitry of Motivational Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P681.07

Topic: G.03. Motivation

Support: NMRC STAR19may-0001

Title: Limited evidence for prioritized loss avoidance during cognitive performance, despite robust loss aversion in decision-making

Authors: C. CHEN, R. LONG, Z. PU, M. W. L. CHEE, ***S. A. A. MASSAR**;
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Abstract: Human behavior is thought to be more strongly motivated by the drive to avoid losses than to pursue gains. This tendency biases individuals to accept more risk, longer delays, and higher effort when choice outcomes are framed as a loss rather than a gain. However, studies measuring cognitive performance under loss and gain incentive conditions did not consistently find that people perform better, or exert more effort when losses are at stake. In a recent study (Massar, Pu, Chen, & Chee, 2020), we found evidence that losses motivated cognitive effort more than gains in a working memory task, especially at the highest effort level. As these results deviated from previous studies, we set out to perform a preregistered, replication, and extension study with an increased sample size informed by a power analysis. Eighty-six participants [mean age (stdev) = 21.95 (2.725), 64 females] performed an N-Back task (1 to 4-Back) under Gain and Loss incentive conditions. To assess effort, pupillometry was recorded during task performance, and subjective effort ratings were taken after each task run. Results showed that contrary to our hypothesis, losses did not enhance working memory performance relative to gains, even at the highest load of the N-Back task. Similarly, no differences in effort allocation as measured by pupil diameter were found between the Gain versus Loss conditions on any task level. Although participants rated that they believed they were exerting more effort in the Loss condition of the highest N-Back level, their subjective feelings of the task did not translate to performance differences between Gain and Loss conditions. In contrast to this absence of loss versus gain effects in N-Back performance, almost all participants did show clear loss aversion in a classical mixed-gamble lottery task. These findings suggest that Gain and Loss incentives may differ in their effects on working memory and decision making.

Disclosures: C. Chen: None. **R. Long:** None. **Z. Pu:** None. **M.W.L. Chee:** None. **S.A.A. Massar:** None.

Poster

P681. Cortical Neurocircuitry of Motivational Processes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P681.08

Topic: G.03. Motivation

Title: Examining the neural substrates of reward circuitry in the lateral septum

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Abstract: The lateral septum (LS) has been implicated in a variety of behaviors ranging from kinship recognition to aggression. Anatomically, it sits at a critical junction between the hippocampus and reward circuitry. Despite numerous anatomical and pharmacological studies that have investigated the function of the LS, how it contributes to such a variety of heterogeneous behaviors remains unknown. This study seeks to elucidate the diverse connectivity of the LS and how its distinct projections contribute to a breadth of behaviors. In order to do this, we focused on three different target populations of the LS that project to downstream regions that have been linked to distinct behaviors: the nucleus accumbens (NAc), the bed nucleus of the stria terminalis (BNST), and the ventromedial hypothalamus (vmH). First, we employed a modified glycoprotein-deleted rabies virus strategy to trace the monosynaptic inputs to these three different projection populations and found that they each received disparate inputs from various brain regions (n = 3). Using whole brain mapping techniques, we found that LS-BNST and LS-vmH recieved inputs from distinct compartments of the hippocampus. The LS-BNST projection appears to receive more inputs from the dorsal CA1 and the ventral subiculum. In contrast, the LS-vmH projection receives more input from the ventral CA1. The LS-vmH projection also receives dense thalamic input. We then performed cellular resolution calcium imaging in freely behaving mice over a variety of naturalistic and reward-dependent assays to better understand how LS neural activity relates to behavior. We found that LS neurons have strong reward responses, including response to multiple naturally rewarding stimuli, such as food and social rewards. Further calcium imaging of the NAc, vmH and BNST projecting LS neurons will allow us to determine how their unique afferents shape their neural activity. Together these data suggest that the LS has distinct projections to diverse downstream targets that receive discrete inputs from upstream brain regions and encode reward-related information.

Disclosures: J. Isaac: None.

Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.01

Topic: G.07. Post-Traumatic Stress Disorder

Title: L-acetylcarnitine (lac) confers metabolic resilience to trauma and mitigates posttraumatic stress disorder (ptsd)-like symptomatology in male mice

Authors: *G. PRESTON, T. L. KOZICZ;
Mayo Clin., Rochester, MN

Abstract: There is growing evidence to suggest that metabolic dysfunction underlies the pathophysiology of several psychopathologies. Mitochondrial metabolic dysfunction has been strongly implicated in the etiology of several psychiatric disorders, including posttraumatic stress disorder (PTSD). We recently identified evidence of profound mitochondrial metabolic reprogramming in mice exposed to a paradigm for the induction of PTSD-like symptomatology. Both reduced brain mitochondrial electron transport chain activity, as well as reduced circulating acetylcarnitine were identified as highly predictive of PTSD-like behavior in these animals. We therefore investigated the efficacy of the novel antidepressant L-acetylcarnitine (LAC) in mitigating PTSD-like behavior in mice. We exposed 96 C57BL/6J male mice age 10 weeks to a PTSD-induction paradigm comprised of two decontextualized sessions of inescapable electric foot shock. Immediately following induction, 48 animals were supplemented with ~100mg/kg/day LAC (0.06% in drinking water ad libitum). All animals were then assayed for light/dark transfer, marble burying, acoustic startle response, and light phase activity, to identify PTSD-like and resilient animals. Animals were sacrificed and metabolomic analysis for mitochondrial organic acids was performed in circulating plasma collected both before and after PTSD induction. Supplementation with LAC confers a metabolic resistance to trauma and PTSD-like symptomatology in mice. Reduced circulating acetylcarnitine was again associated with PTSD-like behavior, and PTSD-like mice supplemented with LAC displayed both reduced severity of PTSD-like behavior and reduced restraint stress corticosterone response relative to PTSD-like animals supplemented with vehicle alone. These effects were observed at a dose below that required for the anxiolytic effects of LAC. Exposure to the PTSD induction paradigm resulted in reduced body mass, multisystem mitochondrial metabolic dysfunction, and increased mitochondrial bioenergetic flux. This mitochondrial metabolic reprogramming was sufficient to discriminate PTSD-like and resilient animals. The mitochondrial metabolic reprogramming associated with trauma exposure was significantly mitigated in PTSD-like animals supplemented with LAC relative to PTSD-like animals supplemented with vehicle alone. Supplementation with LAC appears to improve mitochondrial bioenergetic metabolism through anaplerotic replenishment of the TCA cycle via α-ketoacids, which was associated with resilience to PTSD-like symptomatology.

Disclosures: G. Preston: None. **T.L. Kozicz:** None.

Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.02

Topic: G.07. Post-Traumatic Stress Disorder

Support: Bradley University LAS Summer Research and Artistry Fellowship

Title: Dopamine D1 receptors and PTSD symptom expression in rats

Authors: M. DILLERUD, ***T. KOELTZOW**, J. O'RUSSA, A. MABIE, S. BECKES, W. KOELTZOW, D. C. COOPER, *T. E. KOELTZOW;
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Abstract: The identification of the neurobiological factors that underliethe development of Post Traumatic Stress Disorder (PTSD), as well as thedevelopment of increasingly effective pharmacotherapies, remains a central goalof research. The Single-Prolonged Stress Model (SPS) is a well-established,preclinical rodent model of PTSD (Richter-Levin et al., 2018), and represents avalid model for drug discovery. The mesoaccumbens dopamine (DA) system, whichplays a well-established role in reinforcement learning, is also robustlyactivated by unexpected or aversive stimuli. This attribute may serve to informan understanding of the high comorbidity that has been reported for PTSD andsubstance use disorders. The purpose of the present study is to evaluate theimpact of SPS on DA D1 receptor function. Thirty-six, male, adolescent(PND=50), Sprague-Dawley rats (n=18/group) were randomly assigned to a stresscondition (SPS or SHAM). The SPS procedure consisted of two hours of restraintstress, 20 minutes of forced swimming, and CO^2-inducedloss of consciousness (Lisieski et al., 2018). SHAM controls were exposed toidentical contexts and handling, minus stress exposures. Immediately followingthe SPS/SHAM induction, rats were placed in automated locomotor activitychambers. Following a nine-day incubation period, rats were subjected to abehavioral test battery: open field (10 minutes), elevated plus maze (10minutes), and forced swim (10 minutes) tests. A Greenhouse-Geiser-correctedRMANOVA revealed a statistically significant Time x Stress interaction ($F_{(1,11.51)}$=2.49; p <0.005) as SPS-exposed rats exhibited a hyperactive locomotor response duringthe first three hours of the test. Following incubation, independent samples *t*-testsfailed to identify statistically significant main effects of stress on anybehavioral measure. However, a robust trend associated with strong effect sizesfor rearing was observed: SPS elicited enduring decreases in rearing behaviorin both the Open Field ($t_{(34)}$ = 1.63, p=0.11;d=0.54) and the Elevated Plus Maze ($t_{(34)}$ =1.88; p=0.07; d=0.63). Given the well-established role of DAD1 receptors in vertical motor activation, these findings suggest thepossibility that SPS alters dopamine D1 receptor mechanisms. Thus all rats weresubjected to 1 mg/kg SKF 81297 to assess group differences in the sensitivityof to this DA D1 receptor agonist (data collection and analysis in progress).These data may advance an understanding in the individual differences thatcomprise vulnerability to PTSD and may inform novel treatment strategies.

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Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.03

Topic: G.07. Post-Traumatic Stress Disorder

Support: NRF-2019R1A2C2088377
NRF-2018M3C7A1024736

Title: Function of the insular cortex in post-traumatic behavior induced by acute restraint stress

Authors: *S. PARK[1,2], Y. HUH[2], J. CHO[1];
[1]Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; [2]Dept. of Med. Sci., Catholic Kwandong Univ., Incheon, Korea, Republic of

Abstract: Fear is an integral part of a brain's defensive mechanism that evolved to survive against predation and other ecological risks. Occasionally some fearful events become traumatic lasting for a long period, and dysfunctions of the fear-related circuit are thought to be underlying causes of various post-traumatic symptoms. Recent studies suggested the insular cortex (IC) as an additional component of the fear managing brain network. Functional neuroimaging studies have linked the IC activation to anxiety disorders, such as a simple phobia or post-traumatic stress (PTS). However, the role of the IC leading to PTS have not been understood. Therefore, we investigated the role of the insular cortex in the animal model of PTS. First, we used an animal model of PTS and measured how long the behavioral post-traumatic symptoms lasts. We then investigated the neural activity of IC neurons during post-traumatic behavior. Lastly, we investigated whether the IC is involved in triggering traumatic behaviors by ablating the region. Acute restraint stress was used for our PTS model. Behavioral response to the trauma-reminding object was compared in the restraint and non-restraint control groups. We found that the restraint stress group shows less contacting and more burying of the trauma-reminding object than the control group, confirming that PTS symptoms developed with our model. The restraint stress group maintained these trauma-related behaviors until the 8th week. Single-unit recording in freely moving mice after inducing acute restraint stress revealed a correlation between the neural activity of IC and defensive burying behavior in the restraint stress group. In contrast, the neural activity of IC in the control group showed no correlation with defensive burying behavior. After confirming that acute restraint stress induces trauma-related behaviors and neural activity of IC correlated with defensive burying behavior, the role of the IC in PTS was further tested by making electrolytic lesions. Indeed, traumatic behaviors significantly decreased in IC lesioned group compared to the control, confirming that the IC is involved in inducing traumatic behaviors. Overall, our findings show that the IC is involved in processing trauma-related information and crucial for expressing traumatic behavior.

Disclosures: S. Park: None. **Y. Huh:** None. **J. Cho:** None.

Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.04

Topic: G.07. Post-Traumatic Stress Disorder

Title: Acute and chronic ethanol administration exacerbate the long-term behavioral effects of predator stress

Authors: *C. S. GOODMAN, C. R. DEL VALLE, J. L. DODSON, I. F. SMITH, K. M. ELMOUHAWESSE, E. P. HOPSON, H. R. SPARKMAN, M. M. NAYLOR, P. R. ZOLADZ; Psychology, Ohio Northern Univ., Ada, OH

Abstract: Trauma is frequently associated with alcohol use, yet limited work has examined the impact of alcohol ingestion on the development of post-traumatic stress disorder (PTSD) symptoms. In two separate experiments, we examined the effects of acute and chronic alcohol administration on the development of PTSD-like symptoms in Sprague-Dawley rats exposed to predator stress. In Experiment 1, rats were injected intraperitoneally with alcohol (1.5 g/kg, 20% v/v) or vehicle (distilled H_2O) 30 minutes before being exposed to an adult, female cat for 1 hour. One week later, the rats were tested for anxiety-like behavior and symptoms of hyperarousal. Stressed males, but not stressed females, treated with alcohol prior to stress displayed significantly greater anxiety and a trend toward larger startle responses, relative to stressed rats treated with vehicle. In Experiment 2, rats were injected with alcohol (1.5 g/kg, 20% v/v) or vehicle (distilled H_2O) on Mondays, Wednesdays, and Fridays for 7 weeks. On the Monday of the 7th week, the rats were injected 30 minutes prior to cat exposure. During the 8th week, the rats were tested for anxiety-like behavior and symptoms of hyperarousal. Stressed males and females treated with alcohol exhibited significantly greater anxiety than rats treated with vehicle, and stressed females treated with alcohol displayed significantly exaggerated startle responses. These findings suggest that acute and chronic peri-traumatic alcohol ingestion sex-dependently increases the risk of developing some PTSD-like symptoms.

Disclosures: C.S. Goodman: None. **C.R. Del Valle:** None. **J.L. Dodson:** None. **I.F. Smith:** None. **K.M. Elmouhawesse:** None. **E.P. Hopson:** None. **H.R. Sparkman:** None. **M.M. Naylor:** None. **P.R. Zoladz:** None.

Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.05

Topic: G.07. Post-Traumatic Stress Disorder

Title: Identifying neuronal circuits mediating MDMA's prosocial effects by brain-wide activity mapping

Authors: *D. RIJSKETIC[1], J. SALGADO[1], N. R. WALL[1], P. LLORACH[1], S. SCHLOZMAN[1], Z. RASTEGAR[1], D. BARBOSA[1], D. CARDOZO PINTO[1], P. A. NEUMANN[1], M. HELL[2], K. T. BEIER[1], R. C. MALENKA[1], B. D. HEIFETS[1];
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Abstract: MDMA (ecstasy) shows promise in the treatment of PTSD, facilitating psychotherapy via feelings of social connection, empathy and trust. However, MDMA has abuse potential and long-term heavy use can have complications. Improving on MDMA to develop a safe, scalable treatment requires understanding its therapeutic mechanism. We found that supraphysiological serotonin release in the nucleus accumbens accounts for MDMA's prosocial effect. Elucidating how this local pharmacological mechanism alters brain-wide activity could yield novel targets to mimic MDMA's therapeutic effects. To

image brain-wide activity, *TRAP2* mice (Targeted Recombination in Active Populations 2), in which the neuron firing-dependent *Fos* promoter drives CreER expression, were crossed to a reporter line (*Ai14*). In effect, 4-hydroxytamoxifen transiently enables CreER to trigger tdTomato expression. *TRAP2;Ai14* mice were singly housed and i.p. injected with saline or MDMA (7.5 mg/kg) along with 4-OHT. Mice were later regrouped and injected after 2 weeks with saline or MDMA. 90 minutes later mice were perfused, brains were bisected, immunolabeled, made optically transparent (iDISCO+), and imaged via light sheet microscopy. Using Ilastik, MIRAcL, FIJI, and FSL, we detected active cells, registered the Allen brain atlas to images, quantified regional cell densities, and generated voxel-wise corrected p-value maps. For chemogenetic silencing of social ensembles, hotspots in *TRAP2* mice were bilaterally injected with AAV8-DIO-hM4Di-mCherry or AAV8-DIO-mCherry. The MDMA social ensemble was later TRAPed before a 3 chamber sociability test where mice received CNO and saline or MDMA. MDMA (204404 ± 46560 cells; N = 6) significantly increased the total number of tdTomato$^+$ (active) neurons compared to saline (393627 ± 20811 cells; N = 7). In both social and non-social contexts, MDMA enhanced activity in the nucleus accumbens and several prefrontal cortical regions, such as prelimbic and orbital areas. Voxel-wise analyses revealed preferential activation of the dorsal endopiriform nucleus in the social context. Diffuse chemogenetic silencing of the mPFC MDMA social ensemble left MDMA's prosocial effect intact, whereas silencing this ensemble in the dorsal medial shell of the nucleus accumbens significantly blunted MDMA's prosocial effect. Through unbiased whole-brain mapping of neurons differentially activated by saline vs MDMA in social and non-social contexts we identified a novel network of regions that may mediate MDMA's prosocial effects. We plan to test for causal links between these structures' activity and MDMA's effects on sociability and relief from traumatic experiences.

Disclosures: D. Rijsketic: None. **J. Salgado:** None. **N.R. Wall:** None. **P. Llorach:** None. **S. Schlozman:** None. **Z. Rastegar:** None. **D. Barbosa:** None. **D. Cardozo Pinto:** None. **P.A. Neumann:** None. **M. Hell:** None. **K.T. Beier:** None. **R.C. Malenka:** None. **B.D. Heifets:** None.

Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

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Program #/Poster #: P714.06

Topic: G.07. Post-Traumatic Stress Disorder

Support: VA Merit Award #BX004693
NINDS T32 Award #NS082145

Title: Orexin receptor antagonists reverse neurophysiological and behavioral deficits in a rodent model of stress-induced psychosis

Authors: *H. B. ELAM[1], S. M. PEREZ[1], J. J. DONEGAN[2], D. J. LODGE[1,3];
[1]UT Hlth. San Antonio, San Antonio, TX; [2]Dell Med. Sch. at the Univ. of Texas at Austin, Austin, TX; [3]South Texas Veterans Hlth. Care System, Audie L. Murphy Div., San Antonio, TX

Abstract: Post-traumatic stress disorder (PTSD) is a prevalent condition affecting approximately 8% of the United States population and 20% of United States combat veterans. In addition to core symptoms of

the disorder, up to 64% of individuals diagnosed with PTSD experience comorbid psychosis. Previous research has demonstrated a positive correlation between symptoms of psychosis and increases in dopamine transmission. We have recently demonstrated that the paraventricular nucleus of the thalamus (PVT), which is activated following stressful or aversive events, can regulate dopamine neuron activity in the ventral tegmental area (VTA) through a multi-synaptic pathway that begins with a projection to the nucleus accumbens (NAc). Specifically, inactivation of the PVT leads to a reversal of aberrant dopamine system function and psychosis-like behavior. The PVT receives dense innervation from orexin containing neurons, therefore, targeting orexin receptors may be a novel approach to restore dopamine neuron activity and alleviate PTSD-associated psychosis. In this study, we induced stress-related pathophysiology in male Sprague Dawley rats using a two-day inescapable foot-shock procedure. Following footshock, we observed a significant increase in VTA dopamine neuron population activity, deficits in sensorimotor gating, and hyperresponsivity to psychomotor stimulants. Administration of selective orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R) antagonists (SB334867 and EMPA, respectively) or the FDA-approved, dual-orexin receptor antagonist, Suvorexant, were found to reverse stress-induced increases in dopamine neuron population activity. However, only Suvorexant and SB334867 were able to reverse deficits in behavioral corelates of psychosis. These results suggest that the orexin system may be a novel pharmacological target for the treatment of comorbid psychosis related to PTSD.

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Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.07

Topic: G.07. Post-Traumatic Stress Disorder

Support: ONU Dean's Research Lab Grant
Donation by Bill and Kristen McKell

Title: Ketamine sex- and dose-dependently mitigates behavioral sequelae induced by a predator-based psychosocial stress model of PTSD

Authors: *C. R. DEL VALLE, C. S. GOODMAN, J. L. DODSON, I. F. SMITH, K. M. ELMOUHAWESSE, E. P. HOPSON, H. R. SPARKMAN, M. M. NAYLOR, P. R. ZOLADZ; Psychology, Ohio Northern Univ., Ada, OH

Abstract: Few pharmacological agents effectively treat the array of symptoms involved in post-traumatic stress disorder (PTSD). SSRIs are the most commonly prescribed medications for PTSD, but they lead to remission rates of barely 50% and take weeks to months before producing symptom relief. Therefore, we examined the impact of ketamine, an NMDA receptor antagonist that has rapid antidepressant effects, on PTSD-like symptom development in rats exposed to a predator-based psychosocial stress model of PTSD. Male and female Sprague-Dawley rats were exposed to psychosocial stress for 31 days. The stress procedure involved two separate cat exposures (Days 1 and 11) and daily social instability. Immediately

after the first cat exposure, rats in the stress groups were injected intraperitoneally with ketamine (10 mg/kg or 15 mg/kg) or vehicle (0.9% saline); rats in the no stress groups were injected with vehicle. Three weeks following the second cat exposure (i.e., Day 32), the rats were tested for symptoms of anxiety and hyperarousal. Stressed males treated with vehicle exhibited heightened anxiety on an elevated plus maze and less activity in an open field. Stressed females treated with vehicle displayed exaggerated startle responses, as well as heightened anxiety and less activity in an open field. These effects were prevented by ketamine treatment, particularly the 10 mg/kg dose. Such findings indicate that peri-traumatic administration of a sub-anesthetic dose of ketamine can prevent the onset of PTSD-like symptoms.

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Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P714.08

Topic: G.07. Post-Traumatic Stress Disorder

Title: Mechanisms of susceptibility or resilience to traumatic stress: potential influence of the microbiome

Authors: A. TANELIAN, R. NAHVI, B. NANKOVA, *E. SABBAN;
New York Med. Col., Valhalla, NY

Abstract: Post-Traumatic Stress Disorder (PTSD) is a severe and long-lasting outcome of traumatic life event. Exposure to trauma induces PTSD only in a sub-population of individuals while others remain resilient. The mechanisms and contributing factors differentiating between stress resilient and susceptible subjects are still unclear. We hypothesize that inter-individual differences in the microbiome composition and its function contribute to host resilience or susceptibility to stress-induced psychopathologies. This study aimed to characterize differences in gut microbial community structure and functions in the Single Prolonged Stress (SPS) animal model of PTSD. Sprague-Dawley male rats were divided into SPS treated group or unstressed controls. After 14 days, behavioral analyses were performed using Open Field, Social Interaction and Elevated Plus Maze tests. The animals were sacrificed the following day and cecum, colon, hippocampus, and medial prefrontal cortex were collected. Based on the anxiety measures, the SPS group was further subdivided into SPS-resilient (R) and SPS-susceptible (S) subgroups. Prior to SPS and immediately after the Open Field test, fecal samples were collected from each rat for 16S V3-V4 ribosomal sequencing; whereas urine samples were collected before and 90 minutes after SPS to measure urinary epinephrine (Epi) levels. Analysis of fecal microbiota revealed significant differences among the groups before and after SPS stressors. Before SPS, the SPS-S subgroup harbored microbiota with an overall pro-inflammatory phenotype, such as significantly increased levels of Clostridia, and decreased levels of *Lactobacillus* and *Barnesiella* compared to the SPS-R subgroup. After SPS, among the many changes observed was significant decrease in abundance of *Bacteroides* in SPS-S subgroup. In line with

the shifts in microbiota, levels of cecal short chain fatty acids were also altered, with SPS-S subgroup having significantly lower levels of Acetate, Valerate and Caproate along with shortened colon length. Analyses of different brain regions revealed significant increases in blood brain barrier permeability in SPS-S subgroup relative to the SPS-R subgroup as determined by Claudin-5 expression. Urinary Epi levels were also significantly higher in the SPS-S subgroup. Taken together, our results suggest microbiota is a potential factor in predisposing subjects either to stress susceptibility or resilience. Moreover, SPS triggered significant shifts in the gut microbiota, therefore unravelling these mechanisms could lead to new therapeutic possibilities for PTSD through controlled manipulation of the gut microbiota.

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Poster

P714. Preclinical Models: Stress, Anxiety, and PTSD

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Program #/Poster #: P714.09

Topic: H.08. Learning and Memory

Support: NIH Grant UL1TR003015
NIH Grant KL2TR003016

Title: Effects of diet & exercise on neurobehaviors in mice

Authors: *M. K. SATYAL, C. BUHLER, D. QUETEL, D. F. ENGLISH, J. C. BASSO;
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Abstract: Diet-induced obesity and sedentary behavior are important factors influencing cognitive function decline. Limited research to date has examined the interaction between diet and exercise on exercise behavior and cognitive outcomes. Male and female FVBN/C57B6 mice (N=32) were randomly assigned to consume high-fat (60% kcal fat) or low-fat (10% kcal fat) diet *ad libitum* from weaning. At 9 weeks of age, mice from each diet group were randomized to receive 24-hour access to either an electronic running wheel or a sham locked running wheel for a period of 21 days for a total of 4 groups: (1) low-fat sedentary (LF-S), (2) low-fat exercise (LF-E), (3) high-fat sedentary (HF-S), and (4) high-fat exercise (HF-E). Animal weight and volume of exercise were tracked throughout the intervention period. The open field task and elevated plus maze were used to assess anxiety and blood glycated hemoglobin (HbA1c) was used to assess glucose control at the end of the intervention period.There was a significant interaction effect between time and diet on weight ($F(1.79, 48.36)=3.94$, $p=0.030$). Weekly running distance (km) increased significantly across the 3 week intervention period ($F(1.3, 18.7)=13.692$, $p=0.001$). Additionally, there was a significant effect of diet on running distance ($F(1,14)=4.86$, $p=0.045$) with the high-fat group running more than the low-fat group. There was a significant effect of exercise on time spent in the closed arms of the elevated plus maze ($F(1,26)=10.91$, $p=0.003$) with the sedentary group spending more time in the closed arms. There was no significant main effect of diet or exercise nor an interaction effect of diet and exercise on the time spent in the center of the open field or HbA1c. The distance run in the first week of wheel exposure was negatively correlated with time spent in the center of

the open field (r=-0.532, p=0.034). These findings suggest that high-fat diet and exercise may influence neurobehaviors preceding the onset of metabolic dysfunction.

Disclosures: M.K. Satyal: None. **C. Buhler:** None. **D. Quetel:** None. **D.F. English:** None. **J.C. Basso:** None.

Poster

P716. Cognition

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P716.01

Topic: H.01. Attention

Support: DSI

Title: Non-normative reward biases persist in instrumental information demand

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Abstract: Curiosity guides us through the world, governing which information we take in and which we ignore. Humans are intrinsically motivated to obtain information, sometimes to reduce uncertainty and sometimes merely to anticipate positive outcomes. Although uncertainty-driven information demand is theoretically optimal and maximizes prediction accuracy, a bias toward positive information can interfere with prediction accuracy and result in suboptimal outcomes. Here we show that this bias, traditionally thought to reflect an affective preference for “savoring” over “dread” (anticipating positive but not negative outcomes), may instead reflect the limitations of heuristics that people use to identify informative observations. Participants (N = 610) performed an online task in which they attempted to predict the sum of two prizes by inquiring about the precise value of one of the prizes. Each prize was randomly drawn from a probability distribution with pre-specified variance and expected value (EV). The normative strategy, which minimized the uncertainty of the sum, was to inquire about the prize with the higher variance regardless of EV. We replicated our previous finding that, when information demand was not incentivized (i.e. information was non-instrumental), participants used non-normative strategies, frequently inquiring about the higher-EV prize. If this bias were due to savoring, it should diminish when participants had monetary incentives for minimizing uncertainty. Contrary to this prediction, the bias persisted in two distinct instrumental conditions, resulting in significant loss of rewards. Only 11% of participants consistently adopted the normative strategy despite the fact that this strategy was constant across different conditions and could be calculated with simple arithmetic. These findings suggest that people identify informative stimuli using heuristics that may approximate ideal performance in some tasks but reliably fail in other conditions.

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Poster

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Topic: H.01. Attention

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Title: The neurodevelopment of value-driven attention

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Abstract: Reward plays an essential role in prioritizing the processing of sensory information. Past psychological studies in human adults have shown that rewarding stimuli not only facilitate goal-directed behaviors but also cause distraction when they are irrelevant to the current behavioral task. While neural mechanisms underlying value-driven attention have been increasingly well understood, it is still unclear how the human brain develops to support value-driven attention. To address this question, we measured EEG from typically developing adolescents and healthy adults performing a variant of value-driven attention tasks where we assessed the impacts of low and high reward values associated with the colors of task-irrelevant visual stimuli (i.e., low- and high-valued distractors) on the behavioral performance at discriminating task-relevant targets as well as the amplitude of the N2pc, the well-known event-related potential (ERP) index of covert visual attention related to target selection. Consistent with previous reports, in adults, low-valued distractors did not change behavioral performance at discriminating task-relevant targets and did not modulate the amplitude of target-related N2pc. On the other hand, high-valued distractors led to worse discrimination performance and the reduction in the N2pc amplitude compared to the low-valued-distractor and no-distractor conditions. In contrast, teenagers exhibit different patterns of reward modulations at both behavioral and neural levels. While high-valued distractors increased behavioral inference and reduced the N2pc amplitude in a similar degree as the adult group, low-valued distractors produced much higher attentional capture effects in teenagers compared to adults. These resulted in comparable levels of attentional capture effects between low- and high-valued distractors in the younger group. Together, our findings suggest that the differential effects that low and

high rewards have upon attention in adulthood are caused by the reduced sensitivity of the attentional system to visual stimuli associated with low reward values during development.

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Poster

P716. Cognition

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Program #/Poster #: P716.03

Topic: H.05. Working Memory

Support: American Heart Association, Award #16BGIA27250047

Title: The relationship between cognitive function and depression in people with and without type 2 diabetes mellitus

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Abstract: The coexistence of type 2 diabetes mellitus (T2DM) and depression and a bidirectional relationship between two health conditions are reported (Roy & Lloyd, 2012; Semenkovich, Brown, Svrakic, & Lustman, 2015). A substantial body of literature demonstrates cognitive impairment (CI) in both people with T2DM and depression; CI advances as the severity of T2DM and depression progresses (Gatlin & Insel, 2015; McDermott & Ebmeier, 2009). Additionally, domain-specific cognitive deficits, such as working memory, are reported in people with diabetes mellitus (Christman, Vannorsdall, Pearlson, Hill-Briggs, & Schretlen, 2010; Gorniak, Lu, Lee, Massman, & Wang, 2019; McCrimmon, Ryan, & Frier, 2012). The coexistence of T2DM and depression progresses the CI; however, it is unclear whether the level of depression severity is associated with cognitive function in people with T2DM (Demakakos, Muniz-Terrera, & Nouwen, 2017). Cognitive function may be associated with the level of depression severity and the presence of T2DM. To test our hypothesis, we examined the association between cognitive task performance and the level of depression severity in people with and without T2DM. Finally, we examined a regression model to predict the cognitive task performance. A total of 21 people with T2DM (65.2 + 5.8 years old, all female) years old and 21 age- and sex-matched healthy people (66.2 + 5.7 years old, all female) performed an auditory n-back task, in which subjects were instructed to repeat the nth letter back in a sequentially presented list of letters. The difficulty of n-back task was manipulated by asking subjects to repeat the letter further back in the list. Additionally, we asked subjects to perform the n-back task and a constant grip force tracking task to increase the difficulty of n-back task. There were three levels of difficulty: 0-back, 1-back, and 2-back. Response accuracy and response time (RT) of the n-back task were recorded. Hospital Anxiety and Depression Scale (HADS) depression and Montreal Cognitive Assessment (MOCA) were used to quantify the level of depression severity and general cognitive function, respectively. People with T2DM had a higher score of HADS depression ($p < 0.05$) and a lower score of MOCA ($p < 0.05$) compared to healthy control subjects. Overall, the score of HADS depression was related to response accuracy ($p < 0.01$) and RT ($p < 0.05$).

Finally, multiple regressions demonstrated that n-back condition, group, and the score of HADS depression predicted response accuracy ($p < 0.001$, $R^2 = 0.51$), while only group predicted RT ($p < 0.001$, $R^2 = 0.068$). These results underscore the significance of T2DM and depression in the cognitive task performance.

Disclosures: H. Hibino: A. Employment/Salary (full or part-time):; Research Assistant/TE (part-time).
S.L. Gorniak: A. Employment/Salary (full or part-time):; University of Houston.

Poster

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Topic: H.05. Working Memory

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Title: Tumor suppressor gene Fus1 causes sex-dependent effects in memory impairments

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Abstract: Tumor suppressor gene *Fus1* causes sex-dependent effects in memory impairments
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Memory impairments contribute to the manifestation of diseases such as amnestic mild cognitive impairment (aMCI). Incidences for aMCI are more reported in women than in men, although some studies have demonstrated otherwise. Fusion 1 (*Fus1*), also known as tumor suppressor candidate 2 (*TUSC2*), was originally identified as a tumor suppressor gene, but now is considered as a mitochondrial Ca^{2+} protein that aids the mitochondrial calcium uniporter (MCU) and mitochondrial sodium-calcium exchanger (mNCX). A deletion of *Fus1* gene augments the production of reactive oxygen species (ROS), oxidative stress, and disturbs the homeostasis of mitochondrial Ca^{2+} ($miCa^{2+}$). We have previously demonstrated that *Fus1* knock-out (KO) mice showed deficits in olfactory and spatial memory. However, these results were only tested in females and sex was not considered as a variable. Here, we assessed a potential sex difference in memory impairments in *Fus1* KO and wild-type (WT) mice. To do this, we executed a battery of behavioral tests including, Y-maze, which was conducted for a duration of 8 minutes with an overhead camera recording the series of arm entries made by each individual mouse; Novel object recognition (NOR) was conducted in an open field arena where each mouse was placed individually with either two identical objects in the familiarization period or with two dissimilar objects in

the exploration period; and open-field test (OFT), in which mice were placed in an open-field arena and allowed to move about freely for a 30 minute test duration. All behavioral tests were performed on 17-weeks old mice. Results show that *Fus1* KO males, but not KO females, exhibited a reduced percentage of correct alternations ($p<0.05$, n = 11-14 per group). By contrast, *Fus1* KO females had increased locomotor activity compared to *Fus1* KO males ($p<0.05$, n =4-11). No gene or sex effects were observed in NOR test. Amyloid β_{1-42} peptide was measured and found to be unaltered in male and female KO mice. Thus, Fus1 deficiency show sex-dependent effects in specific behavioral tasks. The findings of this study corroborate that Fus1 deficiency has a comportment on short-term memory as well as locomotor activity as tested *in vivo*. The outcomes of this ongoing study will provide insights on the potential mechanisms that induce memory impairments to give rise to neurodegenerative diseases such as aMCI.

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Poster

P716. Cognition

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Program #/Poster #: P716.05

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: P20GM121301
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AR067858

Title: Trpm8 is important for skeletal acquisition and maintenance in male but not female c57bl6/j mice

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Abstract: Transient receptor potential cation channel subfamily M member-8 (TRPM8) is the thermo-TRP channel responsible for cold thermosensation within sensory neurons. In rodents, loss of TRPM8 greatly diminishes the ability to sense and respond to cold. This also results in altered core body temperature regulation and metabolism. Other TRP channels of the Vanilloid family have established roles in bone via regulation of Ca^{2+} stores and intracellular Ca^{2+} signaling of osteoblasts (bone mineralizing cell) and osteoclasts (bone resorbing cell), but the role of TRPM8 in bone homeostasis has yet to be clearly defined. Previously, we found that cool temperature housing in aged mice (52 weeks old) caused bone loss, independent of TRPM8, but that male mice null for TRPM8 (*Trpm8*$^{-/-}$) had low bone density and cortical bone defects compared to wildtype (WT) mice regardless of housing temperature. To determine whether this was age-related or due to impaired acquisition, we examined bone in young (8 weeks old) mice when trabecular bone density has peaked, and cortical bone is continuing to grow. Similar to aged mice, *Trpm8*$^{-/-}$ males, but not females, have reduced total areal bone mineral content (mg of bone, -10%) vertebral bone volume fraction (Bone Volume/Total Volume, -13%) and trabecular

number (-4.6%) compared to WT mice. The L5 vertebrae from *Trpm8*$^{-/-}$ males had significantly less % bone surface occupied by osteoblasts, and gene expression of the osteoblast marker *Bglap* (Osteocalcin) was reduced in tibia. Additionally, expression of osteoclast marker *Ctsk* (Cathepsin K) was increased in *Trpm8*$^{-/-}$ males. These results suggest altered differentiation and activity of the bone multicellular unit in the absence of *Trpm8*. Interestingly, expression of neurotrophic factors *Ngf* and *Bdnf* were significantly upregulated in the tibia and *in vitro* cultured osteoclasts of *Trpm8*$^{-/-}$ males, suggesting TRPM8 may influence innervation of the bone microenvironment. However, *Trpm8* expression has been reported in tissues outside the nervous system. Using CRISPR-Cas9 we inserted loxP sites in introns 11 and 14 of the *Trpm8* gene to generate a *Trpm8*$^{loxP/loxP}$ strain. *Sox2*-mediated Cre recombinase successfully deleted exons 12-14, which is predicted to cause a frameshift mutation and premature stop codon. Deletion was confirmed by genotyping and qPCR analysis in the dorsal root ganglion. These mice mimic the low bone mineral content observed in the male *Trpm8*^{tm1Jul} (*Trpm8*$^{-/-}$) mice. We will use these mice to test neuronal and bone cell-mediated origins and effects of TRPM8 signaling, which will expand our understanding of the role of TRPM8 in bone development and maintenance.

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Poster

P716. Cognition

Location: Virtual Only

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Program #/Poster #: P716.06

Topic: H.01. Attention

Title: Changes in the distraction potential associated with the side of motor onset of motor symptomatology in Parkinson disease

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Abstract: Neurophysiological studies obtained through the distraction potential, composed by the mismatch negativity (MMN), the P3a and the reorientation negativity (RON) have reported that involuntary attention (IA) is impaired since early stages of Parkinson's disease (PD). It is also known that IA mechanisms are automatic or bottom-up and are regulated by the ventral frontoparietal network, which is largely lateralized to the right hemisphere. Due to an asymmetric degeneration of striatal dopaminergic neurons, PD generally initiates its motor symptomatology unilaterally (left-onset side; right-onset side) which has led a growing body of researchers to explore the cognitive, psychological, and clinical differences between left onset PD patients and right onset PD patients. While such alterations have been described from the aforementioned approaches, much less is known about the neurophysiological dynamics underlying impairments in the IA with respect to the onset side of motor symptomatology in these patients. The aim of this study was to analyze and compare the characteristics of the components of the distraction potential between a PD group with left-sided onset (LPD), a PD group with right-sided onset (RPD), and a control group (HC). Twenty-five patients with LPD onset and 31 with RPD onset

were studied, as well as 24 healthy control subjects. All subjects performed an auditory distraction task while a digital EEG was being recorded. The distraction potential was obtained by averaging methodology. Each wave was analyzed with a Repeated Measures ANOVA test. The main finding of this study was the reduction in the P3a showing lower amplitude in the LPD group with respect to the RPD group and the HC, this results suggests that patients with LPD have reduced involuntary attention. Therefore, this finding may be of interest for clinicians involved with the intervention of these patients, since, if the IA is mostly affected in patients with LPD, strategies at the neuropsychological level can possibly be proposed by differentiating the side of motor symptom onset.

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Poster

P716. Cognition

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Title: Multitasking has a persistent effect on the brake reaction time in simulated car driving

Authors: *O. BOCK[1], R. STOJAN[2], M. MACK[2], C. VOELCKER-REHAGE[2];
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Abstract: Distracting tasks degrade drivers' performance on a subsequent braking task. We have shown (SfN 2020) that this degradation can persist even at stimulus onset asynchronies (SOA) of ≈12 s. Our earlier study dealt with performance measures that are relevant for traffic safety: lane keeping and distance keeping. Here we evaluate a performance measure that reflects drivers' initial and intended response: gas-off reaction time (gRT). Earlier research about the psychological refractory period (PRP) effect suggest that a distracting tasks delays subsequent gRT only if SOA is below about 400 ms, not if SOA ≈12 s as in the present data. In a driving simulator, 120 older adults (69.43 ± 3.70 years old) followed a lead car that mostly drove at a constant speed of 70 km/h, but occasionally braked: its brake lights came on, and the car slowed down to 40 km/h. To avoid collisions, participants had to slow down as well. Eleven trials of this braking task were intermixed with 60 trials of distracting tasks (typing, reasoning, and memorizing, each presented visually or auditorily). SOA between a distracting trial and the subsequent braking trial was 11.3 ± 2.4 s. In a control condition, the braking tasks were administered without distracting tasks. For analysis, SOA was binned into terciles (4.0 to 10.5 s, 10.5 to12.1 s, 12.1 to 24.5 s) and was contrasted against the control condition in a linear mixed-effects model. Covariates were Gender, Age, Distance (to the lad car at brake light onset) and SOA * Distance. Participant ID was

included as random intercept. Dependent variable was gRT. The main effect of Distance was significant (p &lt 0.001, est. = 0.04). SOA contrasts were not significant (all p &gt 0.05), but Distance * SOA-contrast interactions were significant for the contrast of short SOA with control (p &lt 0.001, est. = 0.02), medium SOA with control (p = 0.001, est. = 0.02), and long SOA with control (p = 0.014, est. = 0.01). Thus, responses at short, medium and long SOA didn't differ from control when Distance was low, but they increasingly differed from control as Distance increased. We conclude that distracting tasks led to an increase of subsequent gRT, unless Distance was low and braking responses therefore were urgent. Importantly, the increase was observed even though SOA ≈12 s. Thus, effects of distractions on gRT were much more persistent than classical PRP-effects. We posit that distracting tasks can establish a persistent task set, which must be reconfigured before a braking response can be produced, thus increasing gRT. The presumed reconfiguration was swift if braking responses were urgent, which suggests that persistence may be a matter of convenience rather than necessity.

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Poster

P766. Attentional Networks II

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Program #/Poster #: P766.01

Topic: H.01. Attention

Support: Proyecto DGAPA-PAPIIT IN217918 to AERC

Title: Global and local attention as predictor of intelligence

Authors: *C. D. GUILLERMO-FLORES, E. LOPEZ-GONZALEZ, T. V. ROMAN-LOPEZ, A. LAZARO-FIGUEROA, C. SANCHEZ-GACHUZ, M. MENDEZ-DIAZ, O. PROSPERO-GARCIA, A. E. RUIZ-CONTRERAS;
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Abstract: Several neuroimaging studies indicate the involvement of the prefrontal areas, especially, the dorsolateral prefrontal cortex (DLPFC) in intelligence, which has also been associated with working memory and executive functions. Switching in attention as well as performance on the task are generally related to DLPFC. Frontal N200 and P300 of the event-related potentials (ERPs) have been associated with working memory and cognitive control, thus both are considered characteristics of intelligence. This study evaluated if switching attention into global and local processing can predict intelligence, using the Navon task (letters or numbers composed of smaller letters or numbers), which requires responding to global or local stimuli through switching attention to certain features of the stimuli and ignoring others. A total of 85 young volunteers (44 males and 43 females) answered the Navon task and the Shipley-2 test, to assess global intelligence and fluid and crystallized intelligence. ERPs were recorded in a subsample of 37 subjects (21 men and 16 women) while responding to the Navon task. Regression analysis showed that accuracy in the Navon task for the local condition predicted crystallized intelligence score (r2= 0.0362, p<0.001), and overall intelligence score (r2=0.0412, p<0.001); while in ERPs, mean amplitude of P300 during global condition predicted crystallized intelligence (r2 = 0.0996, p<0.001) and overall intelligence

score (r2=0.125, p<0.001). These results suggest that subjects who are more efficient at inhibiting irrelevant stimuli had higher intellectual performance, which may indicate that selective attention is necessary to improve performance on tasks that require a higher degree of concentration.

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Poster

P766. Attentional Networks II

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Topic: H.01. Attention

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Title: Analysis of information coding and exchange in the multiple demand network in space and time using fMRI-MEG fusion

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Abstract: A multiple-demand network (MDN), composed of frontal and parietal cortices, is activated by, and encodes relevant information in, a wide variety of demanding cognitive tasks. They are proposed to select and integrate task-relevant information from across neural systems (Duncan et al. 2020) but the temporal dynamics of information processing and exchange remain unclear. For example, it is unknown whether information coding arises in sub-regions of the MDN one-after-another or simultaneously. Here, we used fMRI-MEG fusion to obtain spatiotemporal insight into information coding in the MDN during a cognitively demanding task. By comparing the temporal evolution of information (from MEG) to the information contained in different brain regions (fMRI), fusion can reveal the temporal order of information coding across regions. Then, to study the exchange of this information between regions, we developed a novel implementation of Granger-causality-based connectivity analysis using the estimated time-resolved response in each region. On each trial, one of four visual stimuli appeared (white squares on grey background; two in top-right and two in top-left hemi-fields), and participants (MEG: n=24; fMRI: n=30) had to press one of four buttons. They learned two orthogonal stimulus-button mappings (rules; indicated by fixation cross color) in a training phase. Using Representational Similarity Analysis, we fused four aspects of information: coarse stimulus (left vs. right stimuli), fine stimulus (inner vs. outer stimuli), rule and response information. Both coarse and fine stimulus information appeared first in posterior followed by anterior regions of the MDN. Rule information appeared in the same order. Parietal MDN was the region which showed the response information immediately before the response. Our

connectivity analysis showed information transfer from sensory regions to MDN and its circulation within the MDN. Compared to other aspects of information, the fine stimulus information was most dominantly circulated within the MDN. These findings provide evidence for differential roles of MDN sub-regions across different information aspects. The new connectivity method opens opportunities for detailed study of information exchange with high spatial and temporal resolution.

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Poster

P766. Attentional Networks II

Location: Virtual Only

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Program #/Poster #: P766.03

Topic: H.01. Attention

Title: Test anxiety is associated with changes in all three domains of the attention networks task as measured by electroencephalography

Authors: G. M. TALKINGTON[1], *E. A. BOURASSA[2];
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Abstract: Alterations in attentional processes are commonly noted in patients with anxiety disorders as well as in non-clinical populations with trait- or state-anxiety. Test anxiety (TA), although a common entity, is poorly characterized. In this study, the attention networks task (ATN) was used to measure the efficiency of the alerting, orienting, and conflict-resolution domains of attention while simultaneous electroencephalography (EEG) recordings were taken from students with and without TA. It was predicted that students with high test anxiety (HTA) would have poorer conflict-resolution; other attentional networks were expected to be unaffected (in line with other forms of anxiety in most studies). Students were screened for TA using the blue-box stress test; those with and low TA (LTA) were later administered the ATN during EEG recording. Behavioral analysis showed that HTA students had marginally significant lower conflict-resolution efficiency compared to LTA ($p=0.06$); interestingly, HTA students also had lower orienting and increased alerting efficiency compared to LTA. On the alerting domain, both LTA and HTA had larger N1 waves in the central cued condition compared to no cue, but the N1 was larger in HTA than LTA in both conditions. On the conflict-resolution domain, LTA had larger parietal N1 waves in the incongruent condition compared to congruent condition, an effect not seen in HTA. The latency of the N1 was also delayed by approximately 150 ms in HTA compared to LTA in both conditions. The P3b wave was significantly larger in both conditions in HTA. In the orienting domain, the parietal N1 was larger for spatial cues than central cues in LTA, an effect not seen in HTA. In the central cue condition, the P3b was not significantly different between groups, but in the spatial cue condition, the P3b was much larger in HTA compared to LTA; intriguingly, the P3b was smaller in the spatial cue condition in LTA but larger in the spatial cue condition in HTA. Across the attentional domains, event-related spectral perturbations (ERSPs) between conditions and groups showed a variety of theta-power changes in both the parietal and frontal lobes. Taken together, these data suggest that students with TA allocate more attentional resources when alerted to a task and fail to reduce their allocation of attentional resources when less resources are needed. Along with this, orienting of attention requires more

cognitive resources than expected. These changes are consistent with some forms of anxiety (but not others) and also share characteristics with other disorders of attention such as attention-deficit hyperactivity disorder.

Disclosures: G.M. Talkington: None. **E.A. Bourassa:** None.

Poster

P766. Attentional Networks II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P766.04

Topic: H.01. Attention

Title: Brain network dynamics in the transition from wakefulness to sleep

Authors: *S. KUMAR[1,2], J. GONZALEZ-CASTILLO[1], E. TAGLIAZUCCHI[3], I. FERNANDEZ[1], P. MEDIANO[2], A. ARZI[2], C. BAREHAM[2], P. BANDETTINI[1], T. BEKINSCHTEIN[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Psychology, Univ. of Cambridge, Cambridge, United Kingdom; [3]Univ. of Buenos Aires, Buenos Aires, Argentina

Abstract: The brain dynamically transitions between distinct states over time that may correspond with ongoing cognition, metabolic processes, vigilance, etc. This work aimed to show how vigilance alters the functional organization and coordination of brain regions in a dynamic and task-dependent way. In two EEG-fMRI experiments, healthy adults were encouraged to become drowsy and fall asleep inside the MRI scanner. In the first study, drowsy participants (n = 22) additionally performed a simple auditory decision-making task, and the second study was a resting-state session in which a different set of participants (n = 25) passively listened to tones. An EEG-based automatic vigilance classification of “alert” or “drowsy”, based on the Hori stages for sleep onset, was assigned to each timepoint. The classification was derived from a support vector machine algorithm that includes frequency band power and cross-regional coherence as predictor variables. fMRI Regions of Interest (ROIs) were extracted using a whole-brain parcellation, and an instantaneous phase coherence was calculated at each timepoint for each ROI pair. K-means clustering was performed on the phase coherence patterns of both datasets combined. Four patterns were determined to be the optimal number of clusters, and a resulting fMRI-derived pattern was assigned to each timepoint. Within each dataset, a vigilance contrast (alert vs. drowsy) was calculated on concatenated data coinciding with each fMRI pattern. We show that task and vigilance have different effects on the brain depending on concurrent fMRI pattern configuration and the complexity of that configuration, with simpler patterns highlighting more task-dependent differences, particularly within-network. These findings suggest spontaneous within-network functional organization may be modulated by drowsiness, and drowsiness may alter more complex brain configurations in a task-independent way. ROIs in a ventral attention network may contribute to a compensatory mechanism when subjects are actively trying to sustain cognitive function and perform a task while drowsy.

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Poster

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P766.05

Topic: H.01. Attention

Title: Electrophysiological correlates of attention and response inhibition in a food go/no-go task

Authors: *R. GRAHAM[1], V. LEYVA[2], F. DE PALMA[2], N. CEBALLOS[2];
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Abstract: Visual images of food are salient and evocative, making them an effective marketing tool. Yet the neural processes that support this effectiveness are not well understood, especially the role of individual differences such as food preferences, body weight, hunger, dieting behaviors, and general preoccupations with food. These variables may modulate how people initially respond to food images (e.g., cue reactivity) and how more deliberate control processes (e.g., behavioral inhibition) are subsequently engaged. The current study examined whether food tastes and/or preferences play a role in these effects as indexed by event-related potentials (ERPs) using a task involving behavioral inhibition. Twenty-one healthy female college students (mean age = 23.2 years) completed go/no-go tasks with either high calorie sweet or high calorie savory foods as targets (counterbalanced). Self-reported BMI, food preferences, hunger, restrained eating, and state/trait cravings were also assessed. Behavioral analyses revealed greater accuracy for go relative to no-go trials, with no differences for sweet or savory foods. ERP analyses focused on peak latencies and amplitudes of the frontocentral N2 and the centroparietal P3 components. N2 latencies were sensitive to food type and food preferences, with a tendency to peak earlier in response to savory high calorie images but only in people who preferred these foods. In contrast, P3 amplitudes were sensitive to response type such that they were higher during no-go vs. go trials. Follow-up regressions focusing on N2 latencies revealed that latencies during go trials were negatively associated with trait craving, while latencies during no-go trials to preferred foods were positively associated with state craving. Overall, results suggest that the N2 and P3 elicited by food stimuli in a go/no-go task index separate processes. More specifically, the timing of the earlier N2 may be more sensitive to the more automatic, motivational properties of palatable foods, while amplitudes of the subsequent P3 are more sensitive to more controlled processes like behavioral inhibition.

Disclosures: R. Graham: None. **V. Leyva:** None. **F. De Palma:** None. **N. Ceballos:** None.

Poster

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Topic: H.01. Attention

Support: NIH Grant R01-EY025648 (JG)
NSF Grant 1848939 (JG)
NSERC PDF (BD)

Title: Visual distraction disrupts category-tuned attentional filters in ventral visual cortex

Authors: *L. PIDAPARTHI, B. DUBE, J. D. GOLOMB;
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Abstract: To compensate for the complexity of our visual environments, we rely on attention to selectively filter goal-relevant information from irrelevant information. During visual search, for instance, attention prioritizes target-matching information in the environment. However, if distracting information appears during this search, spatial attention can be captured, prolonging search. Does distraction also disrupt feature- or category-based attentional filters that prioritize task-relevant information? To examine this, we measured the neural signatures of attentional filtering specific to object category using human fMRI. In this experiment, participants were presented with 2x2 arrays of hybrid face-house images; they performed a 1-back task based on the designated stimulus category (i.e., attend-faces and attend-houses blocks), with the target item's location indicated by a solid white border. On some trials, a salient distractor (a dotted white border) appeared briefly around one of the nontarget locations. On distractor-absent trials, we found the predicted pattern of attentional modulation: greater BOLD activation in the fusiform face area (FFA) during attend-faces blocks and in the parahippocampal place area (PPA) during attend-houses blocks, illustrating the efficacy of attentional filtering for the target category. On distractor-present trials, however, we observed a relative increase in activation reflecting the processing of the nontarget category (i.e., increased FFA activation during attend-houses and increased PPA activation during attend-faces), suggesting a disruption of the attentional filter selective for object category. Overall, these results indicate that visual distraction by abrupt-onset salient stimuli disrupts both spatial and category-tuned attentional filters, failing to restrict processing of task-irrelevant information.

Disclosures: L. Pidaparthi: None. **B. Dube:** None. **J.D. Golomb:** None.

Poster

P766. Attentional Networks II

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Topic: H.01. Attention

Support: NIH R01 DC016297

Title: Unpacking the influence of attention on the hierarchical multisensory integration of audiovisual speech

Authors: *F. AHMED, A. R. NIDIFFER, E. LALOR;
Univ. of Rochester, Rochester, NY

Abstract: Seeing a speaker's face significantly improves speech comprehension, particularly in noisy environments. This is attributed to the brain's ability to integrate information from auditory and visual sensory modalities through a process called multisensory integration (MSI). In addition, real-life listening environments are often full of multiple competing sources of speech, although listeners are typically interested in following just one of those - known as the 'cocktail-party problem'. Successful communication involves both MSI of audiovisual (AV) speech and selective attention, but how these processes interact with each other is not well understood. This is because the majority of previous studies examined each of these processes in isolation without considering the interplay between the two. Furthermore, most of those studies used relatively controlled stimuli and paradigms that do not reflect the sensory challenges faced in the real world. Here we present the results of three experiments aimed at examining how attention affects electrophysiological signatures of multisensory integration in the context of natural, continuous audiovisual speech. In particular, we wish to test the hypothesis that such multisensory integration occurs at different hierarchical levels of speech processing, each of which can be differentially influenced by attention. All three experiments involve recording EEG from subjects presented with a cocktail-party-like scenario involving continuous AV speech. Following previous research, all experiments involve comparing models of that EEG based on assuming an underlying multisensory process (AV) with those based on assuming two independent unisensory processes (A+V). The three experiments differ in the number and location (relative to fixation) of the visual speech stimuli in such a way as to allow us to assess the multisensory integration of dynamic, low-level visual cues vs detailed, higher- level articulatory cues. Our modeling results point to a limited influence of attention on indices of multisensory integration at lower hierarchical levels. However, at later/higher-stages of processing, the influence of attention varies substantially based on the visual information available to the subject. Overall, our data support the flexible interplay of attention and MSI at different levels of the speech processing hierarchy, depending on the task and the environment.

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Poster

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Research was sponsored by the U.S. Army Research Office and accomplished under contract W911NF-19-D-0001 for the Institute for Collaborative Biotechnologies.

Title: Feature-selective priority maps in human cortex are modulated by top-down and bottom-up attention

Authors: *D. D. THAYER, T. C. SPRAGUE;
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Abstract: The relative importance of a particular location within the visual field can be characterized in a priority map (Itti & Koch, 2001; Wolfe, 1994), which integrates the bottom-up image-computable salience of each location in the scene with the top-down behavioral goals of the observer; the resulting activity profiles across the priority map guide attention to important locations in the environment. Computational priority map models suggest that this map is computed by combining across spatial maps for individual feature dimensions, such as color and motion. At the neural level, previous work has identified retinotopic cortical areas that are sensitive to color (hV4/VO1/VO2; Brewer et al., 2005) as well as motion (hMT+/TO1/TO2; Amano et al., 2009), making these regions strong candidates for 'feature dimension maps'. Here, we used multivariate voxel activation patterns across retinotopic feature-selective cortical regions to characterize spatial feature dimension maps. In Experiment 1, we cued participants to either attend a single feature of a colored moving dot stimulus, or a central fixation cross to assess how activation profiles across maps reflect top-down task goals (under identical visual stimulation). To evaluate how bottom-up feature salience modulates activation patterns, Experiment 2 required participants attend fixation while a salient color or motion singleton was presented in the periphery. If these regions act as feature dimension maps, there would be greater activation corresponding to the location of the stimulus/singleton when attending/shown the preferred feature of a given region (e.g., within color-responsive hV4 when attending color). We found that stimulus and singleton representations within reconstructed priority maps were stronger in color selective regions when color was attended (Expt 1) or salient (Expt 2) compared to motion, and representations in motion selective regions were stronger when motion was attended or salient compared to color. These findings suggest that feature-selective cortical regions support spatial maps of priority indexed for specific feature dimensions, and that top-down and bottom-up inputs can reweight activation profiles across these maps.

Disclosures: D.D. Thayer: None. **T.C. Sprague:** None.

Poster

P766. Attentional Networks II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P766.09

Topic: H.01. Attention

Title: Prior dynamic experience regulates spatial attentional rhythm

Authors: *Y.-A. CHENG, H. LUO;
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Abstract: The brain efficiently organizes its limited resources over external information through attention. Recent studies demonstrate that attention works in a dynamic way, whereby multiple locations, objects, and features are rhythmically sampled over time. However, it remains largely unknown whether attentional rhythm is inherently hardwired or can adapt to prior experience and changes flexibly. Here we used time-resolved behavioral measurements on 25 human subjects to examine whether externally induced rhythm in prior experience would influence spatial attentional rhythm. Specifically, subjects were first exposed to a rhythmic prime display, i.e., a near-threshold stimulus was presented alternatively between two spatial locations for 2500 ms at 3 Hz or 5 Hz. Next, after a varied time interval (200 to 1000

ms in steps of 33 ms), a near-threshold probe appeared at one of the two locations and subjects needed to detect the target and the accuracies were measured. First, behavioral data shows 2.5 Hz attentional rhythm when there is no prior stimulus, largely consistent with previous findings. Most importantly, the attentional rhythm is modulated by the temporal characteristics of prime stimulation, i.e., increasing to 4.5 Hz for 5 Hz prime and remaining at 2.5 Hz for 3 Hz prime, when the probe was presented in the left visual field. Taken together, our results suggest that visual attentional rhythm is not a fixed clock and could be modulated by and adapt to prior dynamic experience.

Disclosures: Y. Cheng: None. **H. Luo:** None.

Poster

P812. Social Cognition Circuits

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Program #/Poster #: P812.01

Topic: H.06. Social Cognition

Support: Seaver Foundation
NIHR01MH116108

Title: A role for paraventricular oxytocin neurons in social recognition memory

Authors: *K. THIRTAMARA RAJAMANI[1], M. BARBIER[1], K. NIBLO[1], S. WAGNER[2], V. GRINEVICH[3], S. NETZER[2], H. HARONY-NICOLAS[1];
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Abstract: Social cognition in mammals is fundamental for several conserved behaviors including distinguishing prey from a conspecific, identification of mating partners and for kinship maintenance. Together these behaviors have a major influence on their ability to maintain evolutionary fitness. Social recognition memory is a form of social cognition that requires the discrimination of a novel from a familiar conspecific. Deficits in social recognition have been reported in several psychiatric disorders including Autism spectrum disorder and Schizophrenia. Thus, identifying the neural and biological correlates of social recognition memory (SRM) can spur a greater underlying of these behaviors in disease. Oxytocin (OXT) is a neuropeptide that is synthesized and released by neurons in the paraventricular (PVN), supraoptic and accessory nuclei of the hypothalamus. It is implicated in social behaviors including maternal care, social bonding, and social recognition memory. Despite a clear role for OXT in SRM, it is still unclear which of the three nuclei within the hypothalamus is necessary for the formation of this form of memory. Furthermore, little is known about what role do downstream neural substrates, targeted by OXT axonal projections, play in SRM. We hypothesized that PVN OXT neurons are necessary for both short- and long-term SRM. To address our hypothesis, we used designer receptors activated by design drugs (DREADDS) to specifically silence OXT neurons (OXT-hM4DGi) in the PVN of male Sprague Dawley rats and assessed their performance on both short and long term social recognition memory. We found that silencing OXT neurons in the PVN, leads to impairments in both long and short-term SRM. In order to identify and investigate downstream targets of OXT neurons

necessary for SRM, we first used an OXT-specific antibody to label OXT projections across the brain. We identified a novel posterior hypothalamic nuclei; supramammillary nucleus (SuM), as a new target of OXT projections. The SuM is known to play an important role in hippocampal learning and memory. We next injected OXT specific anterograde (AAV-OXT-Venus) and retrograde (AAVretro-GFP) viruses into the SuM and confirmed that these OXT fibers originate specifically from the PVN. Finally, we found that blocking OXT receptor activity in the SuM inhibits long but not short term SRM, suggesting that the PVN-SuM may be a novel neural circuit necessary for this form of memory. Taken, together these findings attribute a novel role for PVN-OXT neurons and PVN-SuM neural circuitry in social recognition memory.

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Poster

P812. Social Cognition Circuits

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Topic: H.06. Social Cognition

Support: PA CURE Grant to WJ Gao.
Drexel University College of Medicine's Dean Fellowship

Title: A corticothalamic circuit for top-down inhibitory control of social motivation in male mice

Authors: *N. R. MACK, W.-J. GAO;
Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Deficits in social motivation are common in many neuropsychiatric disorders such as depression, anxiety, and autism spectrum disorders. However, the neural mechanisms by which the brain regulates social behavior remain unclear. Previous research has shown that parvalbumin (PV) interneurons in the prefrontal cortex (PFC) are active during social behavior, and enhancing PV interneuron activity can rescue sociability deficits. However, a population of PFC neurons that may be inhibited by PV interneurons during social behavior has yet to be identified. Our study first tested whether neural connections between the prefrontal cortex (PFC) and the posterior paraventricular thalamus (pPVT) play an essential role in regulating social motivation using a chemogenetic approach. We found that chemogenetic activation of PFC-pPVT neurons abolishes social preference in mice without affecting locomotor behavior in the three-chamber sociability task. Moreover, this effect seems to be specific to male mice. These results are interesting because they replicate findings from others showing that activation, but not inhibition, of the PFC, abolishes social motivation. Our conclusion that chemogenetic activation of PFC-pPVT neurons reduces social motivation predicts that PV interneurons may inhibit this population of neurons for effective social interaction to occur. To test this hypothesis, we implement fiber photometry to assess changes in calcium activity in PFC-pPVT neurons during social interaction. These results will provide evidence for a novel circuit mediating prefrontal top-down inhibitory control of social

motivation. A mechanistic understanding of brain activity during social interaction will help develop better biomarkers for symptomology and better treatment options for social deficits.

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Poster

P812. Social Cognition Circuits

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Topic: H.06. Social Cognition

Support: NSF Award #1707408

Title: Nucleus accumbens population neural dynamics encoding social interactions

Authors: *P. ZHAO, X. CHEN, D. AHARONI, A. BELLAFARD, A. MURUGESAN, J. QUAN, P. GOLSHANI;
UCLA, Los Angeles, CA

Abstract: Deficits in social interactions are the main clinical manifestations of autism spectrum disorder (ASD). These deficits may arise because social interactions are not rewarding for individuals with ASD. However, the neural dynamics driving diminished social reward in autism are poorly understood. Though the nucleus accumbens (NAc) is embedded within 'reward pathway', it is still unclear whether and how NAc and its connected brain regions such as medial prefrontal cortex (mPFC) encode and drive social interactions and social reward. Using miniaturized microscopy, we recorded neural activity of NAc core neurons expressing GCaMP6f in animals freely interacting with a conspecific or exploring an object. We identified a larger proportion of neurons activated during social interaction than during object exploration (16.7% vs 5.4%). In NAc, the percentage of D1R neurons engaged in social interactions was higher than that of A2aR neurons (15.1% vs 8.3%). To determine how neural populations encode social interactions vs object explorations, we trained a Partial Least Squares Regression (PLSR) decoder on NAc neural activity. PLSR decoder could predict epochs of social interaction but not epochs of object exploration. Interestingly, social interactions could be decoded from neural activity of D1R, but not A2aR neurons. As mPFC is also a critical hub for social behavior and has projections to NAc, we recorded neural activity of mPFC neurons. Using the same criteria, we identified a far lower proportion of neurons activated by social interaction (6.3%). Decoder performance showed less specificity in predicting epochs of social interaction when trained with mPFC neural activity patterns. To explore the stability of NAc ensemble firing, we recorded the same neural population as animals interacted with the same conspecific across 6 days. By tracking the same neurons, we found that although there was always a significant proportion of NAc neurons activated during daily social interaction sessions, the probability that a neuron was socially activated across sessions decreased across days suggesting that a stable population does not code for social interactions across sessions in NAc. Moreover, the population of NAc neurons responding to social interactions was distinct from the population responding to sucrose reward, suggesting that distinct ensembles encode social and non-social rewards. Therefore, NAc neurons, especially D1R neurons, robustly encode social interactions specifically, but these representations are not stable across days.

Further work will aim at whether these networks are aberrantly activated in models of autism with impaired social interaction.

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Poster

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Title: Neural projections to the anterior cingulate cortex in adult prairie voles

Authors: *S. BLUMENTHAL[1], K. HORIE[1], H. S. FUTCH[2], L. J. YOUNG[3];
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Abstract: Deficits in in the ability to detect or respond to distress in others are seen many psychiatric disorders including autism spectrum disorders, leading to impaired social functioning. Consolation, or comforting physical contact directed toward a distressed party, is a behavioral output of empathy that has been observed in humans and non-human primates. Recently, our lab reported the first evidence of partner-directed consoling in rodents. Prairie voles (*Microtus ochrogaster*), a socially monogamous and highly affiliative rodent, reliably express empathy-like consoling behaviors by allogrooming their distressed partner. Observing a distressed partner induces neural activity in the anterior cingulate cortex (ACC) and infusing an oxytocin receptor (OXTR) antagonist in ACC eliminates consoling behavior. As a first step toward investigating the neural circuitry of consoling behavior in voles, we traced anatomical neural projections to the ACC in adult prairie voles using viral tracing. Prairie voles received unilateral infusion of AAVrg-hSyn-EGFP to either the left or right ACC. Two weeks later the animals were perfused and their brains sectioned at 30 µM. Immunohistochemistry was performed on sections throughout the brain to detect GFP and sections were imaged on a fluorescent microscope. We found that several cortical and subcortical structures project to the ACC of the adult prairie vole. Projections from cortical structures include the primary somatosensory, visual, auditory, perirhinal, entorhinal, and insular cortices. Projections from subcortical regions include the claustrum, basolateral amygdala, zona incerta, hippocampus, and several thalamic nuclei. Future studies will map inputs specifically to ACC OXTR-positive cells and manipulating projections to those cells using *Oxtr-Cre* prairie voles to better the neural circuit mechanisms of oxytocin-dependent empathic-like consoling behaviors.

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Poster

P812. Social Cognition Circuits

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Topic: H.06. Social Cognition

Support: NIMH: K99/R00 MH106744

Title: The Central Amygdala - a Gate for Visceral Changes In Social Behavior

Authors: *H. LANOVOI[1], I. CARCEA[2];
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Abstract: The Central Amygdala - a Gate for Visceral Changes In Social BehaviorHunter Lanovoi and Ioana Carcea
Somatic health and social behaviors correlate in the human population and in animal models. However, the physiological mechanisms supporting this relationship remain unclear. Social interaction is a dynamic neurobiological process that integrates external social stimuli with internal states. Visceral information about the physiological, immunological, and metabolic state of the internal organs, such as those involved in digestion are directly and indirectly conveyed to the central nervous system. Changes in the composition of microbes residing in the gut, as during indigestion or after antibiotic treatment, can change the inflammatory state of the host through the release of lipopolysaccharide (LPS). These changes have a particularly noticeable effect on engagement in social interactions. These robust behavioral effects likely developed as a safeguard to prevent the spread of disease. A key structure for controlling social engagement is the central amygdala, and particularly its oxytocinergic neuromodulation. We investigate if oxytocin receptor neurons in central amygdala might represent a mechanism for LPS-induced changes in social behavior. For this, we first treated mice with LPS and characterized acute changes in social engagement: social sniffing and approach in a direct social interaction assay and preference for social salience in a salience discrimination task. We find that LPS-treated mice initiate less nose-nose sniffing bouts (Saline: 6.813 +/-0.328, LPS: 2.122 +/- 1.011, $p<0.0001$, n=8) and have no preference for social salience (Saline: -6.870 +/-33.66, LPS: 10.79 +/-13.32, p=1537, n=8). Next, we will manipulate the activity of OXTR+ neurons in central amygdala to determine if they can change behavioral responses to LPS. To determine if OXTR+ cells in central amygdala might receive information about internal visceral state, we performed monosynaptic rabies tracing from these neurons and found inputs from the parabrachial nucleus, a structure that responds to noxious visceral signals. We will determine whether these inputs play a role in the social avoidance and social indifference phenotypes we identified after LPS treatment. This work will contribute to understanding factors that might contribute to disrupted social behaviors in autism and other disorders with a social dimension.

Disclosures: H. Lanovoi: None. **I. Carcea:** None.

Poster

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Topic: H.06. Social Cognition

Support: IBS-R001-D2

Title: The neural oscillatory signature in the anterior cingulate cortex driving observational fear in the mouse, a rodent model of affective empathy

Authors: S.-W. KIM[1], M. KIM[1], ***J. BAEK**[1], C.-F. LATCHOUMANE[1], G. GANGADHARAN[2], Y. YOON[1], D.-S. KIM[3], Y.-S. KIM[4], H.-S. SHIN[1];
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Abstract: The behavioral assay for observational fear in rodents has accelerated in-depth studies of neural circuits and genes underlying vicarious emotional learning. Two alternative behavioral tests for observational fear measures animal's behaviors driven by two different processes: the assay with naïve observer mice measures affective empathy-like responses to other's suffering, and that with prior foot-shocked observers measures adaptive learned responses for self, which is amplified by a similar observation. However, this critical difference has been largely ignored, and consequently, the neural process specifically driving the former, empathy-like behaviors, has not yet been clearly identified. Here, we report that 4-to-8-Hz slow theta oscillations in the right anterior cingulate cortex (ACC) are specifically and causally linked with the emergence of the empathy-like fear responses in mice. These low-frequency neural oscillations in the ACC were selectively increased during socially driven freezing responses but not during self-retrieved responses. Notably, a closed-loop disruption demonstrated that this ACC theta is essential for the observational fear. The oscillations synchronized the ACC and the basolateral amygdala (BLA) activities, and optogenetic inhibition of either the ACC-to-BLA or the BLA-to-ACC pathway selectively impaired the observational fear without affecting classical fear conditioning. The increase/decrease of theta power in these two brain regions induced by optogenetic manipulation of the hippocampal theta also selectively and bidirectionally altered observational fear with the freezing levels correlated with the power. Together, these results indicate that 4-to-8-Hz theta oscillations in the ACC are the selective and essential neural process driving the socially driven empathic fear that is discriminable from the self-retrieved or classical fear.

Disclosures: S. Kim: None. **M. Kim:** None. **J. Baek:** None. **C. Latchoumane:** None. **G. Gangadharan:** None. **Y. Yoon:** None. **D. Kim:** None. **Y. Kim:** None. **H. Shin:** None.

Poster

P812. Social Cognition Circuits

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P812.07

Topic: H.06. Social Cognition

Support: NRF-2019R1A2C1002963
NRF-2020R1A6A3A13076176

Title: The Role of medial prefrontal cortex in fear-related behavior with social exposure in adolescent rats: contribution of GABAergic and Oxytocin system

Authors: *M. JANG, T. JUNG, Y. JEONG, Y. BYUN, J. NOH;
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Abstract: We have identified the decrease of fear response by a social experience with conspecifics, which is as a phenomenon that can be suggested as a social buffering during the fear conditioning in the adolescent male rats. However, this behavioral changes by social exposure on neural mechanism has not yet been fully investigated, especially for the role of medial prefrontal cortex(mPFC). In this study, we carried out passive avoidance test in the single rat-exposed and the pair rats-exposed condition and determined histological and electrophysiological changes in the mPFC. To clarify a cellular mechanism in the mPFC, several drugs were injected into assigned rats via stereotaxically implanted guide cannula in mPFC. The rats exposed with toy rat showed a significant increase in fear behaviors, such as single rats, suggesting that the social buffering requires the existence of a living rat, not an object. We found that the increasing c-Fos expression in the mPFC in association between fear-related behaviors by social stimuli via pair exposure. Anisomysin and GABAzine stereotaxically treated into the mPFC of pair rats showed a significant increase in fear-related behaviors compared with saline-injected pair rats. Muscimol injection into single rats showed a significant reduction in the fear-related behavior compared with saline-injected single rats. Especially the mEPSC/mIPSC frequency ratio in the PL of mPFC in pair rats was significantly reduced compared with that in single rats. In addition, atosiban, oxytocin receptor antagonist, injected into pair rats showed a significant increase in fear-related behaviors and decrease in c-Fos expression like as single rats, whereas carbetocin, oxytocin receptor agonist, into single rats showed a significant reduction in the fear-related behavior and an increase in c-Fos expression like as pair rats. Taken together, our results suggest that pair exposure with conspecifics during fear-inducing situations induces social buffering, by contribution of the GABAergic system and oxytocin system in the mPFC.

Disclosures: M. Jang: None. **T. Jung:** None. **Y. Jeong:** None. **Y. Byun:** None. **J. Noh:** None.

Poster

P812. Social Cognition Circuits

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Program #/Poster #: P812.08

Topic: H.06. Social Cognition

Support: OG 01-122017
IZKSZ3_162109
100019_176016

Title: Cortical thinness underpins ingroup bias

Authors: *P. KANG[1], Y. SUN[2], Y. ZHOU[3], B. LINDSTROM[4], J. KIM[5], H. KIM[5], S. SUL[6], G. HEIN[3], P. N. TOBLER[1];
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Abstract: Ingroup bias is the tendency to favor ingroup members over outgroup members. It is pervasive in humans and occurs both with ad-hoc groups based on incidental aesthetic preferences and with longer-lasting and more coherent groups based on nationality or race. Although many neuroimaging studies investigated the neural mechanisms of ingroup bias, most of them focused on different neural activity elicited by ingroup versus outgroup conditions. In turn, little is known about the brain structures underpinning or protecting against ingroup bias. Here, we investigated whether the cortical thickness of brain areas thought to facilitate perspective taking (temporoparietal junction (TPJ)) and empathy (insula) accounts for individual variation in ingroup bias. Specifically, we combined two studies, performed in different countries, that tested attitudes towards ingroup and outgroup members. In Study 1, thirty three participants (17 female, 25.48±4.70 years old) from South Korea performed an implicit association task towards South (ingroup) and North Koreans (outgroup) with positive and negative words and rated the warmth and competence of South and North Koreans. We found that the cortical thickness of the right TPJ (rTPJ) was negatively correlated with ingroup bias (r =-.34 p=0.05). In Study 2, thirty Swiss participants (all males, mean age 22.74±2.75) rated how close they felt to other Swiss participants (ingroup) and to Middle Eastern immigrants (outgroup). We found that the difference in closeness rating between ingroup and outgroup (ingroup-outgroup) correlated negatively with rTPJ thickness (r =-.40, p=0.033). Together, our results suggest neural structures important for perspective taking contribute to overcoming ingroup bias. We plan to replicate these exploratory findings with an independent confirmation sample.

Disclosures: P. Kang: None. **Y. Sun:** None. **Y. Zhou:** None. **B. Lindstrom:** None. **J. Kim:** None. **H. Kim:** None. **S. Sul:** None. **G. Hein:** None. **P.N. Tobler:** None.

Poster

P832. Hippocampal Interactions I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.01

Topic: H.08. Learning and Memory

Support: R01 NS083402
R01 NS097610
R01 NS100019
R21 NS104293
R21 NS109894
RB21053
Carle Illinois Collaborative Research Seed Grant 083630

Title: Heterozygous loss of KCNQ2 impairs learning and memory in mice

Authors: *G. C. TRACY[1], A. R. WILTON[1], E. C. KIM[1], J. S. RHODES[2,3], H. J. CHUNG[1,3];
[1]Mol. and Integrative Physiol., [2]Dept. of Psychology, Univ. of Illinois At Urbana-Champaign, Champaign, IL; [3]Dept. of Neurosci., Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: Neuronal Kv7/*KCNQ* channels are voltage-gated, slow-activating, and non-inactivating potassium channels. They are critical for the inhibition of neuronal excitability by limiting the repetitive firing of action potentials (APs) and hyperpolarizing the resting membrane potential. Neuronal Kv7 channels are mostly heterotetramers of Kv7.2/*KCNQ2* and Kv7.3/*KCNQ3*. Dominant mutations in *KCNQ2* and *KCNQ3* cause diseases of hyperexcitability, such as Benign Familial Neonatal Epilepsy and Epileptic Encephalopathy. Kv7.2 channels are highly expressed in the hippocampus and cortex indicating a potential role in regulating hippocampal dependent learning and memory.Since mice administered scopolamine to model cognitive deficiencies saw a recovery of cognitive performance when administered XE991, a Kv7 channel antagonist, in this study, we test the hypothesis that a genetic decrease in Kv7.2 expression will lead to an improvement in learning and memory. To test this hypothesis, performed behavior tests with a genetic deletion of a single copy of the *KCNQ2* gene.Using heterozygous knock-out mice (*KCNQ2*$^{+/-}$) we performed learning and memory behavior tasks including the object location test (OLT), novel object recognition test (NORT), contextual fear assay (CF), and passive avoidance test (PA). KCNQ2$^{+/-}$ mice show a systemic reduction in *KCNQ2* expression while our lab has confirmed a reduction in membrane bound Kv7.2 channels in hippocampal neurons. For this study, male and female *KCNQ2*$^{+/-}$ and *KCNQ2*$^{+/+}$ mice performed the passive avoidance test and contextual fear test, which examine learning and memory function dependent on the hippocampus, neocortex, and amygdala. In PA, female *KCNQ2*+/- mice displayed a decrease in memory formation compared to female *KCNQ2*+/+ mice, while male mice showed no difference between genotypes. Male *KCNQ2*$^{+/-}$ show a trend towards a decrease in memory retention compared to male *KCNQ2*+/+ mice during PA while female mice showed no genetic difference in retention. Female mice overall showed increased memory retention over male mice in the contextual fear test. Using the tail flick assay we confirmed there was no difference in heat pain tolerance between *KCNQ2*$^{+/-}$ and *KCNQ2*$^{+/+}$ showing that pain tolerance should not affect foot shock response between the genotypes.In contrast to our initial hypothesis, these findings indicate that genetic down regulation of Kv7.2 impairs learning and memory in mice. This suggests that Kv7.2 could be a potential pharmacological target to treat cognitive impairment dependent.

Disclosures: G.C. Tracy: None. **A.R. Wilton:** None. **E.C. Kim:** None. **J.S. Rhodes:** None. **H.J. Chung:** None.

Poster

P832. Hippocampal Interactions I

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.02

Topic: H.08. Learning and Memory

Support: CMRPD1H0413
MOST 105-2320-B-182-040

EMRPD1I0501

Title: Follistatin mediates learning and synaptic plasticity via regulation of Asic4 expression in the hippocampus

Authors: *Y.-J. CHEN, S.-M. DENG, C.-H. TSAO, H.-W. CHEN, G.-J. HUANG;
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Abstract: Intellectual disability is also known as mental retardation, a disorder which may involve a delay in development or a learning disability. The mechanisms underlying learning disability have not been fully characterized. Mounting evidences have been suggested that learning abilities correlate with hippocampal neurogenesis. In this study, we used a high resolution method for identifying loci associated with neurogenesis by combining genetic mapping with sequencing information. We identified a candidate gene, follistatin (Fst), for further study due to its strong expression in the dentate gyrus. Mice with Fst deficient in the central nervous system exhibited impairments of hippocampal neurogenesis, dendritic spine densities, long-term potentiation (LTP), and spatial learning. To rescue the deficits in Fst KO mice, we injected AAV9 CMV::Fst viral vector into Fst KO mice hippocampi and found spatial learning abilities and LTP deficits could be recovered. Utilizing RNA sequencing, we identified Asic4 could be a possible gene regulated by Fst. With injection of AAV9 CMV::Asic4 viral vector in hippocampi, Fst KO mice improved the spatial learning and LTP abilities. Furthermore, we found that lasting high expression level of Fst in hippocampi could delay the cognition declination accompanying by aging. Here, we demonstrated hippocampal follistatain played a crucial role in cognitive function through changing the expression of Asic4.

Disclosures: Y. Chen: None. **S. Deng:** None. **C. Tsao:** None. **H. Chen:** None. **G. Huang:** None.

Poster

P832. Hippocampal Interactions I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.03

Topic: H.08. Learning and Memory

Title: The effects of ketamine or (2R,6R) hydroxynorketamine treatment on novel object placementtask performance and hippocampal AMPA receptor binding.

Authors: *R. MCNAIR[1], *R. MCNAIR[2], **A. KHAWAJA**[1], A. L. PEHRSON[3,4];
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Abstract: Many psychological and neurological disorders present with impaired cognitive function across multiple domains including learning and memory. These cognitive impairments greatly impact daily life functioning and are a major contributor to the economic burden associated with these disorders. Currently, there are few options treatment that effectively addresses these issues. Recent studies suggest that ketamine produces rapid and sustained changes in hippocampal synaptic plasticity, including increased long-term potentiation, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)

receptor expression or membrane insertion. Additionally, the ketamine metabolite (2R,6R) hydroxynorketamine (HNK) has been implicated as a mediator of ketamine's effects. These data may suggest that ketamine or HNK may have effects on hippocampus-dependent cognitive function 24 hours after a single dose, and the effects of these treatments on cognitive function have not been extensively characterized 24 hours after administration. We used 120 adult male Long Evans rats to investigate the effects of an intraperitoneal injection of vehicle, 3, 10, or 30 mg/kg ketamine (24 hr IP) or vehicle, 1, 3, or 10 mg/kg HNK (24 hr IP) on spatial memory performance in the novel object placement (OP) task, which depends critically on the function of the dorsal hippocampus. Immediately after completion of the OP task, we collected brain tissue in order to examine the effects of these treatments on AMPA receptor expression in the hippocampus using *ex vivo* autoradiography. In study 1, rats were randomly administered a dose of vehicle, 3, 10, or 30 mg/kg ketamine (24 hr IP), while in study 2 rats were randomly administered vehicle, 1, 3, or 10 mg/kg HNK. We found that ketamine treatment had no significant effect on spatial memory performance in the OP task, and had no effect on AMPA receptor expression as measured by EVA. Similarly, HNK treatment had no effect on OP treatment, but induced a small but significant increase in [^{3}H] AMPA binding at 10 mg/kg 24 hr IP. These findings suggest that ketamine and HNK have limited functional effects on hippocampally-dependent memory performance and hippocampal AMPA receptor binding 24 hours after treatment in healthy adult male rodents. Further research is needed to investigate the effects of these treatments in disease models featuring cognitive impairment in both male and female rats.

Disclosures: R. McNair: None. **A. Khawaja:** None. **A.L. Pehrson:** None.

Poster

P832. Hippocampal Interactions I

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Program #/Poster #: P832.04

Topic: H.08. Learning and Memory

Support: VA Merit Award - I01BX003195
NIH - UL1 TR002645
NIH - RO1 MH090127

Title: Hippocampal spatial learning deficits induced by chronic inflammation are mediated by 3-hydroxyanthranillic acid dioxygenase in young adult male mice

Authors: *M. N. MITHAIWALA[1], A. M. GARRISON[1], J. R. MORALES[1], A. M. VAIANA[1], S. E. H. KUHN[1], S. N. KHATRI[2], J. R. PUGH[2], J. C. O'CONNOR[1,3];
[1]Pharmacol., [2]Cell. and Integrative Physiol., UT Hlth. San Antonio, San Antonio, TX; [3]Res., Audie L. Murphy VA Hospital, South Texas Veterans Heath Syst., San Antonio, TX

Abstract: The hippocampus regulates several learning and memory processes. It is also particularly reactive to proinflammatory insults, having been described as a highly "immunovigilant" brain region. We have reported that acute peripheral immune challenge with lipopolysaccharide disrupts hippocampal cognitive performance in wild-type (WT) mice, but targeted deletion of 3-hydroxyanthranillic

dioxygenase (3-HAAO) prevented cognitive disruption. In this study, we hypothesized that structural alterations in the hippocampus following chronic inflammation precipitate spatial learning and memory deficits in a 3-HAAO-dependent manner. To this end, we induced chronic inflammation in male 3-6 month old WT or 3-HAAO knockout with *M. bovis*, BCG. We assessed short-term hippocampal working memory in the Y-maze and novel place preference task. Similar to our previous results following LPS, chronic inflammation induced deficits in WT mice but were absent in 3-HAAO mice. Additionally, we identified marked spatial learning deficits in the Barnes maze induced by infection with BCG in WT mice but not 3-HAAO null mice. To assess non-hippocampal learning, we measured fear-conditioning behavior, which is dependent on amygdala and found no deficits in freezing responses between WT and 3-HAAO mice with or without treatment with BCG. Moreover, we did not observe impairments in short-term or long-term contextual fear memory. Using Golgi-Cox staining, we determined that BCG treatment reduced dendritic spine density and neuronal complexity of CA1 apical dendrites independent of 3-HAAO genotype. Interestingly, BCG treatment significantly reduced hippocampal neurogenesis in a 3-HAAO dependent manner. Under whole-cell voltage clamp conditions, BCG treatment did not affect basal synaptic transmission properties of DG or CA1 neurons from the dorsal hippocampus. These results are the first to suggest that chronic inflammation alters hippocampal spatial learning by causing structural and functional disruption to the hippocampal network that are regulated by 3-HAAO activity and implicate quinolinic acid in regulation of neurogenesis in the adult hippocampus.

Disclosures: M.N. Mithaiwala: None. **A.M. Garrison:** None. **J.R. Morales:** None. **A.M. Vaiana:** None. **S.E.H. Kuhn:** None. **S.N. Khatri:** None. **J.R. Pugh:** None. **J.C. O'Connor:** None.

Poster

P832. Hippocampal Interactions I

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Program #/Poster #: P832.05

Topic: H.08. Learning and Memory

Support: NIH Grant R21MH105746
NIH Grant K01AG054729
NIH Grant P20GM113131
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Title: Neuronal Primary Cilia Regulate Hippocampal Neuronal Priming and Trace Memory Formation

Authors: *Y. ZHOU[1], X. CHEN[1], L. QIU[1], H. WANG[2];
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Abstract: Memory is thought to be encoded by sparsely distributed neuronal ensembles in memory-related regions. We utilized a deep-brain *in vivo* calcium imaging to directly visualize real-time calcium dynamics in freely behaving animals, which were subjected to trace fear conditioning. We have reported that the overall activity levels of hippocampal neurons exhibit a right-skewed lognormal distribution, with a small group of highly active “primed neurons” preferably engaged in trace memory formation. This

study, along with other evidence, underscores the importance of neuronal priming for hippocampal memory formation. Primary cilia are microtubule-based sensory organelles present in most vertebrate cells including neurons. Malfunction of neuronal primary cilia is associated with many neurological disorders including cognitive impairment, intellectual disability, and neurodegeneration. It remains elusive how neuronal primary cilia regulate the activity of hippocampal neurons and hippocampus-dependent memory formation. We utilized IFT88- (a protein essential for ciliogenesis) floxed mice to conditionally ablate primary cilia, combined with *in vivo* calcium imaging and trace fear conditioning study or with EEG recording. Here we show that inducible IFT88 global KOs display a markedly impaired learning than their littermate controls. The overall activity levels of hippocampal neurons of the IFT88 global KOs are significantly decreased compared to controls. Moreover, the burst synchronization of primed neurons is drastically suppressed in IFT88 global KOs. Comparison of EEG recordings in the neocortex under isoflurane anesthesia indicates that temporal ablation of primary cilia in adult mice also drastically decreases overall brain excitability. Further, local ablation of neuronal primary cilia in hippocampal CA1 region also decreases hippocampal neuronal priming and trace memory-associated burst synchronization. Together, we conclude that ablation of neuronal primary cilia impairs trace fear memory by decreasing hippocampal neuronal priming and the formation of burst synchronization.

Disclosures: Y. Zhou: None. **X. Chen:** None. **L. Qiu:** None. **H. Wang:** None.

Poster

P832. Hippocampal Interactions I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.06

Topic: H.08. Learning and Memory

Title: The 5-HT6 receptor of hippocampus tone regulations both Short and Long Term Memory on memory consolidation and amnesia.

Authors: *G. LIY-SALMERON[1], L. APARICIO NAVA[2], R. TELLEZ[3], R. TELLEZ[3];
[1]Hlth. Sci. of UNIDEP, Tijuana, Mexico; [2]Neuropharm., CINVESTAV-IPN, mexico, Mexico;
[3]Chemestry, UNAM, mexico, Mexico

Abstract: To our knowledge, the intrahippocampal serotonergic 5-HT_6 receptor tone on memory and amnesia models remains unexplored. Hence, in the present work, we tested intrahippocampal administration of serotonin or 5-hydroxytryptamine (5-HT)$_6$ receptor experimental molecules with differential intrinsic activity. Methods: In the present study, Automatized Autoshaping memory task was used, useful measuring memory, neural markers, and pharmacological effects. We are hypothesizing that experimental molecules with differential intrinsic activity might reveal serotonergic tone. Particularly, intrahippocampal administration of 5-HT_6 receptor compounds with differential intrinsic activity (i.e., agonistic and antagonistic) might be evidencing a serotonergic tone via this receptor. Bilateral intrahippocampal dose-response curves show that administration of EMD386088 (10 and 100 μg) had no effect or (50 μg) decreased conditioned responses (CR) in short- and long-term memory (STM and LTM, respectively); while SB-399885 (10 or 100 μg) significantly decreased CR in STM and LTM (24 and 48-h) or (50 μg) had no effect; thus suggesting that there is a 5-HT_6 receptor tone regulating both STM and

LTM. Moreover, intrahippocampal inactive doses of EMD386088 (5 μg) plus SB-399885 (0.5 μg) did not affect STM and LTM; however, they partially or completely prevented the scopolamine or dizocilpine-induced amnesia. Thus confirming that both drugs exerted their effects through 5-HT_6 receptor and that there is a hippocampal serotonergic tone under amnesic states, similar to that striatal.

Disclosures: G. Liy-Salmeron: None. **L. Aparicio Nava:** None. **R. Tellez:** None. **R. Tellez:** None.

Poster

P832. Hippocampal Interactions I

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Program #/Poster #: P832.07

Topic: H.08. Learning and Memory

Support: NIH U01DA044339
NIH U01DA04163202

Title: Fear learning and acetylcholinesterase activity in the hippocampus differs by genetic background.

Authors: *P. GARCIA-TREVIZO[1], S. MOONEY-LEBER[2], D. ZEID[1], M. BOGUE[3], S. C. GRUBB[3], G. PELTZ[4], T. J. GOULD[1];
[1]Biobehavioral Hlth., The Pennsylvania State Univ., University Park, PA; [2]Psychology, Univ. of Wisconsin-Stevens Point, Stevens Point, WI; [3]The Jackson Lab., Bar Harbor, ME; [4]Anesthesiology, Perioperative and Pain Med., Stanford Univ., Palo Alto, CA

Abstract: The neurotransmitter acetylcholine plays an important role in the brain. Specifically, in the hippocampus, major processes involved in learning and memory are mediated by acetylcholine. Metabolism of acetylcholine by the primary enzyme acetylcholinesterase(AChE), can provide insights on how learning and memory processes are regulated. Knowing that contextual fear learning, a hippocampus-dependent task, differs by genetic background, we investigated acetylcholinesterase activity levels after fear conditioning in male 129S1/SvlmJ, 129S4/SvJaeJ, 129S8/SvEvNimrJ, A/J, AKR/J, BALB/cJ, BTBRT<+>ltpr3<tf>/J, C3H/HeJ, C57BL/6J, CBA/J, DBA/1J, DBA/2J, FVB/NJ, LP/J, MA/MyJ, NZB/BINJ, SJL/J, SM/J, SWR/J and 129S2/SvPasCrl mice. To assess region specificity, we collected and measured AChE levels in dorsal hippocampus, ventral hippocampus, and cerebellum. Additionally, we correlated our AChE activity with publicly available data from the Mouse Phenome Database (MPD). MPD results showed AChE levels in the dorsal hippocampus were correlated with 3 cognitive assessment errors in the Barnes Maze. For ventral hippocampus, AChE activity levels were correlated with emotional behavioral responses in cued fear testing, light-dark box and variants of the elevated maze. Additionally, findings demonstrated that AChE activity levels as well as fear learning varied by mouse strain in all three brain regions. Moreover, AChE levels in the dorsal hippocampus were negatively correlated with fear conditioning outcomes. Interestingly, AChE levels in the ventral hippocampus and cerebellum were not correlated with fear learning. Our results suggest that acetylcholinesterase activity modulates learning in dorsal hippocampus and demonstrates that dorsal hippocampus and ventral hippocampus are functionally distinct.

Disclosures: P. Garcia-Trevizo: None. **S. Mooney-Leber:** None. **D. Zeid:** None. **M. Bogue:** None. **S.C. Grubb:** None. **G. Peltz:** None. **T.J. Gould:** None.

Poster

P832. Hippocampal Interactions I

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.08

Topic: H.08. Learning and Memory

Support: AFOSR grant 20RHCOR04

Title: Vagus nerve stimulation in healthy male rats: Enhanced cognitive performance and hippocampal neuroplasticity

Authors: *L. OLSEN[1], R. MOORE[1], N. BECHMANN[1], S. CUNNINGHAM[1], V. ETHRIDGE[2], J. ROHAN[2], C. HATCHER-SOLIS[1];
[1]Air Force Res. Lab., Wright-Patterson AFB, OH; [2]Naval Med. Res. Unit Dayton, Wright-Patterson AFB, OH

Abstract: FDA approved vagus nerve stimulation (VNS) has been reported to improve learning and memory, but the mechanisms of this cognitive enhancement have yet to be elucidated. Behavioral performance, electrophysiology, and brain derived nerve growth factor (BDNF) expression were measured after VNS administration to investigate VNS mediated changes in cognition and hippocampal neuroplasticity. Healthy male Sprague-Dawley rats (N = 47) aged 10-12 weeks were implanted with a platinum/iridium electrode cuff around the unsheathed left VN. After recovery, successful implantation was confirmed using the cessation of breathing test and VNS was administered as fifteen 100 µs biphasic pulses at 30 Hz, 0.8 mA constant current every 18 seconds for 30 minutes. Novel Object Recognition (NOR) and Passive Avoidance Task (PAT) training was paired with VNS (N = 28). NOR and PAT testing was measured 24 hr after training and *post-mortem* tissue was collected 48 hr after VNS administration. Electrophysiology recordings were obtained using a microelectrode array system to assess functional effects on hippocampus slices 90 min after VNS (N = 19). All sham rats received the same treatment without VNS and experimenters were blinded throughout data collection/analysis. Stimulated rats exhibited enhanced memory performance in NOR ($p < 0.05$, n = 12) and PAT ($p < 0.05$, n = 14). Stimulated rats also exhibited enhanced hippocampal plasticity as an increase in long-term potentiation (LTP) from CA1 neurons was detected ($p < 0.05$, n = 7-12) 90 min after VNS. Immunohistochemical analysis of perfused and fixed hippocampal tissue from the behavioral experiments demonstrated an increase in BDNF expression in the CA1 ($p < 0.05$, n = 8-9) and CA2 ($p < 0.01$, n = 7-8) 48 hr after VNS, indicating that enhanced neuroplasticity can potentially be sustained for days after VNS administration. The results from this study suggest that VNS-induced cognitive enhancement may be due to increased hippocampal neuroplasticity during memory consolidation. Also, there is indication that a single session of VNS may lead to sustained enhancement of hippocampal neuroplasticity via increased neurotrophic factor expression. These findings significantly contribute to a better understanding of the interplay between VNS and hippocampal neuroplasticity, which may improve clinical utilization of VNS for cognitive enhancement.

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Poster

P832. Hippocampal Interactions I

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Program #/Poster #: P832.09

Topic: H.08. Learning and Memory

Support: R01MH108837
R01MH078064
F30MH122130
T32MH067564

Title: Cholinergic and Glutamatergic Subcortical Inputs to Dorsal Hippocampus Mediate Stress-Induced Generalization of Negative Memories

Authors: *L. REN[1], A. CICVARIC[2], H. ZHANG[2], M. MEYER[1], Z. PETROVIC[2], V. GRAYSON[1], A. L. GUEDEA[1], X. SUN[3], Y. LIN[4], J. M. RADULOVIC[2];
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Abstract: Memories have specific and general features, which allows them to inform behavioral responses in similar situations. However, these features can sometimes become excessively generalized to dissimilar situations, contributing to maladaptive behavioral responses. This is seen in memory overgeneralization, a key cognitive symptom associated with Major Depressive Disorder, Generalized Anxiety Disorder, and Post-traumatic Stress Disorder. Stress increases negative memory generalization through its interactions with dorsal hippocampal (DH) memory systems, though the mechanisms underlying this remain poorly understood. To better understand these processes, we developed a mouse model of stress-induced generalization of negative memories (SIG) to determine SIG's dependence on DH memory circuits and memory engram populations. Using this model along with chemogenetic and optogenetic approaches, we found that cholinergic medial septum (MS) inputs to the DH and glutamatergic ventral tegmental area (VTA) inputs to the DH are necessary for SIG, and stimulation of cholinergic MS inputs to the DH is sufficient to induce fear memory generalization. Moreover, using activity-dependent labeling of DH engram populations, we found that after stress, cholinergic septohippocampal inputs drive reactivation of dentate gyrus (DG) npas4-dependent ensembles that represent specific features of a fear-inducing memory. These findings suggest that SIG results in part from cholinergic-mediated enhanced retrieval of DG specific memory ensembles that interfere with ongoing behavioral responses. Altogether, these results provide mechanistic insights that can inform future therapeutic targets for treatment of memory overgeneralization.

Disclosures: L. Ren: None. **A. Cicvaric:** None. **H. Zhang:** None. **M. Meyer:** None. **Z. Petrovic:** None. **V. Grayson:** None. **A.L. Guedea:** None. **X. Sun:** None. **Y. Lin:** None. **J.M. Radulovic:** None.

Poster

P832. Hippocampal Interactions I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P832.10

Topic: H.08. Learning and Memory

Support: NSERC CGS-M [KM]
NSERC Discovery MOP 506730 [JCK]
CIHR MOP 507489 [JCK]

Title: Evaluating the role of hippocampal inputs to the mammillary nuclei in spatial memory

Authors: *K. MAR[1], J. C. KIM[2,1];
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Abstract: The mammillary bodies (MB) are implicated in processing spatial information however, the role of hippocampal (subicular) inputs to the MB has remained elusive. In the present study, we set the stage for an investigation into the role of subicular inputs to the MB in egocentric and allocentric navigation. We began by characterizing baseline behaviour of male and femaleC57BL/6 mice 1-3 months of age (n = 11) in an egocentric and allocentric spatial assay in a Barnes maze. To characterize baseline egocentric navigation, escape to a previously memorized shelter location was initiated under a red-light condition with an innately aversive auditory stimulus. We show that memory of the goal location can be encoded following a brief exploration of the shelter and that an animal's position relative to the shelter location is constantly updated for effective path integration at escape onset. To investigate allocentric navigation, mice were trained to navigate to a shelter location based on distal cues motivated by escape from the innately aversive brightly lit open field. Across training days, mice displayed a more robust memory for the shelter location compared to naive animals, suggesting animals are able to effectively utilize distal cues for goal-directed escape. In an effort to understand how subicular inputs are distributed within the MB we conducted an exploratory investigation into the anatomical connectivity using anterograde tracing methods. We found MB-projecting subicular neurons are organized topographically such that axons originating from the dorsal or ventral subiculum terminate in the dorsal or ventral portions of the medial MB respectively, with more posterior ventral subicular neurons projecting to more lateral regions of the MB. These parallel pathways may represent a functional differentiation of subicular inputs to the MB and suggest a potential role for the subicular-MB pathways in processing different types of spatial information that merits further investigation. In current experiments, we are using fibre photometry to characterize patterns of bulk activity from subicular terminals in the MB expressing Ca^{2+} indicators achieved by targeted injection of adeno-associated viral vectors in freely moving animals across both spatial assays.

Disclosures: K. Mar: None. **J.C. Kim:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.01

Topic: H.08. Learning and Memory

Support: NSERC Grant RG203596-13

Title: The role of adolescent omega-3 supplementation on visuospatial memory performance and cognitive flexibility: Sex- and age-specific effects

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Abstract: The adolescent period is known for increased neuroplasticity resulting in long-lasting changes to brain integrity and cognition. Additionally, diet plays an essential role in modulating plastic processes during this period. Research has shown omega-3 polyunsaturated fatty acid-rich diets to be linked with enhanced cognitive performance and attention. The goal of this study was to assess the impact of adolescent omega-3 supplementation on visuospatial memory abilities and cognitive flexibility of male and female rats during adolescence and adulthood. To do so, 64 Wistar rats (32 females, 32 males) were supplemented omega-3 rich fish oil (FO) or control soybean oil (CSO) daily by oral gavage (0.3ml/100g body weight) from post-natal day (PND) 28 to 47. Half of the animals in each group (n=8) underwent behavioural testing in the Barnes Maze (BM; 6 acquisition and 3 reversal learning sessions) immediately following the end of supplementation, while the other half underwent testing during adulthood (PND 90). Our results support FO supplementation to reduce the initial distance to find the hidden box compared to CSO-fed rats. As adults, rats used shorter distance to escape than juvenile rats, independently of sex and diet. Overall, distance to the hidden box decreased with trials for all groups. On days 2 and 5 of maze exposure, FO-males' performance was marked by slower travel speed compared to female counterparts during the second trial. When the hidden box was moved (reversal learning trials), rats showed improved performance over days, which was only observed upon re-exposure to the task (the daily trial 2). Overall, these preliminary findings support FO diet to display beneficial effects on cognitive performance, with increased cognitive benefits in females. Consistent with earlier studies, adult rats displayed shorter distance to reach the hidden box, which supports a more rapid acquisition of task contingencies compared to juvenile rats.

Disclosures: A. Morin: None. **M. Poitras:** None. **J. Raymond:** None. **H. Plamondon:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.02

Topic: H.08. Learning and Memory

Support: THC R01

Title: Prenatal cannabinoid exposure affects memory through altered glutamatergic and GABAergic receptor expression and function

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Abstract: With the increase in legalization of cannabis, prenatal exposure to cannabinoids has increased significantly and is expected to continue rising. Currently, there are no therapeutic approaches to treating cognitive deficits associated with prenatal cannabinoid exposure (PCE). This project aims to elucidate mechanisms by which PCE causes learning and memory deficits in offspring by assessing alterations in neuronal signaling regulated by excitatory NMDAR (N-Methyl D-Aspartate Receptor), AMPAR (α-Amino-3-Hydroxy-5-methyl-4-isoxazole Propionic acid), and inhibitory GABAAR (Gamma-Aminobutyric Acid receptor subtype A) interaction. Pregnant Sprague Dawley rats were orally gavaged with either sesame oil or 5mg/kg of pure synthetic α9-tetrahydrocannabinol (THC) from gestational day five to post-natal day 9 (GD5-PND9). In immunoblotting experiments performed on hippocampal synaptosomes, PCE offspring exhibited altered ratios of GluN1, GluN2A, and GluN2B-containing NMDARs, as well as GluA1 and GluA2-containing AMPARs, compared to vehicle-treated animals. To further evaluate if these changes in receptor expression translated into functional changes at the cellular level, we recorded whole-cell spontaneous currents from hippocampal pyramidal cells and field activity from hippocampal CA3-CA1 Schaffer collaterals in PCE offspring. Spontaneous postsynaptic currents driven by AMPAR, NMDAR, and GABAAR channels showed alterations in frequency and amplitude between PCE and control animals. PCE offspring also demonstrated impaired long-term potentiation (LTP), the cellular correlate of learning and memory, within CA3-CA1 signaling pathways. To summarize, our study highlights a substantial role of primary excitatory and inhibitory neurotransmitter receptors (AMPAR, NMDAR, and GABAAR) in controlling hippocampal memory deficits caused by prenatal exposure to cannabinoids.

Disclosures: K.U. Chowdhury: A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **W.D. Smith:** A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **K. McDonald:** A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **P.D. Pinky:** A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **S. Bhattacharya:** A. Employment/Salary (full or part-time):;

Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **M. Reed:** A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. **V.D. Suppiramaniam:** A. Employment/Salary (full or part-time):; Department of Drug Discovery and Development,Harrison School of Pharmacy, Center For Neuroscience Initiative, Auburn University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.03

Topic: H.08. Learning and Memory

Title: A portion of perigestacional drink consumption with sucrose alters learning and spatial memory in the juvenile progeny of Wistar Rats

Authors: *C. PEREGRINO-RAMIREZ[1], N. CORTES-ALVAREZ[2], R. PEDRAZA-MEDINA[1], C. VUELVAS-OLMOS[1], M. ORTIZ[1], J. GUZMAN-MUÑIZ[1], N. MOY-LOPEZ[1];
[1]Univ. of Colima, Colima, Mexico; [2]Dept. of Nursing and Obstetics, Univ. of Guanajuato, Guanajuato, Mexico

Abstract: In recent years, according from the ENSANUT 2018, 85.8% of the Mexican population over 20 years of age consumes soft drinks with a high amount of sucrose. Learning and memory are cognitive processes vulnerable to high sucrose intake during critical periods such as pregnancy and lactation. The objective of this research is to know the effect of sucrose consumption during the perigestacional period on learning and spatial memory of the juvenile progeny. Twelve female Wistar rats were randomized into two groups: control group [CG] (n = 6), and sucrose consumption group [GS] (n = 6). The CG and GS had *ad libitum* access to diet and standard water throughout the study, additionally, the GS had access for 2 hours a day to a bottle containing a solution of 10% sucrose weight volume in water. In the PND-90, the mating process was carried out. Both groups maintained their dietary regimen throughout the pre-pregnancy (PND 69-90), pregnancy (PND 90-111), and lactation (PND 111-132) periods. Offspring received water and food *ad libitum* throughout the experimental period. The pups were subjected to behavioral evaluation: Morris´s water maze (MWM), applied in PDN 29-34 (learning phase) and PDN-42 (memory); and Novel Object Test (NOT) applied in the PDD-41 (habituation) and PDN-42 (Evaluation). No significant differences were observed in maternal body weight of both groups, however, during the whole period, the food intake of GS was significantly lower than that of CG. In the MWM the GS had a

slower learning process than GC. In the NOT (1h, 2h & 4h), the GS only exhibit a preferential exploration of the new object during the 4h evaluation but not in the 1h & 2h; In contrast, the GC exhibited a significant preference in the two last periods of time (2h & 4h). The results suggest that consumption of sucrose (10%) during the perinatal period contributes to the non-preferential exploration of the new object of the GS, this can be interpreted as a possible alteration in learning & memory acquisition; in agreement with the results presented in the MWM that indicate impairments in learning.

Disclosures: C. Peregrino-Ramirez: None. **N. Cortes-Alvarez:** None. **R. Pedraza-Medina:** None. **C. Vuelvas-Olmos:** None. **M. Ortiz:** None. **J. Guzman-Muñiz:** None. **N. Moy-Lopez:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.04

Topic: H.08. Learning and Memory

Support: 1R15 AG060461-(01)

Title: Effects of developmental stage and allosteric AMPA receptor modulators on spatial memory in Juvenile Rats

Authors: *R. OGOE[1], N. R. MILL[1], S. GANJU[1], D. CHEN[1], J. A. PERDOMO[1], S. J. YOON[1], A. SARDANA[1,3], C. L. KIMBALL[1], N. VALIBEIGI[4], D. G. MCHAIL[1], T. C. DUMAS[2];
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Abstract: Cognitive health in adulthood and aging, in large part, is a function of proper maturation of forebrain neural systems. Hippocampal maturation is driven in part by modifications to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) at glutamatergic synapses. Circa the end of the third postnatal week in rodents, AMPAR composition shifts from containing primarily GluA1 subunits to predominantly GluA3 subunits and greater association with transmembrane regulatory proteins (TARPs). These changes lead to greater malleability of synaptic connections by lengthening excitatory synaptic responses and decreasing the threshold for the induction of long-term changes triggered by patterned activity. This receptor subunit switch and the accompanying physiological changes coincide with the emergence of more mature spatial navigation in rats. We have previously demonstrated that delivery of positive allosteric modulators of AMPARs (drugs that extend the excitatory synaptic responses) to rats younger than three weeks lowers the threshold for induction of activity dependent synaptic strengthening and produces more mature Y-maze alternation patterns. Electrophysiological studies revealed age-dependent effects of CX614 with rats older than three weeks showing a decrease in the rate of slow gamma oscillations, but younger animals displaying an increase in fast gamma power. However, limitations of the Y-maze preclude the ability to detect differential effects on spatial learning versus spatial memory. As such, we have expanded this research to include the Barnes Maze. Preliminary results from our research indicates that different dosages of the CX614 have divergent effects on spatial memory depending on the age of the rat (older or younger than one week). Higher doses led to fewer

search errors and shorter escape paths to the goal during learning trials for older rats. Our current research suggests a more mature search strategy during probe trials at high doses of CX614 in younger animals. We continue to build upon these findings to further elucidate how changes in AMPAR dynamics can modulate memory related circuit oscillations. Discoveries emerging from these studies shed light on the complex interaction of AMPAR structure and dynamics on spatial memory and learning can provide potential explanatory mechanisms for memory and learning deficits in neurodegenerative disorders. AMPAR dysfunction has been implicated in the etiologies of Alzheimer's Disease, Huntington's Disease, and Fragile X syndrome and these insights could provide possible avenues for improved targeted interventions.

Disclosures: R. Ogoe: None. **N.R. Mill:** None. **S. Ganju:** None. **D. Chen:** None. **J.A. Perdomo:** None. **S.J. Yoon:** None. **A. Sardana:** None. **C.L. Kimball:** None. **N. Valibeigi:** None. **D.G. McHail:** None. **T.C. Dumas:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.05

Topic: H.08. Learning and Memory

Support: Conacyt Postdoctoral scholarship to MOV 660096

Title: A high fat diet during pregnancy decreased expression of myelin and synaptophysin in the hippocampus and impair spatial learning in the offspring rats.

Authors: *M. ORTIZ-VALLADARES[1], S. RAMOS-MIRAMONTES[1], R. PEDRAZA-MEDINA[1], J. GUZMÁN-MUÑIZ[2], N. MOY-LÓPEZ[1];
[1]Univ. de Colima, COLIMA, Mexico; [2]Univ. de Colima, Colima, Mexico

Abstract: The vulnerable periods during the development of the central nervous system are sensitive to environmental aggressions since they depend on the temporal and regional appearance of critical development processes. Maternal exposure to a high-fat diet (HFD) can alter brain structure and function in offspring. In this study, we analyze the effects of maternal HFD on physical and cognitive development, myelin and synaptophysin optical density in the hippocampus, and memory (SM) and spatial learning (SL) of offspring. Eight litters were used, during gestation four mothers were fed a balanced diet (BD) and four with a high-fat diet. The SL was evaluated with the Morris water maze (MWM) at postnatal day (PD) 28 and the SM at PD42. At PD42, the offspring were sacrificed to take out the brains for myelin and synaptophysin immunohistochemistry and take blood samples for weighs glucose, cholesterol, and triglycerides levels. The results showed effects on physical development, the HFD group had an increased body weight from the fourth week ($p<0.05$), this correlates with food consumption where a significant increase in consumption was observed until the third week ($p<0.01$), in contrast to the BD group. The serum levels only showed increased glucose by the HFD group. Similarly, the HFD group had longs latencies on MWM but not showed significant differences in the memory test. The optical density results revealed decreased expression of myelin on dentate gyrus and corpus callosum

($p<0.01$) and, decreased synaptophysin expression on CA3 and dentate gyrus to hippocampus ($p<0.01$). The results suggest that an inadequate diet as an HFD during pregnancy affects the cognitive development of the offspring and alters to myelination process that could have a relationship with neuronal functionality communication and impairment in synaptophysin expression.

Disclosures: M. Ortiz-Valladares: None. **S. Ramos-Miramontes:** None. **R. Pedraza-Medina:** None. **J. Guzmán-Muñiz:** None. **N. Moy-López:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.06

Topic: H.08. Learning and Memory

Support: University of Guanajuato Grant 2019

Title: High-fat and combined high-fat-high-fructose diets impair episodic-like memory and decrease glutamate and glutamine in the hippocampus of adult mice

Authors: *M. SOLIS-ORTIZ[1], S. DIAZ-CINTRA[4], L. A. REYES-CASTRO[5], C. SANDOVAL SALAZAR[2], J. RAMÍREZ EMILIANO[6], H. MARTÍNEZ OROZCO[3];
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Abstract: Diet-induced obesity is associated with premature cognitive decline and neurodegenerative diseases. Elevated consumption of fats and sugars in human and rodents has been associated with deficits in recognition memory, which is modulated by the hippocampus. Alterations in excitatory and inhibitory neurotransmitters in this area have been observed after hypercaloric diets, but the effects on episodic-like memory are not conclusive. To investigate the effects of hypercaloric diets on memory and their relationship with γ-aminobutyric acid (GABA), glutamate and glutamine in the hippocampus. A control diet (CD), a high-fat diet (HFD) and a combined high-fat-high-fructose diet (HFFrD) were administered to 30 adult mice for 10 weeks. The discrimination indexes and exploration time of the novel object recognition (NOR) task were evaluated, and GABA, glutamate and glutamine concentrations were obtained from the hippocampus. The HFFrD induced lower discrimination indexes, decreased exploration time in the recognition memory task, and lowered the concentrations of glutamate and glutamine in hippocampus. The discrimination indexes of the NOR task were negatively correlated with glutamate in the HFFrD group. These findings suggest that a dysfunction in the hippocampal glutamate and glutamine may underlie the episodic-like memory deficits in mice fed HFFrD diets.

Disclosures: M. Solis-Ortiz: None. **S. Diaz-Cintra:** None. **L.A. Reyes-Castro:** None. **C. Sandoval Salazar:** None. **J. Ramírez Emiliano:** None. **H. Martínez Orozco:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

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Program #/Poster #: P839.07

Topic: H.08. Learning and Memory

Support: Grants from the Ministry of Education, Culture, Sports, Science and Technology (JP17H02188)
Japan Society for the Promotion of Science (JP15K12703)
Research Funding for Longevity Science from the National Center for Geriatrics and Gerontology, Japan

Title: Irs2 deficiency accompanied by type 2 diabetes exerts a negative impact on hippocampal-dependent cognitive function

Authors: D. TANOKASHIRA[1], W. WANG[1], M. MARUYAMA[1], C. KUROIWA[1], M. F. WHITE[2], ***A. TAGUCHI**[1];
[1]Natl. Ctr. for Geriatrics and Gerontology, Obu, Japan; [2]Boston Children's Hospital, Harvard Med. School,, Boston, MA

Abstract: Metabolic disturbances, such as insulin resistance, hyperglycemia, and obesity are associated with an increased risk of cognitive impairment and dementia, including Alzheimer's disease (AD). Insulin/IGF1 signaling mediated by insulin receptor substrate 2 (IRS2) regulates homeostasis of nutrients including glucose. Male mice lacking IRS2 display severe type 2 diabetes mellitus (T2DM), characterized by hyperglycemia and insulin resistance, which promotes premature death. We found that young adult male mice lacking IRS2 on a C57BL/6J genetic background ($IRS2^{-/-}$/6J) survived in different experimental environments. Therefore, our study investigated whether IRS2 deficiency-induced T2DM affected hippocampus-associated cognitive function in young male mice. IRS2 deficiency led to aberrant alterations in energy and nutrient sensors in the hippocamps of young male mice with T2DM. Moreover, inactivation of IRS2 in mice reduced core body temperature accompanied by abnormal change in the temperature sensor in the brain. Finally, male mice lacking IRS2 exhibiteddecreased spontaneous activity, an increase in anxiety-like behavior, and impairment of hippocampus-dependent spatial memory. These results suggest that IRS2 deficiency accompanied by T2DM causes impairments of brain energy metabolism and thermoregulation and exerts a negative impact on hippocampal-dependent emotional responses and spatial memory during young adulthood.

Disclosures: D. Tanokashira: None. **W. Wang:** None. **M. Maruyama:** None. **C. Kuroiwa:** None. **M.F. White:** None. **A. Taguchi:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P839.08

Topic: H.08. Learning and Memory

Support: NSERC

Title: Estrogenic protection against dorsal hippocampal D2-type dopamine receptor antagonism in gonadectomized male and female mice

Authors: *N. BASS, M. HICKEY, S. VAN DEN BERGHE, E. CHOLERIS;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Social learning is an evolutionarily adaptive form of learning that may be defined as learning that occurs during social interaction and/or social observation (Galef, 1998). The underlying neuroregulatory mechanisms of social learning are poorly understood and may be tested in mice by utilizing the social transmission of food preference (STFP) paradigm. Multiple systems including the dorsal hippocampus (HPC), estrogens, progesterone, dopamine (DA) and more recently androgens, have been implicated in the STFP. Specifically, dorsal HPC infusions of the D2-type DA receptor antagonist raclopride blocked social learning in gonadectomized male and female mice but not their gonadally intact counterparts suggesting an interaction between dorsal HPC D2-type DA receptors and gonadal hormones during social learning in mice (Bass et al., 2019). This research intends to identify the *specific* hormone(s) involved. In males, gonadal testosterone may act at either androgen receptors (directly) or estrogen receptors, following aromatization to estrogens. In addition, the enzyme 5a-reductase can convert testosterone to the potent androgen dihydrotestosterone (DHT) which also acts on the androgen receptor. In study 1, we implanted subcutaneous slow releasing silastic capsules of either estradiol benzoate (EB) or sesame oil in castrated (CAS) male “observer” (OBS) mice, and in study 2 ovariectomized (OVX) female OBSs received similar hormone treated. Later studies investigate the role of progesterone and DHT hormone replacement in gonadectomized OBSs. OBSs received bilateral infusions of the D2-type DA receptor antagonist raclopride (18 µg/µL for OVX OBSs or 20 µg/µL for CAS OBSs) into the dorsal HPC 10-minutes prior to a 30-minute social interaction with a recently fed, same-sex, familiar “demonstrator” (DEM) followed by an 8-hour OBS choice test. Social learning is determined if OBSs prefer the DEM diet when given the choice between two novel diets. Findings revealed that long term EB treatment protects against the impairing effects of raclopride on social learning in CAS and OVX (preliminary) mice. These findings suggest a possible interaction between dorsal HPC D2-type DA receptors and estrogen receptors in the regulation of social learning in male and female mice.

Disclosures: N. Bass: None. **M. Hickey:** None. **S. Van Den Berghe:** None. **E. Choleris:** None.

Poster

P839. Hippocampal Interactions: Development and Sex Differences

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Program #/Poster #: P839.09

Topic: H.08. Learning and Memory

Support: Wallenberg Foundation
Vetenskapsrådet 2018-00660
Tore Nilsons Stiftelse för medicinsk forsking

Title: Hippocampal interleukin-6 affects mnemonic functions and emotionality in a sex-dependent manner

Authors: *F. LONGO[1,2], M. ASKER[1,2], O. A. E. ABUAMRA[1], J. E. RICHARD[1], S. BÖRCHERS[1,2], J.-P. KRIEGER[1], K. P. SKIBICKA[1,3,2];
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Abstract: Interleukin (IL)-6 is a central player in the pathogenesis of inflammatory conditions and has been increasingly recognized as a key contributor to central nervous system (CNS) pathophysiology in both adult and developing brain. IL-6 dysregulation contributes to the pathogenesis of a wide range of neuropsychopathologies including autism spectrum disorders (ASD), schizophrenia, and cognitive decline. Recently, increased CNS IL-6 levels were linked to the long-term effects of COVID-19 infection including sleeping difficulties, memory performance, depression, and anxiety. To date, the specific molecular mechanisms, and the brain region through which central IL-6 modulates emotional and cognitive function and exerts its metabolic effects remain poorly understood. The ventral hippocampus (vHPC) represents a critical brain region for the control of memory processes and regulation of emotional/affective behaviors. We found that both IL-6 and IL-6 receptors are expressed in the hippocampus, potentially indicating that local hippocampal IL-6 is positioned to affect hippocampal function. Here we propose that CNS IL-6 contributes to emotional and cognitive behavior through its production, release and action within the vHPC. To evaluate this, we used both neuropharmacological and virogenetic manipulations to alter IL-6 levels in the vHPC of male and female rats. Microinjections of IL-6 into the vHPC impairs memory acquisition and memory retrieval only in female rats, as indicated by reduced novel object exploration in the novel object recognition (NOR) test and reduced ability to locate the platform in Morris water maze (MWM) test. Conversely, reducing hippocampal IL-6 by infusion of the adeno-associated virus (AAV)-siRNA-IL-6 into the vHPC resulted in facilitation of learning and memory process in the NOR and MWM test. Moreover, reduced vHPC IL-6 expression improved anxiety-like and depression-like behavior. Taken together, these results provide new insight into the role of CNS IL-6 highlighting its ability to modulate hippocampus-dependent mnemonic process and affective behaviors in the vHPC. Future studies will evaluate the physiological and pathophysiological conditions, like viral infections or obesity, resulting in activation of this local hippocampal IL-6 actions.

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Poster

P862. Inhibitory Microcircuits and Memory

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P862.01

Topic: H.08. Learning and Memory

Support: JST ERATO (JPMJER1801)
the Institute for AI and 591 Beyond of the University of Tokyo
JSPS Grants-in-Aid for Scientific Research (18H05525)

Title: Preceding inhibition organizes hippocampal spike sequences

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Abstract: Neuronal spike times are essential for neural coding (Buzsáki et al., 1994; Ferster and Spruston, 1995; Singer, 1993). A subset of neurons often emits a series of action potentials and generate sequential activity. The spike times of neurons during sequential activity are regulated at the millisecond level while preserving flexible modifications to embody diverse sequence patterns. Such spike sequences are exemplified by memory replays during sharp wave–ripples (SWRs) (Buzsáki, 2015). Hippocampal pyramidal cells are sequentially activated during exploration or learning, and these spike sequences are subsequently reactivated in time-compressed manner during SWRs while the animal is immobile or asleep (Lee and Wilson, 2002). This internal replay of sequential activity during behavior has been thought to contribute to memory consolidation, memory recall, and navigational planning (Carr et al., 2011; Ólafsdóttir et al., 2018). In spite of these critical roles, the mechanism for enabling such flexible spike sequencing remains to be clarified. In this study, we conducted *in vivo* whole-cell recordings simultaneously from up to three CA1 pyramidal cells and examined the mechanisms underlying flexible spike sequences at the single-cell level. We found that neurons were transiently hyperpolarized prior to SWRs. The pre-SWR hyperpolarizations varied in magnitude across SWR events and individual neurons, and later spike times during SWRs were preceded by larger pre-SWR hyperpolarizations. Intracellular blockade of Cl^--mediated inhibition eliminated the pre-SWR hyperpolarizations and advanced the spike times, indicating that GABAergic inputs underlie the pre-SWR hyperpolarizations and delay spike times. These results suggest that pre-SWR inhibition coordinates the sequential spike times of CA1 pyramidal cells and diversifies the repertoire of sequence patterns.

Disclosures: A. Noguchi: None. **Y. Ikegaya:** None.

Poster

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Topic: H.08. Learning and Memory

Support: Canadian Institutes of Health Research (CIHR)
Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Episodic-like memory related activity of hippocampal VIP interneurons in freely behaving mice

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Abstract: Most of the hippocampal vasoactive intestinal polypeptide (VIP) expressing interneurons (INs) specifically target inhibitory neurons, providing a disinhibitory mechanism for ungating the external inputs onto excitatory neurons. CA1 VIP INs have been shown to aid spatial learning and memory but their role in episodic memory is yet unknown. To address this subject, first, we employed a series of behavioral paradigms to assess various aspects of episodic memory and then a unified paradigm to examine What-Where-Which episodic-like memory. Second, we simultaneously performed in vivo calcium imaging of CA1 VIP INs activity in freely behaving mice using wireless fiber photometry. We found that VIP INs were routinely active in all memory tasks throughout the entire period of exploration. During object exploration periods, VIP INs showed evenly balanced rising and dropping activity patterns, which evolved over the course of the object familiarization. Further, examining VIP INs' activity during various behavioral states revealed distinct activity patterns and higher calcium transients (CaTs) during grooming periods than object exploration and rearing. Additionally, grooming-associated CaTs showed a robust correlation with the duration of grooming. Taken together, these results indicate that VIP INs help to encode novelty during episodic-like memory and certain aspects of behavioral states. Ongoing analysis of VIP INs' activity and experiments using behavioral state-dependent optogenetic perturbations will help us better understand the contribution of disinhibitory interneurons in hippocampal memory processing.

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Poster

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Support: NIH Grant NS116589
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Title: The role of inhibition in shaping hippocampal memory encoding sequences

Authors: *J. TAXIDIS[1], B. A. MADRUGA[2], E. PNEVMATIKAKIS[3], M. Z. LIN[4], P. GOLSHANI[5]; [2]Physics, [1]UCLA, Los Angeles, CA; [3]Ctr. for Computat. Biol., Flatiron Institute, Simons Fndn., New York, NY; [4]Neurobio., Stanford, Stanford, CA; [5]UCLA Dept. of Neurol., Los Angeles, CA

Abstract: Hippocampal spiking sequences can encode external sensory cues and internally link them by tiling the gaps in time between them, tracking the passage of our experiences. But the population dynamics of these sequences are unknown. We employed *in vivo* two-photon calcium imaging in the mouse CA1, during learning of an olfactory delayed non-match-to-sample task (DNMS). We previously described pyramidal cell (PY) spiking sequences composed of 'odor-cells' encoding specific olfactory

stimuli, followed by 'time-cells' encoding time-points in the ensuing delay period after a cue. Odor-cells retained robust and stable fields across days and alterations in the trial structure, whereas time-fields were unstable and readily remapped. During DNMS learning, the number of time-cells increased while odor-cells remained fixed (Taxidis et al., Neuron, 2020). What is the role of feedback inhibition by parvalbumin- (PV) or somatostatin-expressing (SOM) interneurons (IN) in shaping these sensory and temporal representations? By expanding our previous analyses to calcium traces from GABAergic cells, we found that a subset of IN yielded significant odor- and time-fields, collectively forming odor-specific sequences. These 'odor-IN' and 'time-IN' had lower odor-selectivity and noisier activation than PY, yielding poor odor-decoding. Moreover, odor-IN had more stable fields than time-IN, as in PY, but those remapped more than PY fields across days or trial alterations. Importantly, unlike PYs, the number of time-cell INs did not increase during learning. Finally, through *in vivo* high-frequency voltage imaging, using the ASAP voltage indicator, we recorded action potentials and subthreshold membrane dynamics from multiple PV- and SOM-expressing IN during DNMS performance. We followed the same cells across multiple days, before and after DNMS training. We found that IN firing rates increased, on average, during locomotion and confirmed that they exhibited odor-fields with reduced odor-specificity compared to PY. Increased spiking during odor-presentation was accompanied by higher theta power in subthreshold traces. Conclusively, PV and SOM interneuronal ensembles in CA1 provide timed but not cue-specific inhibition, potentially increasing the signal-to-noise-ratio of PY sequences by silencing the rest of the PY population.

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Poster

P862. Inhibitory Microcircuits and Memory

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NIMH5R01MH094705-04 (to ZJH)

Title: Axo-axonic inhibition controls flexible feature coding in the hippocampus

Authors: *B. DUDOK[1], M. SZOBOSZLAY[2], A. PAUL[4,5], P. M. KLEIN[1], Z. LIAO[2], E. HWAUN[1], G. G. SZABO[1], T. GEILLER[2], B. VANCURA[2], B.-S. WANG[4], S. MCKENZIE[6,7], J. HOMIDAN[1], L. KLAVER[8], D. F. ENGLISH[8,7], Z. J. HUANG[9,4], G. BUZSAKI[7], A. LOSONCZY[2,3], I. SOLTESZ[1]; [1]Dept. of Neurosurg., Stanford Univ., Stanford, CA; [2]Dept. of Neurosci., [3]Mortimer B. Zuckerman Mind Brain Behavior Inst., Columbia Univ., New York, NY; [4]Cold Spring Harbor Lab., Cold Spring Harbor,

NY; [5]Dept. of Neural and Behavioral Sci., Penn State Col. of Med., Hershey, PA; [6]Dept. of Neurosciences, Univ. of New Mexico, Albuquerque, NM; [7]NYU Neurosci. Inst., New York Univ., New York, NY; [8]Sch. of Neurosci., Virginia Tech., Blacksburg, VA; [9]Dept. of Neurobio., Duke Univ. Sch. of Med., Durham, NC

Abstract: Hippocampal pyramidal cells (PCs) exhibit location-specific spiking patterns (place fields), which have been implicated as the neural basis of a cognitive map of space. The key subcellular compartment for PC action potential generation is the axon initial segment (AIS), which is under exclusive GABAergic control by the 'chandelier' or axo-axonic cells (AACs). On the basis of *in vitro* studies, it has been suggested that chloride-conducting GABAA receptors on the AIS may increase or decrease PC firing, depending on the state of the innervated PCs. Despite the presumed key role of AACs in controlling action potential initiation and timing, the *in vivo* characteristics of AAC activity dynamics and their effect on PC spiking and place fields remained unknown.
We have used fluorescence- and electron microscopy, *in vitro* and *in vivo* electrophysiology, as well as *in vivo* calcium imaging and optogenetics to characterize a transgenic mouse line (Unc5b-CreER) for the inducible labeling of AACs in adult mice of both sexes. We show that AACs in the hippocampal area CA1 of head-restrained mice are synchronously activated by episodes of locomotion, and by whisking during rest. Optogenetic intervention experiments with large-scale electrophysiological (silicone probe) or optical (two-photon calcium imaging) recording of PC activity illustrated that AACs exert inhibitory effects on CA1 PCs in awake, behaving mice, compared to controls. Specifically, extracellular field potentials evoked by optogenetic AAC activation indicated a net inhibitory postsynaptic effect in the pyramidal layer, and photostimulation resulted a transient reduction in average PC spiking, without triggering synchronous network events. Optogenetic inhibition of AACs, in contrast, resulted in increased PC activity, suggesting that natural AAC activity is tonically suppressing PC spiking. Finally, location-specific AAC inhibition induced novel, persisting place fields near the stimulus location in mice performing a random foraging task on a linear treadmill, demonstrating a critical role of AACs in regulating hippocampal place field remapping. These results together demonstrate brain state-specific dynamics of a critical inhibitory controller of cortical circuits.

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Poster

P862. Inhibitory Microcircuits and Memory

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Topic: H.08. Learning and Memory

Support: NIH/NINDS NS104828

Title: Stratum Lacunosum-moleculare Interneurons of the Hippocampus Coordinate Memory Encoding and Retrieval

Authors: J. GUO[1], H. OLIVEROS[1], S. OH[1], B. LIANG[2], Y. LI[1,2], E. T. KAVALALI[3], D.-T. LIN[2,3], ***W. XU**[1];
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Abstract: Encoding and retrieval of memory are two processes serving distinct biological purposes but operating in highly overlapping brain circuits. It is unclear how the two processes are coordinated in the same brain regions, especially in the hippocampal CA1 region where the two processes converge at the cellular level. Here we find that the neuron-derived neurotrophic factor (NDNF)-positive interneurons at stratum lacunosum-moleculare (SLM) in CA1 play opposite roles in memory encoding and retrieval. These interneurons show high activities in learning and low activities in recall. Increasing their activity facilitates learning but impairs recall. They inhibit the entorhinal- but dis-inhibit the CA3- inputs to CA1 pyramidal cells and thereby either suppress or elevate CA1 pyramidal cells' activity depending on animals' behavioral states. Thus, by coordinating entorhinal- and CA3- dual inputs to CA1, these SLM interneurons are key to switching the hippocampus between encoding and retrieval modes.

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Poster

P862. Inhibitory Microcircuits and Memory

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Program #/Poster #: P862.06

Topic: H.09. Spatial Navigation

Support: NIH 1R01MH124867
NIH 5U19NS104590

Title: Large-scale AOD-based two-photon imaging of CA2/3 inhibitory network dynamics during spatial navigation

Authors: B. VANCURA[1], A. D. GROSMARK[2], *A. LOSONCZY[3], T. GEILLER[1];
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Abstract: The hippocampus is a mammalian brain region responsible for spatial navigation and episodic memory. Both the rapid initial encoding and the consolidation of recently acquired memories are thought to rely critically on the CA2/3 subregions, but precisely how the *in vivo* dynamics of CA2/3 neurons support these cognitive processes remains unknown. In particular, inhibitory GABAergic microcircuits within CA2/3 are hypothesized to regulate many aspects of circuit function that may be critical for memory encoding and consolidation, including the regulation of synaptic plasticity and the generation and control of extracellular network oscillations. However, most available data on the anatomy and physiology of hippocampal inhibitory circuit elements comes from the CA1 subregion. It thus remains unknown how generally the conclusions from CA1 apply to upstream CA2/3, and in particular whether and to what extent the *in vivo* dynamics of CA2/3 interneurons differ from their CA1 counterparts. To close this gap, here we utilize large-scale, AOD-based two photon functional calcium imaging in

combination with *post-hoc* immunohistochemistry to characterize the activity patterns of molecularly-identified CA2/3 interneurons during spatial navigation and awake sharp-wave ripples (SWRs). We observe both region- and subtype-specific differences in interneuron recruitment during behavior, including differences in locomotion modulation, spatial tuning, and responses to contextual manipulations. These results suggest that both the molecular subtype of a given interneuron and its location within the hippocampal network together determine its functional properties during behavior.

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Poster

P862. Inhibitory Microcircuits and Memory

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Topic: H.08. Learning and Memory

Support: NIH Grant1F30MH125638
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Title: Integration of sensory and temporal information in CA3 during working memory

Authors: *S. CHEUNG[1], C. C. DORIAN[3], K. SAFARYAN[2], J. TAXIDIS[1], P. GOLSHANI[4]; [2]Departments of Physics and Astronomy, Neurology, Neurobio., [1]UCLA, Los Angeles, CA; [3]Univ. of California Los Angeles, Los Angeles, CA; [4]UCLA Dept. of Neurol., Los Angeles, CA

Abstract: Memories are temporally organized. When we recall an event, we also recall the relative timing it was experienced. How does the brain compute and store this temporal representation of memory? The hippocampus is a key region for these computations as hippocampal CA1 or CA3 lesions cause impaired coding of sequential events separated by time. The hippocampus bridges stimuli-free gaps between sequential events through neural ensembles that fire sequentially during the delay. These “time cells” fire sequentially encoding successive moments during the delay. Recent work from our lab has shown that the CA1 region of the hippocampus contains neurons that display stimulus-specific sequential firing patterns during the delay period of an olfactory working memory task. CA1 largely lacks recurrent connectivity, so it is unlikely that it generates these sequential firing patterns on its own. CA3 is an upstream region with direct connections through the Schaffer collaterals to CA1, has extensive recurrent connections and is therefore a candidate region that generates these stimulus-specific sequential firing patterns. CA3 also receives input from the lateral entorhinal cortex, which processes nonspatial sensory information and receives direct connects from the olfactory bulb. Given the unique attributes of CA3, we propose that CA3 is where sensory and temporal information is integrated and then this code is passed onto CA1.Using chronic in vivo two-photon calcium imaging, we monitored CA3 neuronal population activity during a delayed non-match-to-sample (DNMS) olfactory working memory task. We have identified stimulus-specific sequentially firing cells that tile the delay period of the DNMS working memory task. We propose that these cells generate robust representations of stimulus-specific time that is

then passed onto CA1 cells. These findings will lay the groundwork for understanding how elements of a memory are unified and coded within CA3 as dynamic attractors.

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Poster

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NIH F31MH117892

Title: Signatures of rapid synaptic learning in the hippocampus during novel experiences

Authors: *J. B. PRIESTLEY[1], J. BOWLER[2], S. V. ROLOTTI[1], S. FUSI[1], A. LOSONCZY[1]; [1]Neurosci., [2]Neurobio. and Behavior, Columbia Univ., New York, NY

Abstract: Neurons in the hippocampus exhibit striking selectivity for specific combinations of sensory features, forming representations which are thought to subserve episodic memory. Even during a completely novel experience, ensembles of hippocampal “place cells” are rapidly configured such that the population sparsely encodes visited locations, stabilizing within minutes of the first exposure to a new environment. What cellular mechanisms enable this fast encoding of experience? Here we leverage virtual reality and large scale neural recordings to dissect the effects of novelty and experience on the dynamics of place field formation. We show that the place fields of many CA1 neurons transiently shift locations and modulate the amplitude of their activity immediately after place field formation, consistent with rapid plasticity mechanisms driven by plateau potentials and somatic burst spiking. These motifs were particularly enriched during initial exploration of a novel context and decayed with experience. Our data suggest that novelty modulates the effective learning rate in CA1, favoring burst-driven field formation to support fast synaptic updating during new experience.

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Poster

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Program #/Poster #: P862.09

Topic: H.08. Learning and Memory

Support: HHMI

Title: An entorhinal cortex instructive signal shapes experience-dependent CA1 representations

Authors: *C. GRIENBERGER[1,2], J. C. MAGEE[1];
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Abstract: A crucial function of the brain is to produce useful representations of the external world. Previous results demonstrate that a non-Hebbian type of synaptic plasticity, behavioral timescale synaptic plasticity (BTSP), has a fundamental role in novel place field formation in hippocampal area CA1. BTSP has several distinct characteristics, including that it is driven by dendritic plateau potentials (plateaus) instead of APs. As axons from layer 3 entorhinal cortex (EC) impinge onto the site of plateau initiation and their activity regulates plateau probability, we hypothesized that this EC input might shape CA1 representations during learning. To test this hypothesis, we used two-photon calcium imaging in mice exploring a novel linear track for the first time. We observed the experience-dependent development of place cell representations in CA1, which featured an increased place field density (2-3x) around the reward location. Several findings implicated BTSP: (1) the abrupt appearance of new place cells; (2) the width of the new fields was correlated with the animal's running speed during induction; (3) new fields were shifted forward in space with respect to their induction; (4) the development of the representation was severely attenuated by plasticity and calcium spike blockers, APV and SNX-482. We next performed two-photon calcium imaging of layer 3 EC axons. Individual axon activities fell into three categories, axons that were positively or negatively velocity-tuned and untuned axons. We further found the average population activity to be constant throughout the linear track. However, correcting for the spatial profile of running speed revealed that the EC input rate (df/f per cm) was elevated around the reward location by a factor of 2-3. This result suggests that the EC may provide a signal to CA1 capable of increasing plateau probability and BTSP-driven new place field formation around the reward location. To test this hypothesis, we optogenetically reduced EC axon activity around the reward and this abolished the reward site-associated increase in place field formation. Furthermore, we modified our behavioral learning task in order to generate a peak in EC input at a second location away from the reward site. This manipulation produced a significantly higher number of place fields in this location. Taken together, these two pieces of evidence indicate that EC activity is both necessary and sufficient to shape CA1 population activity. Our results identify the layer 3 entorhinal cortex input as a key signal that instructs CA1 neurons in how to represent an environment.

Disclosures: C. Grienberger: None. **J.C. Magee:** None.

Poster

P862. Inhibitory Microcircuits and Memory

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Program #/Poster #: P862.10

Topic: H.09. Spatial Navigation

Support: NIH 1R01MH124867
NIH 5U19NS104590

Title: Population dynamics underlying sharp-wave ripple formation in 3D imaged, molecularly identified CA2/3 interneurons

Authors: *B. VANCURA[1], T. GEILLER[1], A. LOSONCZY[2], A. D. GROSMARK[2];
[2]Neurosci., [1]Columbia Univ., New York, NY

Abstract: The CA2/3 network of the hippocampus is critical for mammalian cognition through both the initial encoding and the subsequent consolidation of episodic memories. The consolidation process is thought to occur largely during sharp-wave ripples (SWRs), fast oscillatory network events initiated by the synchronous activation of CA2/3 pyramidal neurons coordinated by strong inhibitory feedback signals. During SWRs, the time-compressed reactivation of behaviorally-relevant neural trajectories in the hippocampus is thought to underlie the transfer of nascent memories to the neocortex for long-term storage. Despite the significance of SWRs, the circuit mechanisms supporting their formation and maintenance remain only partially understood, largely because the single-cell and population-level activity patterns of identified cell types within the CA2/3 microcircuit during SWRs remain unknown. Here, we take a step towards a mechanistic understanding of SWR formation by utilizing AOD-based two-photon calcium imaging, in combination with simultaneous LFP recordings and post-hoc immunohistochemistry, to provide the first description of the dynamics of populations of simultaneously imaged, molecularly-identified CA2/3 interneurons during physiologically identified offline states. Through these methods we describe the unique CA2/3 inhibitory patterns which predict, and then evolve during, awake SWRs.

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Poster

P871. Grid Cells

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Kavli Foundation

Title: Large-scale two-photon calcium imaging in freely moving mice

Authors: *W. ZONG, H. OBENHAUS, E. SKYTØEN, H. ENEQVIST, N. JONG, M. JORGE, M.-B. MOSER, E. I. MOSER;
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Abstract: New generations of portable microscopes for calcium imaging enable observation of activity in hundreds-to-thousands of neurons while animals perform experimental tasks, allowing researchers to identify the underlying neural dynamics and computational algorithms, goals that would be out of reach if cells were recorded one by one or a few at a time. For high-resolution imaging *in vivo*, investigators have mostly relied on stationary benchtop two-photon (2P) microscopes where mice are head-fixed under the objective. However, head-fixed protocols are suboptimal for studies of self-guided non-stationary behavior such as navigation, and they preclude, to a large extent, the identification of cells that are inherently spatial in their firing patterns, and that depend on proprioceptive-vestibular information, which is compromised by head-fixation. Due to the unsuitability of benchtop imaging for behavior that requires voluntary movement, investigators have tried, for almost two decades, to develop miniature 2P microscopes - 2P miniscopes - that can be carried on the head of freely moving animals. Early versions of 2P miniscopes did not catch on, however, because they lacked the capacity to image sensitive calcium indicators such as GCaMP6, because their scanning speed was slow, because the miniscopes were heavy and difficult to carry for rodents, or because optical cables were stiff and inflexible. These constraints motivated the development of a new generation of 2P miniscopes (Zong, et al.,2017, Zong, et al.,2021) with 2P benchtop-comparable resolution, fast speed, *z*-scanning capability and large field of view (FOV). However, while these 2P miniscopes represented major advances in imaging quality, their applicability in tasks that require movement remains limited, due to heavy weight, stiff optical cable and low cell yield. We developed a new portable 2P microscope (MINI2P) for fast high-resolution calcium imaging of over 1,000 neurons at a time. Behavior of MINI2P-carrying mice was indistinguishable from that of untethered unimplanted animals on half-hour free-foraging trials. With successive recordings from matrices of neighboring regions, more than 10,000 neurons could be imaged. These advances were achieved through a new optical system design with an increased FOV, a novel technique for successive imaging of adjacent FOVs, a new micro-tunable lens that increased the Z-scanning speed and range, lighter weight, and a new type of flexible connection cable. Large-scale recordings were obtained from visual cortex, medial entorhinal cortex, and hippocampus, and neurons with strong spatial tuning were shown in all areas, including visual cortex.

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Poster

P871. Grid Cells

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Title: Grid cell modules remain coordinated after neural activity is dissociated from external sensory cues

Authors: T. WAAGA[1], ***H. AGMON**[2], V. NORMAND[1], A. NAGELHUS[1], R. GARDNER[1], M.-B. MOSER[1], E. I. MOSER[1], Y. BURAK[2,3];
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Abstract: The representation of an animal's position in the medial entorhinal cortex (MEC) is distributed across several modules of grid cells, each characterized by a distinct spatial scale. The population activity within each module is tightly coordinated, and jointly restricted to a two dimensional toroidal manifold, which is preserved across environments and behavioral states. Little is known, however, about the coordination of activity patterns across modules. We analyzed the joint activity patterns of hundreds of grid cells, simultaneously recorded in animals that were foraging in light and complete dark conditions to eliminate visual cues. We found that the states of different grid modules are tightly coordinated, even in darkness, when the internal representation of position within the MEC deviates substantially from the true position of the animal. These findings suggest that internal brain mechanisms dynamically coordinate the representation of position in different modules, to ensure that grid cells jointly encode a coherent and smooth trajectory of the animal.

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Poster

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Title: A novel theta-rhythmic directional signal in entorhinal cortex

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Abstract: A large proportion of cells in the medial entorhinal cortex and parasubiculum (MEC/PaS) show tuning to the animal's head direction (HD), but are distinguished from HD-tuned cells in other regions by their broad tuning curve shapes and their strong theta-modulation. These unique characteristics may indicate that these cells are actually not truly tuned to HD, but rather represent a distinct directional signal correlated with HD. Motivated by this hypothesis, we used Neuropixels silicon probes to record large populations of MEC/PaS cells (n≈1000 per session) in rats exploring 2-D and 1-D environments.
We applied a Poisson Gaussian process latent variable model (P-GPLVM) to population spike trains of MEC/PaS cells, and thus extracted a novel latent directional signal which we term "internal direction" (ID). When we compared cells' relative tuning strength to ID and HD, we found that ID- and HD- tuned cells were from largely non-overlapping populations: ID-preferring cells were more strongly theta-modulated and had broader HD tuning curves than HD-preferring cells.
The extracted ID latent variable displayed unique temporal dynamics which distinguished it from HD. ID was distributed bimodally relative to the animal's head direction, and over consecutive theta cycles it systematically alternated between pointing to the animal's left and right side. Left/right alternation (LRA) was most reliable when the animal ran directly towards a goal in the open-field foraging task - however, we observed the same result on a linear track, where left- and right-going trajectories do not represent possible future paths. Therefore, it appears that ID does not directly represent ongoing or future navigation behaviour.
If LRA is a fundamental characteristic of ID, it may be expected to occur also during REM sleep, when activity in the hippocampal-entorhinal circuit is entirely internally-driven. Indeed, we found that REM contained periods of sustained LRA highly similar to wake, in agreement with the idea that LRA is an intrinsic property of the networks responsible for generating ID.
In summary, we discovered ID, a novel directional signal with theta-rhythmic, left-right-alternating dynamics. The ID signal might be used as a directional input to the grid cell network to generate theta sweeps in arbitrary directions (Gardner et al., this session).

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Poster

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Title: Coordinated direction- and position-coding dynamics during grid-cell theta sweeps

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Abstract: During alert states, place- and grid-cell activity is temporally organized within theta waves, which travel from dorsal to ventral poles of the hippocampal-entorhinal system. Neural activity in each theta cycle represents a stereotyped spatial trajectory ("sweep") which travels outwards from the animal's location. It has been proposed that grid cells contribute to generating sweeps, because some theoretical models allow grid cells to generate arbitrary linear trajectories from a directional input. A candidate for this directional input is the "internal direction" (ID, see Vollan et al., this session) represented by cells in medial entorhinal cortex and parasubiculum (MEC/PaS). To investigate this possibility, we examined population recordings of position- and direction-modulated cells in MEC/PaS. Recordings were obtained in rats exploring 2-D and 1-D environments, implanted with Neuropixels silicon probes.
Supposing that ID were the directional driving input for sweeps, ID dynamics should be aligned with the directions of sweeps. We therefore applied a Poisson Gaussian process latent variable model to extract the latent 2-D position representation in the open field. Sweeps, evident as linear trajectories radiating outwards from the animal's location, were reliably aligned to ID. Sweeps were most strongly represented by burst-firing, position-modulated cells, which included grid cells and conjunctive grid-by-direction cells. Furthermore, ID was aligned to grid-cell sweeps during REM sleep, suggesting that grid dynamics may be constitutively coupled with ID across all conditions.
Examining single modules of grid cells revealed that each module represented a restricted segment of the population sweep, with the segment length proportional to the grid spacing. This scale relationship, combined with sequential activation of modules associated with the dorsoventral travelling theta wave, allows for the joint activity of multiple modules to represent a single coherent trajectory.
Finally, if sweeps are generated by grid cells, the periodic nature of the grid pattern may allow sweeps to extrapolate beyond the limits of the physical environment. When we examined 2-D latent position, we observed that, during sweeps which were directed towards nearby environmental boundaries, the latter portion of the sweep represented unvisited, out-of-bounds locations.
In conclusion, we show that coordinated activity of ID and grid cells is consistent with the hypothesis that sweeps are generated by MEC/PaS circuits using ID input: sweeps are reliably aligned to the ID signal, and occur with highly stereotyped geometry independently of the physical context.

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Poster

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Title: Toroidal topology of population activity in grid cells

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Abstract: Entorhinal grid cells, so-called because of their hexagonally tiled spatial receptive fields, are organized in modules which, collectively, are believed to form a population code for the animal's position. One major debate revolves around the possible mechanisms that may underlie the grid pattern. Although multiple alternatives have been hypothesized, the stability of the correlation structure of the activity of grids cells, across environments and arousal states, has favoured a class of recurrently connected models known as continuous attractor networks (CANs). However, because previous samples of co-recorded grid cells have been small, it has remained unclear whether grid cell networks exhibit continuous attractor dynamics, and if so, how such dynamics interface with environmental cues.
Here, we apply topological data analysis to simultaneous recordings of hundreds of grid cells, and show that joint activity of grid cells within a module lies on a toroidal manifold, consistent with a two-dimensional CAN. Each position of the animal in its physical environment maps to a single location on the torus, and each grid cell is preferentially active within a single "field" on the torus. Toroidal firing positions persist between environments, and between wakefulness and sleep - as predicted by CAN models, but not by feed-forward models which generate grid patterns from external inputs by means of Hebbian plasticity.
Finally, we compare the toroidal tuning of three distinct grid-cell subtypes which differ in burst-firing, theta-modulation and spike-waveform characteristics, and we show that the toroidal representation is preferentially carried by a population of burst-firing, weakly-theta-modulated grid cells. Conjunctive grid-by-direction cells also demonstrated selectivity to the torus, but more weakly, in accordance with the higher dimensionality of the conjunctive code.
In conclusion, our present observation of grid-cell ensemble dynamics on a toroidal manifold constitutes the first population-level description of CAN dynamics in grid cells.

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Poster

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Title: Behaviour Of Medial Entorhinal Cortex Cells During A Radial Eight Arm Maze Task

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Abstract: Across species the medial temporal lobe region of the brain is known to be involved in spatial navigation. Historically the grid cells of the medial entorhinal cortex (mEC) have been of interest. Their (relatively) rigid, grid-like firing pattern has played a significant role in furthering our understanding of how space is represented in the brain. The mEC, however, has a myriad of other very interesting cells that exhibit spatial properties but are not grid per say. The role of these non-grid spatial cells during navigation is still not well understood. In addition, the mEC has been shown to replay independently of the hippocampus. The role of this independent replay is as yet unknown. The aim of the project is to elucidate the role of this replay and to understand how different cell types in the mEC behave differently during a complex navigation task.
We performed multichannel, extracellular electrophysiology on 4 adult, male Long Evans rats while they performed a radial eight arm maze task. The rats were implanted with microdrives targeting the dorsal CA1 and layers II/III of the mEC. The rats performed an eight arm maze task where, everyday, they were expected to learn which 3 arms (out of the 8 arms) were rewarded. Each trial started with a delay of 1min. Animals performed 30 trials per day. The recorded data was preprocessed and putative single units were isolated using a semi-automated clustering algorithm. All further analysis was then performed on these isolated units using custom code.
We establish how the different kinds of spatial cells in the mEC behave during this task. We show how grid and non-grid spatial cells behave differently at different phases during the task - during the 1min delay period, during the first half of the learning block (when the animal is still learning the reward locations and makes mistakes) and during the second half of the learning block (once the animal has learnt the reward locations). We show how at key moments of immobility (when the animal is at the centre - a decision point; or when the animal is at a reward location) the trajectory replayed by mEC cells isn't always the same as that replayed by hippocampal CA1 cells. Here we show what the role of the independent replay and the non-grid spatial cells of the rodent medial entorhinal cortex is during complex spatial navigation tasks. These results are a demonstration of the influence of non-geometric factors on the firing properties of the mEC space coding cells. The results also demonstrate how the independent replay in the mEC could be part of a parallel memory formation circuit in the brain.

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Poster

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Title: Out of place: the anticipatory nature of the hippocampal cognitive map

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Abstract: The hippocampal formation contains a variety of spatially sensitive neurons, thought to form key components of the cognitive map. As a rat moves throughout an enclosure, place cells fire at particular locations, while grid cells fire at each vertex of a triangular grid tiling the entire enclosure. The firing patterns of these cells are normally viewed as functions of an animal's current position. Previous studies have shown that these cells are biased towards encoding position prospectively, as they mostly fire spikes just before the animal moves through the cell's preferred spatial location(s). On shorter timescales, grid cells have been suggested to fire in both prospective and retrospective modes.
We analysed the firing patterns of grid cells and place cells, simultaneously recorded in freely moving rats. We shifted each cell's spike times by fixed intervals back and forth along the animals' trajectories, to see if this sharpened the resulting rate maps. Both types of cells exhibited prospective coding, firing ~100 ms before the animal entered a cell's preferred location. When co-recorded, grid cells generally have smaller time-shifts than place cells (median 80ms and 160ms respectively). There was also no clear correlation between time-shifts in co-recorded grid cells and place cells, suggesting that this prospective offset is not coordinated between the hippocampus and the entorhinal cortex.
To explain the heterogeneity of these time-shifts, we looked at their relationship to the local field potential (LFP) theta rhythm (7-12 Hz). Many grid and place cells exhibit theta precession, where spikes fall on progressively earlier theta phases as the animal traverses a firing field. We found that place cells that are more strongly locked to theta phase show larger time-shifts. We also looked at whether the heterogeneity in these shifts could be explained by latent variables acting at shorter timescales. Such variables may cause momentary fluctuations in the apparent time-shift of a cell's firing, which would be obscured by averaging across a recording session. We expected prospective shifts to correlate between consecutively traversed grid fields. However, we found no evidence for correlated fluctuations in prospective time-shifts.
We conclude that grid cells and place cells show predominantly prospective coding. We conjecture that the difference between their time-shifts reflects a flow of information from place cells to grid cells. These results also suggest that particular phases of the theta rhythm are associated with prospective coding.

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Poster

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Title: Egocentric tuning in hippocampal neurons: Using simulations to estimate misclassification rates

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Abstract: Navigation relies on the integration of incoming sensory information with a stable schema that can be applied to map the current environment. This integration results in a dynamic map of the animal's position based on coordinate systems which have origins centered either on the navigator him/herself (egocentric) or on some distal, world-centered cue (allocentric). In open-field recordings from the hippocampus, neurons have typically been understood to represent information within an allocentric frame of reference, whereas the investigation of spatial information in egocentric reference frames in this brain structure has received little attention. Here, in agreement with previous work (Sarel et al., 2017; Jercog et al, 2019); any other), we find indications for modulation of place cell activity by egocentric bearing using previously defined methods for detection in real data from open field environments. However, our findings also raise the possibility that activity in hippocampal neurons may often be falsely attributed to egocentric orientation as a result of tuning to related covariates. By developing a simulation framework composed of functional cell types with various kinds of spatial tuning and by applying large populations of these simulated neurons to egocentric classification methods, we find higher than expected false positive rates among simulated neurons not tuned to egocentric orientation. False positive rates vary across cell types, behavioral sessions, noise levels, and firing field sizes, pointing to factors that might potentially account for misattribution to egocentric tuning in experimental studies. We propose here that with simple improvements in experimental design and analysis, such issues can be mediated. Further, we suggest that such studies of potential confounding factors should be investigated prior to data collection.

Disclosures: J. Carpenter: None. **J. Blackstad:** None. **B. Dunn:** None. **E.I. Moser:** None. **M. Moser:** None.

Poster

P873. Spatial Memory and Navigation in Humans

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Title: Probing neural representations of spatial memory and navigation in the human hippocampus and thalamus with augmented reality in the real world

Authors: *S. MAIDENBAUM[1], V. KREMEN, JR[2], A. PATEL[5], K. MILLER[2], J. VANGOMPEL[2], B. BRINKMANN[3], V. SLADKY[3], G. A. WORRELL[4], J. JACOBS[6];
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Abstract: Spatial memory and navigation are a crucial part of our lives. However, neural research on spatial navigation and rehabilitation in humans is typically limited by our current imaging technologies. Conventional human brain imaging methods, such as fMRI, MEG or ECoG, do not allow subjects to freely move around a spatial environment, thus limiting the realism of tasks. Other brain recording methods, such as EEG or fNIRs, allow increased mobility but do not offer the signal quality or coverage of deep brain regions.
To address these concerns, we studied data from a rare set of patients (N=4) with drug resistant mesial temporal lobe epilepsy, who were implanted with invasive neural stimulator (INS) enabling continuous wireless brain recording (investigational Medtronic Summit RC+STM), which allowed them to move and navigate completely freely in a real-world spatial environment. We targeted main deep brain structures in the temporal lobe, hippocampus (Hc) and anterior nucleus of thalamus (ANT) bilaterally. To probe the neural basis of real-world navigation in these participants, we designed a custom Augmented Reality (AR) spatial memory task. In this task, augmented treasure chests were placed throughout the room the patient was in. In each trial the patient had to memorise the location and content of the object inside each chest. Then, following a distractor task patients were cued by object and had to return to the location where that object was previously found. Each trial included 4 chests in different locations and patients received feedback after every trial. We also ran this paradigm on a group of healthy participants (N=24) to establish a baseline.
Both healthy participants and patients performed the task significantly well. Patient results were similar to those of the healthy control participants, and both were twice as the baseline established for this task in virtual reality in previous work. In the neural recordings from the patients we found increased oscillatory power in the theta band (5-8Hz) by movement and by task stage. We also found a significant modulation of theta oscillatory power by movement direction in the patients' anterior thalamus. Our findings validate that integrating AR with chronic neural implants can lead to improved techniques for spatial memory research, more precisely identifying movement-related neural signals and revealing new directional neural representations.(note that authors 1 and 2 contributed equally to this work, as did authors 8 and 9)

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Poster

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Title: The influences of immersive virtual-reality experience on brain activity of spatial navigation: an fMRI study

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Abstract: Spatial navigation is recognized to involve the multiple cognitive processes of guiding and determining the trajectory between focusable elements within cognitive maps of a specific environment. Animal and human neuroimaging studies have suggested that the hippocampus and associated brain regions are critical for neural computation of cognitive maps and serve as neural substrates underlying successful spatial navigation. In this human neuroimaging study, we used functional magnetic resonance imaging (fMRI) to investigate whether and how the sustained experiences of using immersive virtual reality with a head-mounted display (HMD) influence the neural processing of visuo-spatial navigation. Thirty-six immersive virtual reality users (VR group) and thirty-eight healthy adults without VR experiences (Non-VR group) were instructed to perform a virtual maze-like task and control task for navigating a virtual environment during fMRI scanning. Behavioral results showed no significant differences in findings landmarks in the virtual environment during maze-like task between VR and non-VR group. The whole-brain fMRI analysis, however, showed that VR group had reduced neural activation in hippocampus, cerebellum, posterior parietal cortex, and supplementary motor area, probably indicating a more efficient spatial-navigation brain network for performing VR-based maze task. Our fMRI results suggested that the sustained experiences in practicing VR may modulate the neural substrates underlying successful spatial navigation and the findings provide supportive evidence for neural efficiency mechanism of the human brain in spatial navigation.

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Poster

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Title: Sex Differences in Head Direction Signals When Learning a Complex Environment

Authors: *Y. CHENG[1], E. R. CHRASTIL[2,1];
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Abstract: Sex differences have frequently been reported in human wayfinding, but it is unknown whether there are sex differences in head direction signals when navigating in a complex environment. In an fMRI study, we tested 105 participants (55 males, 50 females) in a cardinal-direction-aligned virtual maze. The navigation task consisted of an exploration phase and a test phase. During the 16-minute exploration phase, participants freely explored to find 9 objects located in the environment and were instructed to remember their locations. During exploration, participants made decisions about where to go next while they were stationary at each intersection. The program then showed movement going forward to the next location. For each of the 48 test trials, participants started at one object and were directed to go to another object, without feedback and with a limited time. We conducted an intra-subject multivariate pattern classification for the four head directions (north, south, east, west) in five a priori regions of interest (ROIs): thalamus, retrosplenial cortex, precuneus, extrastriate cortex, and early visual cortex. Our analysis focused on the stationary decision-making period during the exploration phase, parsed by sex. For people who completed the experiment, we were successfully able to discriminate between head directions in early visual cortex in females (n = 45) and in thalamus and precuneus in males (n = 53). Classification strengths in precuneus were higher in males than females. 7 participants (2 males, 5 females) dropped out during the test phase due to motion sickness. There were some indications that head direction classification strength differed for males with motion sickness compared to those without. Overall, this study indicates that there are sex differences in basic head direction signals during navigation. In particular, the head direction signals during stationary decision-making indicated that the ROIs where the classifier could successfully discriminate between the four directions differed between males and females. These findings suggest the primary building blocks of navigation have early differences that differ by sex, which could affect later navigational abilities.

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Poster

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Topic: H.09. Spatial Navigation

Title: Hippocampal-dependent navigation strategies are associated with increased vicarious trial-and-error in human virtual navigation

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Abstract: Vicarious trial-and-error (VTE) in rodents occurs during deliberation between potential options and is associated with hippocampal activity. VTE is also associated with the use of spatial (e.g.

allocentric, flexible) navigation strategies in rodents, and VTE-like behavioral measures have been observed in humans using allocentric strategies in virtual navigation tasks. To determine if VTE is related to the use of hippocampal-dependent strategies in humans, we examined performance in two radial maze tasks (the 4 on 8 Virtual Maze, 4/8 VM, and the Concurrent Spatial Discrimination Learning Task, CSDLT) developed by our lab to assess the use of hippocampal-dependent memory in healthy adults. Both the 4/8 VM and CSDLT begin with a dual-solution phase, where either spatial (e.g. "choose the path next to the mountain") or nonspatial (e.g. "choose the left path") strategies can be used to find objects hidden in the radial maze paths. After reaching criterion performance, probe trials (removing the extramaze cues in the 4/8 VM, shifting the arms presented in the CSDLT) are administered to assess the use of hippocampal-dependent spatial strategies, and the 4/8 VM also includes a strategy assessment based on the participant's self-report. In a sample of undergraduates and Amazon Mechanical Turk workers tested on the 4/8VM (n = 521, 258 females), and the CSDLT (n = 140, 69 females), measures of VTE were associated with the use of hippocampal-dependent strategies in both tasks on probe trials, and with self-reported use of spatial strategies on the 4/8 VM. VTE was attenuated, but remained elevated, when distal cues were removed during the 4/8 VM probe trial, indicating that VTE was not simply related to scanning the environment for landmarks. Under dual-solution conditions, VTE in participants using spatial strategies was elevated in the first trial of the CSDLT, and throughout the 4/8VM. These behavioral patterns parallel imaging studies, indicating that elevated VTE is observed in spatial learners in each task when hippocampal activity is elevated, suggesting that episodes of VTE may serve as a behavioral index of hippocampal activation as spatial navigation strategies are employed.

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Poster

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Title: Medial temporal codes for distorted spatial memory during virtual navigation

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Abstract: As we navigate through the world, we pick up on spatial patterns of locations we encounter. Our prior work has shown that human navigators use such patterns when searching for new locations. How memories of individual past locations are influenced by this pattern extraction process remains unknown. In statistical learning tasks, spatially co-occurring objects are later judged as being closer together in space, suggesting a hypothesis by which extracting spatial patterns during navigation may distort individual locations to be remembered as closer together than reality. These distortions may

originate in the medial temporal lobe, and the hippocampus in particular, which has been linked to both statistical learning and spatial navigation. To test these predictions, we recruited nine epilepsy patients implanted with intracranial electrodes for seizure monitoring. They performed a virtual navigation task in which they moved through a circular, beach-themed arena and learned five locations, with each location marked by a uniquely colored disk. At the beginning of each training trial, participants saw a color word prompt, informing them of the disk color they were going to find. The disk then appeared in the arena and they navigated to it. After repeatedly navigating to each location across training trials, participants completed a test phase. On each test trial, participants again saw a color prompt, but the arena remained empty with no disk appearing. They were instructed to navigate to the remembered location of the cued disk, providing an estimate of its location based on training. Applying an inverted encoding model to intracranial EEG data collected concurrently, we reconstructed spatial representations of the five learned locations from oscillatory activity in the hippocampus. Variation in the reconstructions corresponded to differences in spatial error during the test phase, as well as to a behavioral spatial pattern bias from the distribution of locations. Thus, we show that "place codes" for learned locations can be reconstructed from local field potentials in human hippocampus, and that these reconstructions are subject to cognitive biases acquired during spatial learning.

Disclosures: K.N. Graves: None. **B.E. Sherman:** None. **I.H. Quraishi:** None. **E.C. Damisah:** None. **N.B. Turk-Browne:** None.

Poster

P873. Spatial Memory and Navigation in Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P873.06

Topic: H.09. Spatial Navigation

Support: NIH U01 Grant NS121472
McNair Foundation

Title: Human single neuron activity encodes future trajectories

Authors: *T. DONOGHUE[1], S. E. QASIM[1], A. PATEL[1], H. AZAB[2], E. H. SMITH[3], R. MATHURA[2], J. MYERS[2], A. ANAND[2], J. ADKINSON[2], H. G. REY[2], J. D. ROLSTON[4], T. E. J. BEHRENS[5], M. BOTVINICK[6], S. A. SHETH[2], J. JACOBS[1];
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Abstract: Navigating through the world, including tracking current location in the environment and using this information to make decisions and move through the world according to one's current goals, is an important task to thrive in dynamic environments. While much prior work has demonstrated how the medial temporal lobe encodes spatial information, including place cells which contain information about one's current location in space, it is unclear how such representations relate to navigational goals and contribute to upcoming decisions. Related to this, in rodent work, place cells have been reported to

encode current positions while also being modulated by future trajectories. To investigate whether this kind of encoding can also be found in humans, we recorded single-neuron activity from the medial temporal lobe and surrounding ventral prefrontal cortex in neurosurgical patients who performed a virtual spatial-navigation and memory task. In this task, subjects navigate a fixed-track virtual world and, at a navigation choice point, are instructed to alternate between choosing to go down either the left or right side of the track. In addition to having to remember previous trajectories, patients are also engaged in a spatial memory task in which they have to learn and then later retrieve the location of treasure chests along the track. By analyzing single-neuron activity while subjects navigate this virtual world, we find both 'place' and 'distance' cells, whose firing reflects spatial position and distance along the track, respectively. In addition, we find 'splitter' cells, whose firing rates are modulated by the future trajectory of the subject, including both 'splitter place cells', in which cells have differential firing at a particular location along the track as subjects move that reflects future left or right turns, and 'splitter time cells', in which cells have differential firing for future left and right turns at particular times during the stationary pause period in which subjects are making the navigation decision. Our results demonstrate how spatial encoding relates to current context and future decisions with human subjects engaged in a complex spatial navigation and memory task. This finding suggests that single neuron activity in human medial temporal lobe and surrounding areas not only encodes one's current position in space, but also systematically relates to upcoming choices about future actions and upcoming trajectories, suggesting these cells are likely involved in processes such as planning and decision making.

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Poster

P873. Spatial Memory and Navigation in Humans

Location: Virtual Only

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Program #/Poster #: P873.07

Topic: H.09. Spatial Navigation

Support: Institute for Collaborative Biotechnologies
California Nanosystems Institute

Title: The relationship between hippocampal subfield volumes and human spatial navigation

Authors: *A. S. TU, C. MCINTYRE, E. R. CHRASTIL;
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Abstract: Navigation is a critical skill, important for finding resources and returning to safe locations. Despite its importance, there are large individual differences in human navigation ability. Although studies in navigation experts and older populations have shown a relationship between overall hippocampal volume and navigation ability, this relationship in the healthy, young adult population has recently been called into question. The medial temporal lobe (MTL) regions of the brain, specifically the

hippocampus, relate to learning and memory ability and can aid in successful navigation. However, there are mixed findings on whether volumes of certain hippocampal subfields can explain the variability in navigational performance across the young adult population. This study tested the abilities of 25 young adults to successfully navigate a new virtual desktop maze environment. After freely exploring the maze for 16 minutes, participants were asked to go from one object in the maze to another, while taking the shortest route. T1-weighted, T2-weighted, and high-resolution T2 MRI brain images were collected and automatically segmented into four hippocampal subfields and three adjacent MTL regions via the Automatic Segmentation of Hippocampal Subfields (ASHS) pipeline. The volumes of the segmented hippocampal regions were then used to measure whether individual regions within the hippocampus correlate with navigation ability. We theorize that successful navigation of this maze involves pattern separation ability, since many of the hallways look similar, and participants needed to discriminate between partially overlapping routes to reach the target. Thus, we hypothesize that the Cornu Ammonis 3 (CA3) and Dentate Gyrus (DG) regions, which have been shown to be involved in pattern separation ability, will be correlated with individual differences in navigation of this population. If pattern separation is not important, we still predict that the CA1, CA2/3, and DG volumes are correlated with navigation performance due to their relations with recall of target objects. Our findings suggest that subfield volumes - not overall hippocampal volume - are informative to understanding the link between brain and navigation behavior in the healthy, young adult population.

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Poster

P873. Spatial Memory and Navigation in Humans

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Program #/Poster #: P873.08

Topic: H.09. Spatial Navigation

Support: NIH Grant 1-R21AG063131

Title: Creatures of habit? Examining navigation strategies across the lifespan

Authors: *P. MAXIM, S. D. MOFFAT, T. I. BROWN;
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Abstract: How we navigate our world depends on many factors, however not everyone holds equal expertise or ability. Research suggests that aging negatively impacts flexible navigation performance, perhaps in part due to memory integration and route memory deficits, so it is imperative we understand how memory influences navigation strategies and what factors lead to navigation differences as we age. The present study tested young adults (YA, 18-40) and older adults (OA, 65-80) across two days in a virtual navigation task. Participants are trained on specific paths through six virtual towns, and after a 24-hour period, are tested during fMRI on their memory of these now-familiar routes (FR). Participants are then given novel goals and permitted to reach the goal using any strategy (unbound to the FR). Some trials are designed so that the optimal route (OR, optimal shortcut) follows the same direction as the FR (forward-shortcut), while in others the OR requires traveling backward relative to the direction of the FR

(backward-shortcut) - i.e., greater heading conflict between OR and FR. The relationship between strategy (familiar vs. shortcut) and execution (efficiency of strategy) is not clear-cut. Preliminary analyses show no significant differences in navigation strategy and efficiency between age groups for forward-shortcuts. But during the backward-shortcut trials, when given the choice between a) backtracking or shortcutting in a "conflicting" direction with the FR vs. b) traveling along the familiar forward direction, YAs show a significant bias toward more closely following the FR than the OR that, interestingly, the OAs do not. Unlike YAs, the OAs did not significantly differ in their strategy across forward and backward trials, but group data show they tend to take fewer FRs compared to the YAs when the goal is backward relative to the FR. Parallel analyses suggest nearly every OA underperformed in FR memory tests compared to the YAs, indicative of a more effortful experience when trying to remember the FR. Together, these findings suggest that route familiarity and directional conflict may be important moderators of past evidence that aging leads to decreased flexibility/increased route-based navigation. By examining fMRI correlates in the frontal and medial temporal circuitry, we unpack the neural bases of how these individuals execute their navigational strategies and which factors play a role in these abilities as we age.

Disclosures: P. Maxim: None. **S.D. Moffat:** None. **T.I. Brown:** None.

Poster

P873. Spatial Memory and Navigation in Humans

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Program #/Poster #: P873.09

Topic: H.09. Spatial Navigation

Support: Consejo Nacional de Ciencia y Tecnología (Conacyt), Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica, Beca Programa Nacional de Posgrados de Calidad (PNPC).
Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT) DGAPA Proyecto IN231720.

Title: Virtual Maze Adaptation to Study Navigation Ability in Children

Authors: *C. O. ZURITA BAUTISTA, I. Y. DEL RIO-PORTILLA, G. D. ORTIZ-LAGUNES;
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Abstract: There are many paradigms utilized for behavioral experiments with children which use an avatar or the children's body to navigate and guide self-location with landmarks, located inside and outside the environment. Using virtual mazes is common during electroencefalography studies with adults. The virtual arena used by Jacobs et al. (2013) has been utilized to identify the place and grid cells in humans. The characteristics of the labyrinth are an important factor to compare the results obtained. Werweg and Kahana (2018) point out that navigating in circular environments could lack the rotational symmetry associated with the grid cells activity. So, characteristics may play an important role in brain activity. Brain electrical activity (EEG) during navigation has been studied in different species, including adult humans. In children, most navigation studies focus on behavioral variables, and the development of

EEG activity is a wide field to investigate. When working with children, we need to keep in mind the difference in the cognitive development between adults and kids. There are differences in the level of language understanding, attention ability to keep the focus on the task among other cognitive functions between both groups. Throughout time EEG navigation paradigms have been designed for adults. Hence, when testing children some adjustments are required on them. In that way, findings with children may help following changes between EEG activity until they reach mature brain oscillations. Therefore, it is important to assess the virtual environment for navigation, adapted from adult's paradigms, but at the same we need to take in to account the previous findings in behavioral navigational paradigms with children. Consequently, our group adjusted the virtual arena developed by Jacobs et al. (2013) for children. We replaced the landmarks and scenarios of the virtual arena and assessed instructions and duration of trials in three conditions: baseline, encoding, and recall of landmarks. The task was applied to seven children (6-12 years old). In contrast to adult paradigms, we found that children needed an average of 28 s for trials in the baseline condition, 25 s for the encoding, and 28 s in the recall condition. Besides, the scrolling speed to walk and turn right or left through the virtual arena was an important factor for the kid's attention to the landmarks. Regarding the instructions, the participants proposed explanations and word synonyms that were easier for them to understand and keep them interested in the task. Based on the outcomes, we propose modifications to the virtual arena paradigm, useful in EEG research with children.

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Poster

P873. Spatial Memory and Navigation in Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P873.10

Topic: H.09. Spatial Navigation

Support: NSERC Discovery Grant RGPIN-2020-05169

Title: Lower spatial memory performance in childhood is associated with increased substance use, depressive symptoms and externalizing problems in adolescence

Authors: *L. TRUDEL[1], V. KURDI[2], C. FOUQUET[2], R. SCHACHAR[3], M. BOIVIN[4], P. HASTINGS[5], P. ROBAEY[6], V. D. BOHBOT[2], G. L. WEST[1];
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Abstract: When navigating in a novel environment, people can memorize spatial locations using a hippocampus-dependent strategy (learning the relationship between landmarks) or a strategy that recruits the caudate nucleus (using a rigid stimulus-response pattern). The caudate nucleus forms a part of the reward system and supports procedural learning and the formation of habits. Previous work from our lab has shown that healthy young adults who use caudate nucleus-dependent memory to solve a radial arm maze consume higher levels of addictive substances and take more risks in a gambling task. It, however,

remains to be determined if memory performance during childhood is associated with the development of higher levels of substance use and behavioural problems later in life. To test this hypothesis, we examined data from the Quebec Newborn Twin Study (QNTS), a prospective longitudinal study of twins born between 1995 and 1998. When the children were 8 years old, they completed a radial arm maze (4 on 8 Virtual Maze adapted for children [a4/8 VM]) that measures hippocampus-dependent memory, spatial learning and working memory. Hippocampus-dependent memory is measured during a probe trial at the end of the task where all environmental landmarks around the maze are occluded. We compared memory performance in the a4/8 VM at age 8 to self-reported measures of substance use, depressive symptoms and externalizing behavior problems at ages 14 and 16. We found that lower hippocampus-dependent memory as measured by the probe trial at age 8 was associated with higher levels of depression in adolescence. Lower rates of spatial learning at age 8, meaning taking more trials to reach the criterion of no errors, was associated with increased substance use (cigarettes, cannabis and other illicit drugs) and behavioural problems in adolescence. Lastly, working memory errors at age 8 were associated with increased substance use (alcohol, cigarettes, cannabis and other illicit drugs) behavioural problems and increased depression in adolescence. These results suggest that memory performance in childhood, reflecting the integrity of memory systems and reward sensitivity, might have some predictive value in determining future maladaptive behaviors in adolescence.

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Poster

P873. Spatial Memory and Navigation in Humans

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Program #/Poster #: P873.11

Topic: H.09. Spatial Navigation

Title: Relationship of nicotine use and cessation to impulsivity, foraging and hippocampal-dependent navigation

Authors: *Y. WANG[1], J. LAWSON[1], K. WILSON[1], V. D. BOHBOT[2], N. C. SCHMITZER-TORBERT[1];
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Abstract: Why do some people successfully quit nicotine use while others struggle to do so? One obstacle is that nicotine use is associated with altered decision-making, such as increased discounting of future rewards, which is well-known. However, nicotine use has also been associated with a broader range of decision-making correlates, which may be important in supporting nicotine cessation. In this study, we examined the relationship between current nicotine use (cigarettes and e-cigarettes) and decision-making parameters derived from survey measures and virtual navigation tasks. Participants (Amazon's Mechanical Turk, undergraduates, and local community members) completed surveys including measures of delay-discounting and nicotine use. Consistent with the literature, cigarette (but not e-cigarette) use was associated with stronger delay discounting. Discounting rates were also negatively

related to self-reported intentions to quit using nicotine, and positively to self-reported nicotine dependence.Participants also completed a foraging (Movie Row) and a spatial memory (4 on 8 Virtual Maze, 4/8 VM) virtual navigation task. In the Movie Row, participants navigated around a virtual track presented on standard desktops/laptops. Rewards (4-sec video clips presented on movie screens) were offered in four zones (each with a different category of video), available after a variable delay. E-cigarette use was related to greater enjoyment of video rewards, especially in females, but with earning fewer total rewards. Participants typically made slower choices and showed increased vicarious trial-and-error when making poor decisions (e.g. accepting a bad offer), but this relationship was reduced in cigarette users. Unexpectedly, deliberation associated with poor decisions was reduced in nicotine users reporting weaker nicotine dependence. Cigarette users also showed increased deliberation when presented with difficult offers.The 4/8 VM (a radial maze task) was used to assess spontaneous preference for hippocampal-dependent spatial navigation strategies or striatal-dependent response navigation strategies. Nicotine use was not related to navigation strategy (spatial versus response), consistent with previous reports. Exploratory analyses suggested that navigation strategy may moderate the relationship between lifetime years of nicotine use and discounting rates, and to intentions to quit using nicotine.These results suggest that nicotine use is related to disruptions in several decision-making systems, which may differ across the modality of nicotine use, and may relate to motivation to quit using nicotine.

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Poster

P873. Spatial Memory and Navigation in Humans

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Program #/Poster #: P873.12

Topic: H.09. Spatial Navigation

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project number 327654276 – SFB 1315

Title: Spatial navigation in amyotrophic lateral sclerosis

Authors: P. M. MAIER[1], D. IGGENA[1], T. MEYER[1], C. FINKE[1], *C. J. PLONER[2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is characterized by a progressive degeneration of upper and lower motor neurons. Beyond motor symptoms, up to 50% of patients develop cognitive deficits of executive function, memory, language, and social cognition. Consistent with these impairments, recent studies found ALS-specific hippocampal pathologies including atrophy and shape alterations. However, the behavioral relevance of hippocampal damage remains unclear since it can be observed in patients without overt memory deficits. We investigated hippocampus-dependent behavior in ALS with a spatial navigation paradigm.
Sample: Forty-five ALS patients (13 f., 32 m.) were included. Thirty-four patients were diagnosed with

typical amyotrophic lateral sclerosis (upper and lower MN affected), four with primary lateral sclerosis (upper MN-variant of ALS) and seven with progressive muscular atrophy (lower MN). Patients with fronto-temporal dementia were not included. On average, patients were 60.3 years old and diagnosed 20.2 (0-114) months before testing. All patients had sufficient hand motor function to control a joystick (ALS-functional rating scale (FRS): mean 39.3 (29-46); FRS-progression / month: mean: 0.40 (0.05-2.33)). Additionally, forty-five age-, sex- and education-matched healthy controls were tested.
Methods: Participants performed a spatial navigation task that requires memory-guided navigation based on landmarks and/or memory of movement sequences. Previous studies suggest that these navigational patterns depend on hippocampal integrity. Furthermore, we administered neuropsychological tests for spatial memory, spatial fluency and perspective taking. Results: Contrary to our expectations, we did not find impaired performance in patients relative to controls in landmark-based or sequence-based spatial navigation. We also did not find deficits in neuropsychological measures for immediate and delayed spatial memory, spatial fluency and perspective taking.
Discussion: Our findings argue against clinically relevant spatial memory and navigation deficits in early- to mid-stage ALS patients. Previous studies showed that memory and executive functions remain rather stable during disease progression, suggesting that impairments should present already at disease onset. These and our findings can be reconciled by assuming significant cognitive reserve in ALS patients mitigating the behavioral effects of hippocampal dysfunction, even in behavioral contexts that usually recruit the hippocampus.

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Poster

P873. Spatial Memory and Navigation in Humans

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Program #/Poster #: P873.13

Topic: H.09. Spatial Navigation

Support: Hellman Family Foundation

Title: The relationship between navigation abilities and mental disorders

Authors: N. HATAMIAN, R. F. WOODRY, B. TRANQUADA-TORRES, A. YEE, E. R. CHRASTIL; Univ. of California, Irvine, Irvine, CA

Abstract: This study examined the relationship between aspects of navigational ability and behavioral traits associated with various mental disorders. We propose that navigational ability may utilize the same brain circuitry that has dysfunction in certain mental disorders and may be a beneficial early marker for these disorders. This study was inspired by the Research Domain Criteria (RDoC), a framework outlined by NIMH to study the basic dimensions of functioning that span the range of behavior from normal to abnormal. For example, we hypothesized that spatial perspective taking, which is important for navigation, could be associated with social perspective taking in disorders such as autism spectrum disorder or eating disorders. To test this question, participants recruited online through Amazon

Mechanical Turk (n>350) completed two web-based spatial cognition tasks and a self-report measure of navigational ability. They also completed a battery of standardized questionnaires to capture non-pathological ranges of mental disorders. The Open Field Task (OFT) is similar to a virtual Morris water maze. It tests an individual's ability to recall, locate, and navigate to four hidden objects scattered in an open field environment from a first-person perspective. The Spatial Orientation Task (SOT) tests spatial perspective taking by imagining different viewpoints in a layout of objects. The Santa Barbara Sense of Direction Scale (SBSOD) is a self-report measure of navigational ability. The behavioral questionnaires assessed pathological and non-pathological levels of mental disorders such as depression, anxiety, autism, and schizotypy to examine individual variability within the healthy population. Preliminary correlations indicate relationships between navigational ability and several mental disorders. In particular, obsessive-compulsive disorder and impulsivity showed relationships with performance errors in the SOT. These preliminary results also identify relationships between apathy as well as eating disorders and errors in the OFT. Together, these findings suggest that the circuitry for navigation and certain mental disorders could overlap, leading to new avenues for understanding these disorders.

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Poster

P873. Spatial Memory and Navigation in Humans

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Topic: H.09. Spatial Navigation

Support: NSERC Discovery Grant RGPIN-2020-05169

Title: The Effect of Aging on Basal Cortisol in Participants using Spatial versus Response-dependent Navigation Strategies

Authors: *G. WEST;
Univ. of Montreal, Montreal, QC, Canada

Abstract: This study examined how the relationship between endogenous cortisol, navigation strategy, and episodic memory is affected by age. We compared cortisol samples collected from a group of healthy younger adults (N = 66; mean age= 21.7) with samples collected from a group of older adults (N= 139, mean age= 65.77). All participants completed the 4-on-8 virtual maze task (4/8 VM) and neuropsychological measures of memory (i.e., Rey-Osterrieth Complex Figure Test (RO); Rey Auditory Verbal Learning Test (RAVLT). The 4/8 VM is solved using one of two spontaneous navigation strategies while learning the new environment. The spatial strategy involves learning the relationship between environmental landmarks and is associated with increased grey matter and activity in the hippocampus. In contrast, the response strategy involves using a rigid pattern of turns and is associated with increased grey matter and activity in the caudate nucleus. Our previous work has shown that basal cortisol is higher in young adult spatial learners compared to response learners. Further, higher basal cortisol levels are associated with increased spatial memory performance amoungst spatial learners while

higher cortisol is detrimental to spatial memory performance of response learners. In the current study, we found that with age, older adult spatial and response learners had equally low basal levels of cortisol, similar to young adult response learners. When comparing the older and younger adult groups, we found that cortisol levels appear to decrease with age uniquely amoungst spatial learners. No significant difference in neuropsychological measures of memory between older spatial and response learners were observed. Results are discussed in the context of previous work demonstrating that older spatial learners display more grey matter in the hippocampus and that a decrease in basal cortisol with age from a previous higher point is associated with better cognitive outcomes.

Disclosures: G. West: None.

Poster

P881. Associative Learning

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Program #/Poster #: P881.01

Topic: H.10. Human Learning and Cognition

Support: NIMH Internal Funding

Title: Reinforcement learning models quantify behavioral dynamics underlying threat learning in anxious and healthy adults

Authors: *J. NAPOLI[1], R. ABEND[1], S. G. RUIZ[1], A. L. GOLD[1], J. C. BRITTON[2], K. J. MICHALSKA[3], T. SHECHNER[4], A. M. WINKLER[1], E. LEIBENLUFT[1], D. S. PINE[1], B. B. AVERBECK[5];
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Abstract: Learning about potentially harmful stimuli and events is critical in shaping adaptive behavior in a changing environment. This type of learning, in which one forms an association between neutral stimuli and aversive outcomes, is known as threat learning. Several influential neurodevelopmental theories propose that person-to-person variation in this process can result in varying anxiety symptoms. Here, we studied a sample of people with a wide range of age and anxiety severity on a threat learning task, and used computational models to quantify the mechanisms underlying their behavior. Finally, we tested the parameters estimated by our models to discover links among the threat learning processes, neuroanatomical substrates, and anxiety severity. Our participant sample consisted of 215 individuals, made up of both those with anxiety and healthy volunteers ranging from 8-50 years old. Participants engaged in a threat learning task, in which photographs of two women displaying neutral expressions served as the conditioned threat and safety stimuli (CS+ and CS-, respectively). The unconditioned stimulus (UCS) was a presentation of the same actress displaying fear and co-occurring with a female scream, immediately following the CS+. Structural MRI images of the subjects were taken and skin conductance responses were recorded while the participants engaged in the task. We used the skin conductance data to model the learning effects, and used the parameters estimated from our models to assess associations among this behavior, whole-brain morphometry, anxiety severity, and age. We found

that threat conditioning was optimally modeled with a Rescorla-Wagner model that featured Bayesian learning and response decay terms. A lower threat generalization rate, the rate at which participants acquired a fear response to the CS-, was significantly associated with higher anxiety severity, but only in participants under the age of 13 years. Next, we will be looking at correlations between the parameters of our extinction model with anxiety, age and brain morphometry. Ultimately, these findings relate the dynamic processes underlying threat learning to neuroanatomy and learning theories of anxiety.

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Poster

P881. Associative Learning

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Topic: H.10. Human Learning and Cognition

Support: NIH R01MH112558
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Title: Bad from the start: Pupil diameter and fixational eye movements distinguish aversively-associated from innocuous visual locations

Authors: *W. M. FRIEDL, S. R. MILTENBERGER, A. KEIL;
Psychology, Univ. of Florida, Gainesville, FL

Abstract: Learning environmental cues that predict aversive events aids animate beings in avoiding foreseeable harm, promoting survival. To illuminate neural foundations of aversive associative learning outside of the traditional “fear circuit” centered on the amygdala, pupil activity and gaze direction of human participants (N=51, mean age=19.49, 19 male) undergoing classical aversive conditioning were recorded. High-contrast Gabor patches were individually presented at one of five different on-screen locations, with only one spatial location paired with an aversive 90 dB white noise auditory stimulus for the final 200 (out of 350 total) trials. Both pupil activity and rapid, intermittent deviations from fixation (microsaccades) showed responses indicating a binary discrimination between noise-paired and unpaired locations. Bayes factors strongly support a paired-versus-unpaired distinction in pupillary responses beginning approximately 1 second following stimulus onset and persisting throughout the remainder of a trial. Meanwhile, microsaccades towards the spatial location of the aversivly-paired Gabor patch were relatively inhibited from 200-400 milliseconds post stimulus onset. These results indicate that learning aversive associations via classical conditioning impacts perceptual processing from the very earliest stages. Specifically, both the autonomic nervous system-mediated pupillary response and the microsaccade generating circuit featuring the superior colliculus and pontomedullary reticular formation selectively respond to conditioned spatial locations. Furthermore, neither pupillary re-dilation nor microsaccade rate differentiate between non-conditioned locations as a function of distance from the

aversivly-associated Gabor location. Exploratory results presented here enrich previously reported findings of graded response changes in visuocortical population-level activity when viewing conditioned spatial locations.

Disclosures: W.M. Friedl: None. **S.R. Miltenberger:** None. **A. Keil:** None.

Poster

P881. Associative Learning

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P881.03

Topic: H.10. Human Learning and Cognition

Support: National Research Foundation (NRF) of Korea (NRF-2018R1C1B3007313)
Creative-Pioneering Researchers Program through Seoul National University
BK21 FOUR Program [5199990314123]

Title: Identifying the neurocognitive role of associative memory in acute stress-induced craving to smoke

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Abstract: Tobacco use disorder has a chronic course that is characterized by repeated relapse. Previous studies have revealed several triggers of relapse including stress and exposure to drug cues. While literature suggests that both stress and the memory system play a critical role in relapse to tobacco use, it remains unclear (1) how stress affects memory associated with drug cues (2) whether craving for smoking is related to drug-specific associative memory. Here, we developed a novel laboratory task to investigate the effect of stress on smoking-associated memory and the urge to smoke. We first created a controlled set of visual stimuli consisting of pairs of scenes with the same background but differing in their foreground object's association with smoking and plain objects (e.g., a cigarette vs, a pen). In Study 1, a group of smokers was recruited to validate the stimuli set on their arousal, valence, and subjective complexity ratings. In Study 2, an independent group of smokers seeking abstinence were recruited for two visits that took place on two consecutive days. On the first visit, participants performed an encoding task to build associations between smoking/neutral items and the background contextual scenes. On the second visit, participants were tested on their associative memory from the first day and reported their preference for each stimulus. We used the socially evaluative cold pressor test (SECPT) to induce psychosocial stress. Subjective level of perceived stress and salivary cortisol was collected to ensure the manipulation of stress. Based on the preliminary results, we hypothesize that (1) smokers under stress would show better memory of scenes related to smoking and that (2) this memory bias would be associated not only with a bigger urge to smoke but also with a higher preference in smoking-associated neutral stimuli. These findings will shed light on the role of associative memory bias in stress-induced craving for tobacco.

Disclosures: J. Lee: None. **S. Kang:** None. **S.U. Maier:** None. **S. Lee:** None. **W. Ahn:** None.

Poster

P881. Associative Learning

Location: Virtual Only

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Program #/Poster #: P881.04

Topic: H.10. Human Learning and Cognition

Support: Kavli Institute for Neuroscience at Yale
Yale Center for Clinical Investigation (YCCI)
NeuroNext Fellowship

Title: Multimodal interrogation of statistical learning and episodic memory in human epilepsy

Authors: *A. ALJISHI[1], B. E. SHERMAN[2], D. M. HUBERDEAU[2], A. SIVARAJU[3], N. B. TURK-BROWNE[2], E. C. DAMISAH[1];
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Abstract: Memory impairment is a direct and leading cause of morbidity in all forms of epilepsy. Prior human studies suggest that Episodic Memory (EM; i.e., ability to remember individual events) and Statistical Learning (SL; extraction of patterns over time and space) both depend on the medial temporal lobe (MTL). EM has been the focus of most memory-related studies in epilepsy, yet it is not known whether SL and EM are equally affected in epilepsy. To address this gap, we developed novel behavioral methodologies combined with structural imaging and functional interrogation of the MTL. 38 epilepsy patients and 29 age- and sex-matched healthy controls underwent computer-based behavioral testing designed to separately evaluate SL and EM. Clinical data, including seizure frequency, seizure onset zone (SOZ), MTL structural abnormalities, and antiepileptic drugs (AEDs) taken, were obtained from the patient cohort clinical profiles. Manual segmentation of MTL was performed in 25 of the patients to obtain volumes of structures using MRI scans. Multivariable regression and analysis of variance for the behavioral scores and clinical characteristics showed that seizure frequency was the most important predictor of SL: patients with poorly controlled seizures performed worse in SL relative to healthy controls and patients with well-controlled seizures. Notably, seizure frequency did not predict EM performance. Rather, consistent with prior literature, anti-seizure medications and the presence of MTL lesions were the most important predictors of EM. Volumetric analysis of MTL demonstrated correlations between SL performance and MTL volumes within epilepsy patients. To assess the causal role of the MTL in SL, a subset (4) of epilepsy patients underwent 1-Hz direct electrical stimulation (DES) designed to temporarily inactivate function in the MTL. Transient DES of the hippocampus during the learning phase of the SL task led to impaired SL performance. This impairment was specific to the MTL: no impairment resulted from stimulating a control non-MTL region. Together, these results suggest that SL is a hippocampal-dependent learning system affected by seizure severity in epilepsy patients. Further, compared to EM, SL was a better predictor of cognitive function in epilepsy. These findings may lead to a more comprehensive understanding of memory impairment in epilepsy, and provide an assortment of patient-centered memory-related endpoints used to evaluate the efficacy of novel treatments.

Disclosures: A. Aljishi: None. **B.E. Sherman:** None. **D.M. Huberdeau:** None. **A. Sivaraju:** None. **N.B. Turk-Browne:** None. **E.C. Damisah:** None.

Poster

P881. Associative Learning

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Program #/Poster #: P881.05

Topic: H.10. Human Learning and Cognition

Support: MH114877
Philanthropic support

Title: Modality-specific parameters and interference contribute to better-fitting bimodal associative learning models

Authors: H. D. HUANG[1], F. R. BAUMGARDT[1], B. LAHNER[2], *R. M. G. REINHART[1];
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Abstract: Perceiving and processing different sensory inputs are crucial to understanding adaptive learning. Here, we develop and validate a computational model that combines the prediction-error updating of reinforcement learning with the fast, robust componentry of working memory to examine the role of interference between auditory and visual stimuli. Human subjects performed a bimodal associative learning task, in which, on each trial, a single visual or auditory stimulus was mapped to a button-press response. New stimulus-action pairings were randomly selected at the beginning of each block, and subjects had to learn the correct pairings based on binary feedback at the end of each trial. We adopted a Reinforcement Learning Working Memory (RLWM) framework from previous studies with two major modifications: 1) each modality can take on different parameter values and 2) pairings can interfere with each other between modalities and between blocks. Our results show that model instances embedded with the above modifications can better describe bimodal learning. Learning rates were generally higher at the beginning of each block when new pairings were introduced and later decreased, while perseveration started low and later increased, suggesting that the participants became more adept at the task and more prone to sporadic errors as they reached a steady state of learning. Interestingly, the group of subjects who showed improved learning over time were best fitted by a different model (RLWM with all interference) compared to those who did not (RL with no interference from the opposite modality in the previous block). This suggests that a strategy towards improved learning involves utilizing a broader range of previous knowledge and a balanced mixture of both RL and WM components. For the improved group, the weighting towards WM increased with task familiarization, which likely relates to the higher decay rate of the Q matrices for the RL component compared to the non-improved group. Additionally, learning rate and perseveration seem to have reached a steady state in later blocks for the improved group, while substantial fluctuation upon new pairing introduction was observed for the non-improved group. The results show that the nuance of bimodal learning is better captured by separate sets of parameters, that different kinds of interference (or prior information) play a role in successive learning, and that different learning strategies could be identified by computational behavioral models. Future research seeking to identify the neuroanatomical loci and neurophysiological events associated with key parameters from our model is implicated.

Disclosures: H.D. Huang: None. **F.R. Baumgardt:** None. **B. Lahner:** None. **R.M.G. Reinhart:** None.

Poster

P881. Associative Learning

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Program #/Poster #: P881.06

Topic: H.10. Human Learning and Cognition

Support: KIBM UCSD

Title: Evolution of problem-solving strategies with learning and architecture in recurrent neural networks

Authors: *B. TSUDA[1,2], B. J. RICHMOND[3], T. J. SEJNOWSKI[2,1];
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Abstract: Objective and Rationale--Problems can often be solved by multiple strategies. Recent studies of humans and monkeys have provided evidence of such variability in strategy adoption for problem solving, yet the underlying neural basis for the strategy differences is unknown. We adopted a computational modelling approach to help elucidate how two critical network features - network size and amount of experience - may lead to unique problem-solving strategies when encountering the same problem. Following the observation by Wittig et al. (2016, *Learning and Memory*) that monkeys and humans adopt different strategies on a set of working memory tasks, we trained recurrent neural network models of different sizes on the same tasks and analyzed their strategy development and progression throughout learning.
Methods--For our studies, we used recurrent neural networks (RNNs; long-short term memory networks in our implementation) that have been demonstrated in prior works to be useful models of working memory computations in the brain. The networks were trained by reinforcement learning on computational implementations of the three tasks from Wittig et al. 2016. For each task, we varied the size of the RNNs (n=[5,10,25,50,100,200,500]) and the amount of training (task episodes=[0,10,20,30,40,50]x10^3) and ran 10 independent replicate RNNs per condition. We then assessed network strategy by measuring two main metrics derived from results reported in Wittig et al. 2016: non-target yes-response linear fit slope and residual. Using these two metrics we could effectively identify different strategies employed and any switching between them during training.
Results--We found that networks evolve from non-selective to selective response strategies with more experience, while able to achieve relative task proficiency across both strategies. Larger network sizes led to more rapid transitions from non-selective to selective strategy during training, even when overall task performance remained similar. Interestingly, on particular tasks we observed that networks' strategies progressed through an evolution of a random-non-specific response strategy, to a recency-based strategy, and finally to a highly selective strategy.
Conclusions--These results recapitulate key aspects of the strategy differences observed by Wittig et al. between monkeys and humans on these tasks. Our results suggest monkeys may adopt different strategies from those used by humans due to limitations of learning speed and neural capacity that constrain what neural computations they can use to perform the task.

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Poster

P881. Associative Learning

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Topic: H.10. Human Learning and Cognition

Support: NIH/NIDA Grant R01DA045716

Title: Effects of depressive symptomatology on reversal learning in a probabilistic classification task

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Abstract: Depression and substance use disorders are highly comorbid, suggesting that common neurocognitive mechanisms may contribute to both. Here we examine the idea that measures of depression may be related to increased habitual responding, leading to increased liability for substance use disorders. To investigate this relationship, 44 young adults (21 ± 3.26 years old) completed a version of the Weather Prediction Task (WPT), a classification task in which cues were associated with two outcomes ("sun" or "rain") probabilistically. After 100 trials, the probabilities were reversed for each cue stimulus unbeknownst to the participant and they completed another 100 trials with the new probabilities. We calculated habitual responding as the preponderance of initial contingency responding during the probabilistic reversal phase, indicating reduced flexibility and goal-directed responding. Participants completed questionnaires examining early-life stress (Childhood Trauma Questionnaire), depression (Beck Depression Inventory [BDI]), state and trait anxiety (State-Trait Anxiety Inventory [STAI]), and subjective SES (MacArthur Scale of Subjective Social Status). Results from linear regression analyses revealed significant interactions concerning subjective SES with BDI (b = -0.007, p = 0.012, η^2 = 0.005) and state anxiety scores (b = 0.006, p = 0.012, η^2 = 0.165) on the measure of habit responding. These results reveal differential effects of depression and anxiety on habit responding dependent on perceptions of socioeconomic status. In particular, among individuals with lower perceptions of SES, individuals with higher BDI scores (b = 0.0134, p = 0.004) and lower state anxiety scores (b = -0.0124, p = 0.006) are expected to exhibit greater habit responding. Results further revealed a significant interaction between subjective SES and BDI scores on lose-shifting behavior in the reversal phase of the WPT (measured as the proportion of response shifting based on previously incorrect answering; b = -0.004, p = 0.023, η^2 = 0.0167), such that among individuals with lower perceptions of SES, individuals with higher BDI scores exhibit a greater proportion of lose-shifting behavior during the reversal phase (b = 0.006, p = 0.027), consistent with previous research suggesting a hypersensitivity to punishment in people experiencing symptoms of depression. These results support the involvement in depression of striatal circuits that have been shown to subserve stimulus-response learning and processing aversive outcomes. Our results also indicate that SES modulates the effect of depression on these behavioral measures.

Disclosures: C.Y. Franco: None. **H.P. De Guzman:** None. **B.J. Knowlton:** None.

Poster

P881. Associative Learning

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Topic: H.10. Human Learning and Cognition

Support: NIH Grant 1R21MH127842-01

Title: Oscillatory Mechanisms of Context Dependent Cognitive Maps in Human Memory

Authors: *O. ASHMAIG[1], K. R. SHERRILL[3], N. W. MORTON[5], L. L. COLGIN[4], R. J. BUCHANAN[6], A. R. PRESTON[7], A. WATROUS[2];
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Abstract: Everyday choices depend on the situation in which they are made, such as packing for a trip differently based on the destination. Dominant theories posit that context-guided memory relies on both associating and separating representations for objects, values, contexts, and locations. Rodent studies show that the hippocampus (HPC) encodes these cognitive maps in a hierarchy based on their behavioral relevance and that the medial prefrontal cortex (mPFC) then provides top-down signals to refine context-sensitive representations. Much less is understood about the mechanisms that support context-dependent behavior in humans. We analyzed intracranial recordings from epilepsy patients as they performed a VR-based associative memory task with context-dependent reward values. We first identify behavior-dependent theta and high-frequency gamma activity using our recently published oscillatory detection algorithm (ORCA) and then employ a novel, phase-based representational similarity analysis to characterize phase coded representations. We show that theta-gamma phase-amplitude coupling (PAC) within the HPC and mPFC provides temporal coordination for the formation and expression of context-dependent memory. Combining novel behavioral and signal-processing methods with analysis of human recordings, this project suggests that oscillations within HPC and mPFC support context-dependent choice.

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Poster

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Program #/Poster #: P881.09

Topic: H.10. Human Learning and Cognition

Support: ONR N00014-16-1-2832
ONR N00014-17-1-2304

NSF 1625552

Title: Successful context-dependent associative rule learning involves tuning the dimensionality of representational spaces

Authors: *S. S. P. LIAPIS[1,2], A. E. CHANG[2,3], J. T. MCGUIRE[1,2,3], C. E. STERN[1,2,3];
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Abstract: Prior research has identified a prominent role for prefrontal cortex (PFC) and medial temporal lobe (MTL) regions in context-dependent rule learning. Here, we sought to explore whether these regions mediate flexible learning by maintaining a high-dimensional space for activity patterns encoding possible rules, while simultaneously pruning away irrelevant features from the problem space, effectively tuning the dimensionality of representational space. To test this hypothesis, we re-analyzed an existing dataset from an fMRI study of healthy adults learning context-dependent associations (Morin et al., 2021). Participants (N=30) learned, through trial and error, rules linking cues and associates depending on their spatial context. We employed a data-driven approach to examine the dimensionality of representations for cues and associates (Mack et al., 2020). Voxelwise activity patterns for each presentation of a cue or associate were extracted using beta-series regression (Mumford et al., 2012). We then derived a dimensionality score for these representations using principal components analysis. We predicted greater dimensionality for cue relative to associate representations as well as a decrease in dimensionality over the course of learning. We also expected greater dimensionality for cue representations in participants who learned the task compared to those who failed to do so. Lastly, we anticipated that dimensionality would explain learning by tracking accuracy over the course of the experiment. The results demonstrated higher-dimensional representations for cues relative to associates in PFC and MTL areas. Additionally, cue patterns were higher-dimensional for successful learners, while associate patterns were similar across learners and non-learners. Over the course of learning, PFC and MTL representational spaces were compressed. However, successful learners diverged from non-successful participants over time, limiting compression to maintain higher-dimensional representations. Within PFC, we found that representational dimensionality in orbitofrontal cortex tracked accuracy over time. These findings are consistent with the use of higher-dimensional representations to encode rule relationships while filtering out irrelevant features. The results suggest that PFC and MTL regions facilitate context-dependent associative rule learning by balancing the compression and maintenance of high-dimensional representational spaces and that dimensionality is a key marker of learning.

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Poster

P881. Associative Learning

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Topic: H.10. Human Learning and Cognition

Support: NIH R01 MH069456

NSF GRFP

Title: Mechanisms and dynamics of statistical learning across levels of abstraction

Authors: *B. E. SHERMAN[1], A. ALJISHI[2], K. N. GRAVES[1], I. H. QURAISHI[3], A. SIVARAJU[3], E. C. DAMISAH[2], N. B. TURK-BROWNE[1,4];
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Abstract: We regularly encounter the same objects, people, and places, and they appear in predictable configurations and sequences across experiences. The human brain is deftly attuned to such structure, quickly extracting spatial and temporal regularities via statistical learning. Recent studies have used a technique known as frequency tagging to detect the representation of such structure in the brain during scalp and intracranial EEG. Frequency tagging capitalizes on neural entrainment to stimuli presented at a regular rate, but can also reveal learning by tracking entrainment to the frequency of repeating sequences (even in the absence of segmentation cues). In past studies, these sequences consisted of multiple repetitions of the exact same stimuli in a particular order. However, regularities in the real-world often involve variance across repetitions (e.g., different speakers of the same language, the layout of sections in different grocery stores, traffic patterns and detours on a daily commute). Accordingly, a critical function of statistical learning is to generalize across this variance to represent more abstract regularities. Here we test how the human brain generalizes during statistical learning using frequency tagging in epilepsy patients with intracranial EEG. Patients were presented with series of scene photographs that contained regularities at one of two levels of abstraction. In the exemplar-level condition, the same scene images were presented repeatedly in pairs (e.g., scene A was always followed by scene B). Consistent with prior work, we found reliable entrainment at the frequencies of both the images and pairs, suggesting statistical learning of the pairs. In the category-level condition, all scene images were trial-unique, but certain subcategories were reliably paired (e.g., a beach was always followed by a mountain). We again found reliable entrainment at the frequencies of both images and pairs. Because the pair structure existed at only the level of categories, this demonstrates abstraction during online statistical learning. This extends prior work in which categorical statistical learning was revealed through behavioral tests, which could have been supported by abstraction at test rather than during learning as shown here. We found reliable overlap in the electrode contacts that entrained to image and pair frequencies across conditions, with the effects manifesting primarily in visual cortex. In ongoing work, we are testing the hypothesis that the hippocampus is causally involved in statistical learning, examining whether cortical frequency tagging is altered by hippocampal stimulation.

Disclosures: B.E. Sherman: None. **A. Aljishi:** None. **K.N. Graves:** None. **I.H. Quraishi:** None. **A. Sivaraju:** None. **E.C. Damisah:** None. **N.B. Turk-Browne:** None.

Poster

P896. Learning and Memory in Aging: Humans

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P896.01

Topic: H.12. Aging and Development

Support: CIHR, MOP 123294

Title: Altered functional connectivity in late middle-aged and older patients with obstructive sleep apnea

Authors: *G. MARTINEZ VILLAR[1,2], V. DANEAULT[1,2,3], M.-È. MARTINEAU-DUSSAULT[1,2], C. ANDRÉ[1,2], A.-A. BARIL[2,4,5], C. LAFOND[1,2], J. MONTPLAISIR[1,2], J. CARRIER[1,2], N. GOSSELIN[1,2]; [1]Univ. de Montréal, Montréal, QC, Canada; [2]Ctr. for Advanced Res. in Sleep Medicine, Hôpital du Sacré-Coeur, Montréal, QC, Canada; [3]Univ. of Sherbrooke, Montréal, QC, Canada; [4]McGill Univ., Montréal, QC, Canada; [5]Douglas Mental Hlth. Inst., Montréal, QC, Canada

Abstract: Background: Obstructive sleep apnea (OSA) is associated with changes in resting-state functional connectivity (FC) in young and middle-aged adults. These changes especially occur between regions of the Default Mode Network (DMN) and the limbic system, which are known to be crucial for cognitive and memory functions. However, it remains unclear whether these changes are also observed in older adults with OSA, who could be at risk of cognitive decline. **Objective**: To characterize the association between OSA severity indices and resting-state FC among regions of the DMN and the limbic system in late middle-aged and older adults. **Methods:** 97 participants (25 females; 65.8±7.0 years old; 15.3±3.3 years of education) underwent a neuropsychological assessment, full-night polysomnography and 3T magnetic resonance imaging protocol including a 3D T1-weighted (MPRAGE) and 2 resting-state fMRI time series (T2*-weighted). OSA severity was reflected by the apnea-hypopnea index (AHI), the oxygen desaturation index and the microarousal index. The whole sample included 24 controls, 36 participants with mild OSA ($5 \geq AHI < 15$) and 37 individuals with moderate to severe OSA ($15 \geq AHI$). CONN toolbox was used to perform multiple regression analyses between OSA severity variables and FC values between each pair of regions of interests of the DMN (medial prefrontal cortex, posterior cingulate cortex, precuneus and lateral parietal lobes) and limbic system (hippocampi and parahippocampal gyri). All analyses were performed while controlling for age, sex and level of education. **Results:** Greater OSA severity (higher apnea-hypopnea and oxygen desaturation indices) was associated with lower FC between the hippocampi and multiple regions including medial prefrontal cortex, posterior cingulate cortex, precuneus, lateral parietal lobes and parahippocampal gyri ($Fs > 4$; $ps < 0.05$ FDR-corrected). Moreover, higher apnea-hypopnea index was associated with higher FC between the anterior and posterior parahippocampal gyri ($F=5.88$; $p=0.017$ FDR-corrected). No significant association was found between the microarousal index and FC values. **Conclusions:** Greater OSA severity in late middle-aged and older adults is associated with decreased FC between the hippocampi and multiple regions of the DMN and limbic system, and increased FC within the parahippocampal gyri. Further analyses will aim at testing whether these FC changes predict cognitive decline, and whether treating OSA may normalize FC patterns.

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Poster

P896. Learning and Memory in Aging: Humans

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Program #/Poster #: P896.02

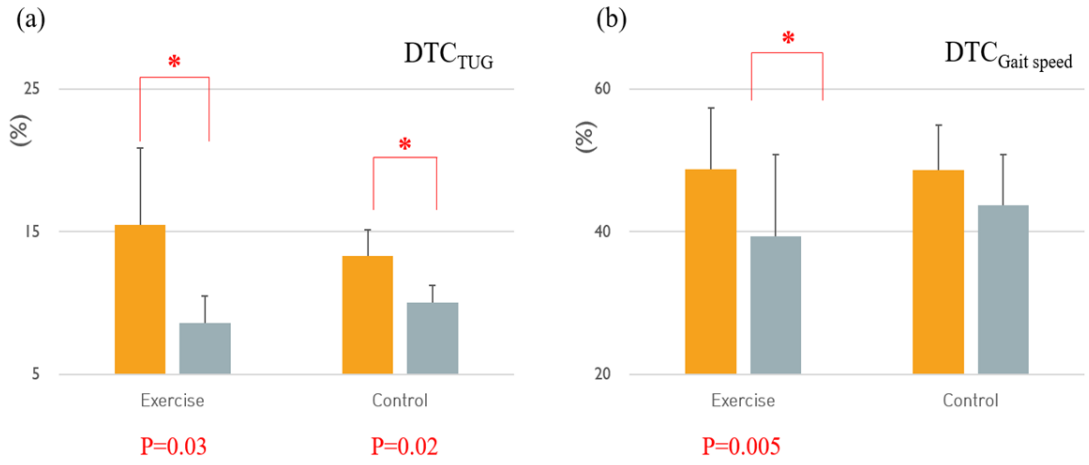
Topic: H.12. Aging and Development

Support: the Rehabilitation Research & Development Support Program (NRCRSP-EX20004), National Rehabilitation Center, Ministry of Health and Welfare, Korea

Title: Dual-task exercise program for older adults with mild cognitive impairment: a randomized controlled trial

Authors: *S. JUNG;
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Abstract: INTRODUCTION Dual-task (DT) exercise training is a multidimensional exercise intervention that combines motor and cognitive tasks to affect on motor-cognitive interplay. We aimed to investigate the effect of DT exercise program on cognitive, physical, and psychological function of older adults with mild cognitive impairment (MCI). **METHOD** Twelve older adults with MCI (MOCA-K≤25 or K-MMSE≤28) were recruited and randomized either to an exercise group (n=6) or to control group (n=6, Table 1). The exercise group underwent 8-week, 60-minute group exercise sessions, 3 times a week, with moderate intensity exercise combined with simultaneous cognitive tasks. They also performed moderate intensity weekly home aerobic exercises for 60 minutes or longer for 8 weeks. The control group performed 60-minute home stretching and yoga sessions, 4 times a week for 8 weeks after an initial exercise education. DT cost, cognitive function, physical performance, body composition, level of physical activity, health-related quality of life, and exercise psychology were assessed at baseline and after the intervention. Resting state functional brain MRI were also obtained at baseline and after the intervention. **RESULTS** The ratings of perceived exertion was 6.02±0.52 for exercise group. The amount of physical activity during the intervention period was higher in exercise group (35379.0±15785.4 MET min/week) than control group (19833.0±8968.7 MET min/week). Exercise group improved significantly on DT cost (Figure 1), executive function, memory function, physical performance, leg lean mass, and exercise psychology. Exercise group showed significantly higher satisfaction on intervention than control group. There was no adverse event during the intervention. **CONCLUSION** DT exercise program which combined moderate intensity exercise with simultaneous cognitive tasks could improve cognitive, physical, and psychological function in older adults with MCI.



Disclosures: S. Jung: None.

Poster

P896. Learning and Memory in Aging: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P896.03

Topic: H.12. Aging and Development

Title: Interaction of APOE ε4 and KIBRA T-allele on cognitive and neuroimaging markers in cognitively unimpaired older adults

Authors: *N. NIKKHAHMANESH[1], M. MALEK-AHMADI[2], Y. SU[2], V. DEVADAS[2], V. GHISAYS[2], J. LUO[2], Y. CHEN[2], H. PROTAS[2], K. CHEN[2], R. CASELLI[3], E. REIMAN[2];
[1]Univ. of Arizona, Scottsdale, AZ; [2]Banner Alzheimer's Inst., Phoenix, AZ; [3]Mayo Clin., Scottsdale, AZ

Abstract: Background: The ε4 allele of the APOE gene is a major genetic risk factor for Alzheimer's disease (AD) and decreased cognitive performance. T allele carriage of the kidney and brain (KIBRA) gene has demonstrated neuroprotective qualities for neuron survival, learning and memory, and network connectivity. Previous studies have demonstrated that KIBRA-T allele carriage is associated with increased hippocampal volume and episodic memory performance, however its interaction with APOE carrier status is unclear. The aim of this study was to assess the interaction of APOE genotypes with KIBRA genotypes on episodic memory and hippocampal volume in cognitively unimpaired (CU) older adults.
Methods: Data from 198 CU older adults age 65 years and older were analyzed from the Arizona APOE

cohort. Delayed Recall (DR) and Total Learning (TL) scores of the Auditory Verbal Learning Test (AVLT) were used as the dependent variables in linear mixed-effects models where a three-way interaction of Time, APOE ε4 carrier status, and KIBRA-T carrier status was used to assess longitudinal cognitive performance. Cross-sectional analyses were analyzed using generalized linear models (GLMs) where neuroimaging biomarkers for hippocampal volume, white matter hyperintensity volume, glucose metabolism, amyloid load, and tau load were used as outcome variables and the interaction of APOE ε4 carrier status and KIBRA-T carrier status was the predictor variable of interest. The LMEs and GLMs adjusted for age, sex, and education.
Results: The time-based interaction of KIBRA-T carrier status and APOE ε4 carrier status for AVLT DR was statistically significant (β = 0.15, 95% CI: (0.03, 0.26), p = 0.01) where ε4 carriers who lacked the KIBRA-T allele had the fastest rate of decline. APOE ε4 carriers who also carried the KIBRA-T allele had rates of decline that were similar to that of APOE ε4 non-carriers. A similar finding was noted for hippocampal volume among APOE ε4 carriers where KIBRA-T carriers had significantly greater volumes relative to KIBRA-T non-carriers (β = 7.35e-04, 95% CI: (8.12e-05, 1.39e-03), p = 0.03). No significant interactions for KIBRA and APOE were noted for the other neuroimaging outcomes. Significant main effects for APOE ε4 status were noted for hippocampal volume and glucose metabolism.
Conclusion: These findings indicate a neuroprotective effect associated with the KIBRA-T allele among APOE ε4 carriers on episodic memory and hippocampal volume. Although this effect was not found for other AD-related biomarkers, KIBRA-T allele carriage appears to mitigate the effects of age-related cognitive decline and hippocampal atrophy.

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Poster

P896. Learning and Memory in Aging: Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P896.04

Topic: H.12. Aging and Development

Support: AG063775
Philanthropic support

Title: Enduring memory improvements in older adults using high-definition transcranial alternating current stimulation

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Abstract: Normal and pathological age-related cognitive decline is characterized by a variety of memory impairments. Neuroscience studies have shown that synchronized activity in the theta-frequency band (3-8 Hz) of intraparietal lobe (IPL) is associated with working memory and synchronized activity in the gamma-frequency band (30-100 Hz) of dorsolateral prefrontal cortex (DLPFC) is associated with long-

term memory. Recent evidence using transcranial alternating current stimulation (tACS) in healthy young adults has suggested that these brain-behavior relationships may be causal. Yet, it remains to be seen whether working and long-term memory improvements can be selectively induced in an older population (65+ year) based on the spatiospectral parameters of tACS, and moreover, whether stimulation applied over multiple consecutive days can confer more potent and enduring memory benefits than a single "dose". Here, we conducted a randomized, double-blind, sham-controlled study (N=60) targeting the memory performance of older adults (68-88 years) with a chronic (4-day) administration of high-definition tACS (HD-tACS) designed to facilitate synchronous cortical activity in the high gamma range (60 Hz) of left DLPFC or the low theta range (4 Hz) of left IPL. During stimulation, subjects performed a classic auditory-verbal free recall task allowing us to isolate changes in long-term memory and working memory, separately, indexed by the canonical primacy and recency serial position curve effects. Memory performance was evaluated at baseline before intervention, on each stimulation day, and 1-month postintervention. Gamma HD-tACS preferentially improved the primacy effect at day 1, day 2, day 3, day 4, and 1 month, while theta HD-tACS preferentially improved the recency effect at day 3, day 4, and 1 month, relative to baseline. The rate of "online" memory improvement over 4 days predicted the size of "offline" memory benefits 1 month later at the group and individual level. Interestingly, baseline general cognitive performance played a significant role in determining stimulation effectiveness with low cognitive functioning older adults experiencing the largest and most enduring memory improvements. The results argue in favor of dual storage theories of human memory and set groundwork for developing circuit-based therapeutics aimed at improving memory in normal and pathological aging populations.

Disclosures: W. Wen: None. **S. Grover:** None. **V. Viswanathan:** None. **C.T. Gill:** None. **R.M. Reinhart:** None.

Poster

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Title: Machine-learning defined precision tES for improving cognitive function in older adults

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Abstract: Transcranial electrical stimulation (tES) is widely investigated as a family of therapeutic tools for enhancing cognitive function in older adults with and without neurodegenerative disease. Prior research demonstrates that direction and intensity of electrical current are essential features for producing favorable outcomes of stimulation. While these features are directly related to electrode placement and injected current, they vary extensively with differences in individual anatomy. This pilot study used machine learning and MRI-derived computational models of tES to define a personalized medicine strategy for transcranial electrical stimulation. Fourteen healthy older adults (age 65-87) received 20 min of 2mA tES stimulation (F3-F4) during a two-week cognitive training intervention. Computational models of tES current density were generated from T1-weighted MRI images to estimate the intensity and direction of the tES electric field. Constructed models were normalized to MNI space using the University of Florida Aging Brain-587 tissue probability map. Normalized maps were passed through a binary support vector machine-learning algorithm (SVM) to identify the critical features for producing tES-based working memory improvements. Weighted Gaussian Mixture Model (WGMM) optimization was used to optimize the electrode placement and injected current by maximizing the likelihood of treatment response in tES non-responders as well as within an independent sample of treatment naïve participants. Optimized models were passed back into the deployed SVM model for reclassification to assess the performance of the GMM. Optimization via GMM reduced inter-individual electric field intensity and direction variability by 61.7%. GMM optimization also produced an average treatment response likelihood estimate of 99.96%. The optimized models successfully converted 100% of non-responder predictions to responders within the deployed SVM. Similarly, 100% of independent treatment naïve optimization solutions were also successfully classified as responders. While clinical applications of tES have grown exponentially, reproducibility of these studies remains a challenge. At present, the optimal stimulation parameters remain unknown, making it difficult to ensure optimal treatment response on an individual basis. Findings from this study clearly demonstrate the advantages of employing personalized stimulation parameters in tES protocols through artificial intelligence and precision dosing. The current study provides a method to build personalized medicine models for a variety of therapeutic tES applications.

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Poster

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Topic: H.12. Aging and Development

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Title: Regional Cortical Thickness Predicts Top Cognitive Performance in the Elderly

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Abstract: While aging is typically associated with cognitive decline, some individuals are able to diverge from the characteristic downward slope and maintain very high levels of cognitive performance. Prior studies have found that cortical thickness in the cingulate cortex, a region involved in information processing, memory, and attention, distinguish those with exceptional cognitive abilities when compared to their cognitively more typical elderly peers. Others major areas outside of the cingulate, such as the prefrontal cortex & insula, are also key in successful aging well into late age, suggesting that structural properties across a wide range of areas may better explain differences in cognitive abilities. Here, we aim to assess the role of regional cortical thickness, both in the cingulate and the whole brain, in predicting Top Cognitive Performance (TCP), measured by performance in the top 50th percentile of memory & executive function. Using data from National Alzheimer's Coordinating Center, we examined cognitively normal subjects aged 70-89. We found that, while thickness in cingulate regions can predict TCP status with some degree of accuracy, a whole-brain, network-level approach out-performed the localist, cingulate models. These findings suggests a need for more network-style approaches and furthers our understanding of neurobiological factors contributing to preserved cognition.

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Poster

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Topic:

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Hellman Family Foundation

Title: Age-related differences in memory-guided decisions are driven by a trade-off between multiple decision systems

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Abstract: Recent findings have identified a key role in decision-making of memory content, in addition to reinforcement learning. This leaves open the possibility that observed decision-making difficulties in older adults are driven by age-related declines in memory, reinforcement learning, or both decision systems. In the present study, we examined the effect of aging on these memory-guided decisions in a lifespan sample of adults who completed a task that allowed us to separately assess the contributions of recent reinforcement, item memory, and context memory to choices. Participants learned to choose between 3 decks of cards with probabilistic rewards, where each trial was tagged with a unique object image to serve as item-level reminders of each choice (learning phase), and then continued to choose between the same 3 card decks with occasional presentations of a memory probe from the learning phase (test phase). At the group level, we found that these memory probes biased subsequent choices to be more consistent with the reminded trial from the learning phase, with a larger effect in older than younger

adults. Strikingly, however, whereas younger adult decisions were consistently influenced by a combination of both recent reinforcement and memory content, older adult decisions exhibited a marked trade-off between memory and reinforcement learning: Individuals who were more influenced by recent rewards were less influenced by memory, and vice-versa. These findings suggest that age-related differences in memory-guided decisions may stem from a focus on one decision system over another, perhaps reflecting the judicious use of limited cognitive resources.

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Poster

P906. Schizophrenia: Circuits and Systems

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Program #/Poster #: P906.01

Topic: H.13. Schizophrenia

Support: Roche Postdoctoral Fellowship

Title: Baclofen partially rescues MK-801 induced circuit deficits

Authors: *P. JANZ[1], M. NICOLÁS[2], A. HONRUBIA[2], M. VALENCIA[2], R. REDONDO[1];
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Abstract: Cognitive deficits and impaired sensory processing are hallmarks of neurodevelopmental and neuropsychiatric disorders, such as schizophrenia and autism. N-Methyl-d-aspartate receptor (NMDAR) hypofunction is considered to contribute to these deficits by disrupting excitation-to-inhibition balance in neuronal circuits. Based on preclinical data, activation of GABAB-receptor is hypothesized to restore this imbalance, but its effect on translational electrophysiological circuit readouts is poorly understood.Therefore, we studied the physiology of limbic-auditory circuits under pharmacological NMDAR blockade (using MK-801) and GABABR activation (using Baclofen) in freely-moving rats, implanted with electrodes in key brain areas. The pharmacological effects were assessed using resting-state EEG, auditory-induced oscillation and mismatch-negativity paradigms.Across brain areas, MK-801 increased the power of both resting-state and auditory-induced brain oscillations, mainly in the gamma and higher frequency ranges. Baclofen partially normalized this aberrant oscillatory activity. Coherence analysis indicated that network interactions are substantially altered by MK-801, with increased functional coupling in limbic thalamocortical circuits in the gamma range, and increased coupling of the frontal cortex with the auditory cortex and the amygdala in the theta band. Baclofen normalized the coherence between frontal cortex and amygdala, but augmented the MK-801-driven increase in thalamocortical coherence. Finally, we report that Baclofen intensified the MK-801-induced deficits in auditory mismatch responses.In summary, while GABABR activation normalized gamma abnormalities upon MK-801, it disrupted functional coupling and context-dependent auditory processing. The complex circuit modulation by GABABR activation described in this study invites an updated interpretation of its therapeutic value for neurodevelopmental disorders associated with NMDAR-hypofunction.

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Poster

P906. Schizophrenia: Circuits and Systems

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Program #/Poster #: P906.02

Topic: H.13. Schizophrenia

Support: NIH Grant MH115188

Title: A dorsal hippocampus to ventral tegmental area polysynaptic pathway underlies psychomotor behavior in mice

Authors: *J. ZHANG, M. NAVARRETE, Y. WU, Y. ZHOU;
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Abstract: The heterogeneity of psychiatric disorders poses major difficulties in deciphering the underlying etiology of these conditions. Thus, delineating clinical features of distinct neural circuits may provide paramount information that will facilitate a better understanding of the underlying pathophysiology. The mesolimbic dopamine (DA) system, which originates from DA neurons in the ventral tegmental area (VTA), is thought to be dysregulated in patients experiencing psychosis. However, the source of the disturbance and the underlying neural circuitry remain unknown. Here, we address these knowledge gaps by utilizing chemogenetics and neuronal activation analysis to dissect a polysynaptic circuit that originates from the dorsal hippocampus (dHP) in mice. We show that inhibition of 14-3-3, a family of schizophrenia-associated proteins, in the dHP activates VTA DA neurons, and such activation is necessary in eliciting novelty-induced locomotor hyperactivity (psychomotor behavior) in mice. We find that an increased activation of the lateral septum (LS) neurons is necessary for over-activation of DA neurons and psychomotor behavior induced by 14-3-3 inhibition in the dHP. Moreover, 14-3-3 inhibition-induced neuronal activations and behavioral alteration can be mimicked by selective activation of LS-projecting dHP neurons. Collectively, these findings demonstrate how loss of function of one pivotal family of proteins in the hippocampus contributes to activity alterations in the dHP-LS-VTA pathway, which may underlie key pathophysiology of schizophrenia-related symptoms.

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Poster

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National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Phase modulation of resting-state fMRI BOLD signal in cases of schizophrenia with medication

Authors: *C.-Y. YU[1], S.-J. TSAI[1,2,4], A.-C. YANG[1,2,3,5];
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Abstract: Background and objectives: Few studies focused on the abnormal phase modulation of the time-frequency analysis in functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) signal in schizophrenia. The present research aimed to investigate the instantaneous phase relationship among different brain regions in individuals with schizophrenia (SCZ) on antipsychotic medication. We anticipated finding differences of phase coherence or phase difference from functional connections in certain brain regions between SCZ and healthy controls (HC). The association of antipsychotics with functional BOLD signal might be identified by using this novel signal analysis approach. **Methods:** The data in the study was from Taiwan Aging and Mental Illness Cohort (TAMI), which is an MRI and whole genome sequence study at Taipei Veterans General Hospital and National Yang-Ming University since 2012. The BOLD signals of 200 SCZ and 200 HC acquired from TAMI were analyzed with Hilbert-Huang Transform (HHT) and phase analysis at identified frequency bands. In addition, a two-sample t-test with Bonferroni correction was used for examining between-group differences. Finally, the forward stepwise method for multiple linear regression (MLR) models with significantly different connections and controlled demographic variables were built to predict Chlorpromazine (CPZ) dosage. **Results:** This study showed that six intrinsic mode functions (IMFs) were extracted from BOLD signal with ensemble empirical mode decomposition (EEMD) in HHT. The second IMF from EEMD was selected for analysis based on its neuronal correlates according to the previous study's recommendations. Subsequently, the between-group statistically significant number of connection pairs was 616 in phase coherence and 44 in phase difference, while five in both the two phase patterns. MLR models showed that CPZ dosage was associated with phase coherence between left caudate nucleus and left lenticular nucleus, pallidum, phase coherence between right cuneus and right middle occipital gyrus, phase coherence between right postcentral gyrus and right supramarginal gyrus, and phase coherence between postcentral gyrus and left inferior parietal, but supramarginal and angular gyri. **Conclusions:** Our findings using phase coherence and phase difference analysis of BOLD signal support the notion that antipsychotics are associated with alteration in functional brain network. These brain regions may be related to both treatment and side effects of antipsychotics.

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Poster

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Program #/Poster #: P906.04

Topic: H.13. Schizophrenia

Support: NIMH Grant Nos. R61MH112793 and R33MH112793

Title: Designing a BCI to improve working memory in patients with schizophrenia

Authors: Y. LIN[1], *I.-W. SHU[2], S.-H. HSU[3], B. CASTILLO[2], R. SEN[2], V. GANDARA[2], J. A. PINEDA[4], E. GRANHOLM[2], F. SINGH[2];
[1]Electrical and Computer Engin., [2]Psychiatry, [3]Swartz Ctr. for Computat. Neuroscience, Inst. for Neural Computation, [4]Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: *Intro*. Working memory (WM) is critical for optimal cognitive function and often impaired in patients with schizophrenia. Optimal WM performance requires greater neural synchronization in dorsal-lateral prefrontal cortical (DLPFC) areas of the brain (e.g., greater gamma power). Conversely, in patients with schizophrenia, impaired WM is generally associated with attenuated DLPFC activity, including decreased frontal gamma power. We thus hypothesized that training participants with schizophrenia to enhance frontal gamma activity would improve WM. *Methods*. We used EEGLAB (an open-source suite of MATLAB toolboxes) to design a brain-computer interface (BCI) enabling participants to practice increasing frontal gamma activity (i.e., gamma neurofeedback, or NFB). *Results*. To validate BCI effectiveness, we randomized participants with schizophrenia to active (n = 9) or mock (n = 7) gamma-NFB (twice-weekly 30 min sessions for 12 weeks). In support of BCI effectiveness, frontal gamma activity increased by about 0.26 standard deviations (SD) after active NFB, but fell by about 0.50 SD after mock NFB. Furthermore, active NFB improved WM performance by about 0.18 SD, in contrast to a decline of about 0.30 SD with mock NFB. Training-related changes in WM improvement positively-correlated with training-related changes in gamma activity (R = 0.380). Preliminary analyses indicate that active NFB produced greater frontal P3 event-related potentials (ERP), as well as greater frontal gamma and high beta power, during WM (e.g., N-Back); in contrast, mock NFB was associated with declines in frontal P3 amplitudes, no changes in frontal high beta power and a weaker increase in frontal gamma power. *Conclusions*. Gamma-NFB training using a EEGLAB/MATLAB-based BCI effectively increased frontal gamma activity, WM performance and WM-related ERP and high-beta/gamma activity in participants with schizophrenia receiving active NFB, compared to mock NFB. Future studies will focus on identifying neurophysiologic markers of brain changes underlying effective training/learning and improvements in WM performance.

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Poster

P906. Schizophrenia: Circuits and Systems

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Topic: H.13. Schizophrenia

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Title: Comprehensive and simultaneous 3-D imaging of interneuron subtypes in CA1 depict deficits in interneuron activity resulting in microcircuit imbalance in a mouse model for the 22q11.2 deletion syndrome

Authors: *S. HERRLINGER, B. RAO, A. TUTTMAN, T. GEILLER, B. VANCURA, J. GOGOS, A. LOSONCZY;
Zuckerman Inst., Columbia Univ., New York, NY

Abstract: Adults and children with the 22q11.2 deletion syndrome (22q11.2DS) demonstrate cognitive, social and emotional impairments. 22q11.2 deletions are also one of the strongest genetic risk factors for schizophrenia (SCZ). Cognitive impairment in 22q11.2DS and in SCZ, in general, include episodic memory dysfunction. Episodic memory encoding is dictated in part by place cell activity and tuning in the CA1 region of the hippocampus. Using calcium imaging to record place cell activity in live behaving mice in a goal-directed learning and memory task our group previously showed that episodic memory and place cell dynamics in a mouse model for the 22q11.2DS (*Df(16)A*$^{+/-}$) are impaired. However, the mechanisms underlying these deficits are still unexplored. The activity of hippocampal place cells is under strong inhibitory control by several heterogeneous subtypes of GABAergic interneurons (INs). A wealth of evidence points toward deficits in local microcircuits and IN dysfunction as a key factor in the pathophysiology of SCZ; however, most studies have focused selectively on reduced parvalbumin-expressing IN activity, which is associated with disorganized network function in various mouse models for SCZ, despite recent studies implicating dysfunction in other IN types, including Somatostatin+, VIP+ and Neuropeptide Y+ expressing INs in various cortical circuits. Preliminary data further examining CA1 principal neuron dynamics and plasticity collected *in vivo* and *in vitro* suggest that inhibitory circuits are either over-compensating *in vivo* or are intrinsically deficient themselves. In addition, we know very little about how specific *in vivo* activity dynamics of hippocampal IN subtypes are affected by 22q11.2 deletions or other SCZ risk mutations, and we lack basic information on the activity dynamics of identified CA1 interneuron types during *in vivo* behavior in SCZ mouse models. We hypothesized that an inhibitory-disinhibitory microcircuit motif which gates CA1 place cell excitability and plasticity is disrupted by 22q11.2 deletions. We have tested these hypotheses by functionally and molecularly characterizing CA1 inhibitory circuits and their influence over CA1 place cell firing field formation during learning by carrying out large-scale, unbiased 3D AOD GCaMP-Ca^{2+} imaging *in vivo* of collective CA1 IN dynamics with post hoc molecular identification of IN types, and assessed baseline and learning-related changes in *in vivo* activity of INs in *Df(16)A*$^{+/-}$ and littermate controls. Preliminary results identify subtype-specific alterations in IN dynamics, contributing to microcircuit imbalances in this model.

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Poster

P906. Schizophrenia: Circuits and Systems

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Program #/Poster #: P906.06

Topic: H.13. Schizophrenia

Title: Optogenetic inhibition of posterior caudatoputamen indirect pathway neurons causes auditory cortical activation in rodents

Authors: *Z. YELLOWMAN[1], R. YANG[2], T. J. ZAFAR[1], E. M. NIKULINA[1], R. P. HAMMER, Jr.[1]; [1]Basic Med. Sci. & Clin. Translational Sci., [2]Basic Med. Sci., Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: The "auditory striatum" has emerged as a prominent source for regulating elements of auditory information. Our laboratory has shown that dopamine infusion into a region of the posterior caudatoputamen of rats activates neurons within the primary auditory cortex (Au1). This region of the caudatoputamen in rodents is analogous to the auditory striatum. We utilized optogenetics to explore the involvement of indirect pathway neurons in the context of auditory cortical activity. Indirect pathway neurons of the auditory striatum in adult male Sprague Dawley rats (~250 grams) were identified and unilaterally transfected with retroAAV expressing Jaws-GFP (#65014-AAVrg, Addgene; n=9), ChR2(H134R)-GFP (#58880-AAVrg, Addgene; n=6) or GFP (#50465-AAVrg, Addgene; n=7) by unilateral stereotaxic infusion into the globus pallidus (coordinates: -1.8 mm AP, 3.9 mm ML, -6.2 mm DV; Paxinos and Watson, 2013). Overexpression of the retrograde construct containing Jaws is known to inhibit neurons, while ChR2 overexpression activates neurons upon ontogenetic stimulation. Rats were implanted with an LED fiber optic probe targeting the auditory striatum, and wireless optogenetic stimulation was performed in sound-attenuated chambers for 30 min. Following perfusion and tissue processing, immunohistochemical labeling of Fos in the caudal striatum (-1.8 mm AP) and Au1 (-4.3 mm AP) were quantified and compared using one-way ANOVA. Fos labeling in Au1 was significantly greater in Jaws as compared to GFP ($p<0.001$) or ChR2 ($p<0.01$) groups. Ipsilateral Au1 showed significantly more Fos expression compared to contralateral Au1 only in the Jaws group ($p=0.001$). Significantly greater Fos labeling was present in striatal indirect neurons transfected with ChR2 compared to Jaws ($p<0.01$) or GFP ($p<0.01$), suggesting that ChR2 activated while Jaws inhibited these neurons. Indirect striatal projection neurons are less likely to fire in the presence of dopamine due to their predominant expression of D_2-like receptors. We show here that optogenetic inhibition of caudal striato-pallidal neurons significantly increased Fos expression in Au1. By contrast, Au1 activation present during auditory hallucinations is presumably blocked by antipsychotic drug-induced D_2-receptor antagonism. Therefore, dopamine- or optogenetically-induced inhibition of auditory striatal indirect pathway neurons may lead to activation of Au1 neurons, producing a perception of auditory activity. These findings may elucidate a pathophysiological mechanism underlying auditory hallucinations as defined within a novel auditory striato-pallido-thalamo-cortical brain circuit.

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Poster

P906. Schizophrenia: Circuits and Systems

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Program #/Poster #: P906.07

Topic: H.13. Schizophrenia

Title: Haloperidol pretreatment reduces auditory cortex Fos expression caused by posterior striatal dopamine infusion in proestrus female rats

Authors: T. J. ZAFAR, Z. YELLOWMAN, E. M. NIKULINA, *R. P. HAMMER, Jr.;
Basic Med. Sci. & Clin. Translational Sci., Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: Schizophrenia-related brain mechanisms are poorly understood, but a prevalent theory involves dopamine over-stimulation as all major drug treatments block D_2-like dopamine receptors (D2Rs) in the brain. We have shown that 50 nM dopamine infusion into the auditory striatum activates primary auditory cortex (Au1) in male and female rats, and dopamine increases Au1 Fos expression during proestrus, but not other stages of the estrous cycle. To determine whether D2R antagonist pretreatment would block dopamine-induced Fos expression in Au1, haloperidol was administered prior to striatal dopamine infusion in proestrous female rats. We hypothesized that haloperidol pretreatment would inhibit Fos expression in the Au1 after striatal dopamine infusion in female rats. Infusion cannulas were implanted targeting the posterior caudatoputamen (CP; AP: -1.80 mm, ML: 4.4 mm, and DV: 5.0 mm), and daily vaginal smears were conducted to determine the estrous stage. While in proestrus, rats received systemic haloperidol pretreatment (0 or 0.5 mg/kg, IP in saline vehicle). Rats were then transferred to a sound-attenuated chamber with 70 dB background noise and 30 min later received striatal infusion of dopamine (0 or 50 nM in saline vehicle) at 0.2 µl/min for 5 min, then were returned to the sound-attenuated chamber for 90 min (n=6 per group). Twenty µm sections from CP and Au1 were processed for Fos immunolabeling with statistical comparisons by 2-way ANOVA and Tukey's tests. Striatal dopamine infusion following saline pretreatment significantly increased Fos expression in the CP ($p < 0.0001$) and in the Au1 ($p < 0.0001$) compared to saline-saline treatment, as well as compared to haloperidol-saline treatment in the CP ($p < 0.0003$) and in the Au1 ($p < 0.0001$). Haloperidol pretreatment significantly reduced Fos expression in the CP ($p < 0.05$) and in the Au1 ($p < 0.005$) compared to saline-dopamine treatment, although dopamine with haloperidol pretreatment increased Fos labeling in the CP ($p < 0.006$) and in the Au1 ($p < 0.05$) compared to saline-saline treatment. Haloperidol alone did not alter Fos labeling in CP or Au1. The results reveal that pretreatment with a moderate dose of haloperidol significantly reduced Au1 activation caused by striatal dopamine infusion in proestrus female rats, while this dose of haloperidol alone did not induce Fos in the CP. Thus, striatal dopamine probably acts on indirect pathway neurons to produce Au1 activation, as these neurons express predominantly D2Rs which are blocked by haloperidol to reduces this effect. These results provide a better understanding of the brain mechanism which may underlie dopamine-induced auditory hallucinations.

Disclosures: T.J. Zafar: None. **Z. Yellowman:** None. **E.M. Nikulina:** None. **R.P. Hammer:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: RF1MH121274

Title: Cell-type and age-dependent bias of PHP.eB serotyped adeno-associated viruses for mouse neocortical cell types

Authors: *J. BENDRICK[1], M. WALKER[2], C. TRADER[1], S. YAO[1], B. TASIC[1], T. L. DAIGLE[1]; [1]Allen Inst. For Brain Sci., Seattle, WA; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Recombinant adeno-associated viruses (AAVs) are widely used tools in modern neuroscience and have enabled unprecedented access to brain regions and cell-types within the mammalian brain. These AAVs are versatile and can be engineered to deliver a diversity of gene cargoes into the brain via local or systemic injections, to support basic neuroscience research and targeted gene therapy applications. Specifically, PHP.eB serotyped AAVs allow for delivery of virus throughout the central nervous system, which enables access to neuronal cell types throughout the brain. While previous studies elucidated how PHP.eB serotyped AAVs cross the blood brain barrier, little is known about how well these AAVs infect genetically-defined inhibitory and excitatory neurons across the cortical sheath or the critical factors affecting viral transduction following systemic delivery. In this study, we evaluate the efficiency of PHP.eB serotyped AAV transduction in the brain following retro-orbital delivery of virus into mice from seven Cre;Ai14 double transgenic crosses that label major excitatory and inhibitory cell types. We demonstrate that PHP.eB serotyped viruses preferentially infect parvalbumin (Pvalb) and somatostatin (Sst) subclasses, and layer 5 excitatory neurons and are biased against (i.e. least efficiently transduce) vasoactive intestinal peptide (Vip) and layer 4 excitatory neurons. These cell-type specific biases in infectivity were found to be well maintained in the several cortical regions analyzed and could not be improved by delivery of up to ~1.0E+12 genome copies (GC) of virus. Additionally, we found an age-dependent decrease in viral transduction across diverse mouse neocortical cell-types. Collectively, our results reveal the inherent biases of PHP.eB serotyped AAVs for mouse neocortical cell types and identify age as a key factor to consider when delivering these viruses systemically.

Disclosures: J. Bendrick: None. **M. Walker:** None. **C. Trader:** None. **S. Yao:** None. **B. Tasic:** None. **T.L. Daigle:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH GM-123582
NIH MH-120823
HHMI

Title: Genetically encoded biosensors for typical antidepressants

Authors: *Z. BLUMENFELD[1], A. L. NICHOLS[1], L. LUEBBERT[1], P. M. BORDEN[3], A. K. MUTHUSAMY[2], J. S. MARVIN[3], C. KIM[1], S. GRANT[2], D. P. WALTON[2], H. J. KNOX[2], J. H. WANG[1], L. L. LOOGER[3], D. A. DOUGHERTY[2], H. A. LESTER[1];
[1]Biol. and Biol. Engin., [2]Chem. and Chem. Engin., Caltech, Pasadena, CA; [3]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Major depressive disorder (MDD) is often treated with selective serotonin reuptake inhibitors (SSRIs), with the assumption that elevated extracellular serotonin concentration underlies the therapy. That SSRIs bind to the serotonin transporter (SERT) on the plasma membrane (PM) is indisputable; however, SSRIs typically require 2-6 weeks before a response to treatment can be observed, and events during this delay remain elusive. We propose that SSRI-SERT interactions *within organelles* are crucial aspects of the therapeutic mechanism of SSRI treatment, especially within the endoplasmic reticulum (ER). Therefore, we have developed genetically encoded fluorescent biosensors to study the subcellular pharmacokinetics of SSRIs. OpuBC, a monomeric bacterial periplasmic binding protein (PBP), has a ligand-binding site that can be mutagenized for the evolution of biosensors. We inserted a circularly permuted "superfolder" GFP (cpGFP), flanked by several residue linkers, within the PBP interdomain hinge regions. By applying directed evolution of binding pocket residues, we have produced $\Delta F/F_0$ &gt 1 at 1 μM for two sensitive SSRI-biosensor pairs, termed "**i**ntensity-based **Esc**italopram-**S**e**n**sing **F**luorescent **R**eporter" (iEscSnFR) and "**i**ntensity-based **Fluox**etine-**S**e**n**sing **F**luorescent **R**eporter" (iFluoxSnFR). These are selective sensors which bind neither to endogenous molecules - including neurotransmitters - over the range of pharmacologically-relevant concentrations, nor to other exogenous compounds. Results obtained with our biosensors in mammalian cells (HeLa) using targeting and retention sequences that direct the constructs to the ER or the PM show that escitalopram and fluoxetine enter the lumen of the ER at concentrations similar to those detected on the extracellular surface of the plasma membrane, seconds after the SSRI enters the extracellular space. In mouse primary hippocampal neuronal cultures, we likewise measure entry into the ER, though the compounds appear to enter and leave neurons much more slowly. These experiments provide first evidence for the existence and relevance of SSRI inside-out drug action. To probe "inside-out" mechanisms further, we synthesized quaternized (permanently positively charged) derivatives, and we confirmed that these compounds do not enter the ER, though they interact similarly to the parent compounds with both the PM-targeted constructs as well as in purified protein. We hope that further application of these tools will show the initial steps in the pathway of SSRI intracellular pharmacokinetics, helping to elucidate the role "inside-out" neuropharmacology in therapy for MDD.

Disclosures: Z. Blumenfeld: None. **A.L. Nichols:** None. **L. Luebbert:** None. **P.M. Borden:** None. **A.K. Muthusamy:** None. **J.S. Marvin:** None. **C. Kim:** None. **S. Grant:** None. **D.P. Walton:** None. **H.J. Knox:** None. **J.H. Wang:** None. **L.L. Looger:** None. **D.A. Dougherty:** None. **H.A. Lester:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Howard Hughes Medical Institute
Harvard University

Title: A protein reporter for recording brain-wide neural activity at the single-cell level

Authors: *D. LIN, X. LI, A. E. COHEN;
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Abstract: Behavior emerges from the interacting activity of widely distributed ensembles of neurons. A central goal in neuroscience is to identify the neural ensembles associated with distinct sensory inputs, behaviors or physiological states. To understand the distinct roles of different subsets of neurons in complex brain states, one would like to perform multiple experiments in a single animal, and to identify the neural ensembles activated in each condition, with single-cell resolution. To our knowledge, no such tool exists. Here we present a protein-based approach to map brain-wide dynamics of immediate early gene (IEG) activation. A soma-localized protein reporter (soma-HaloTag) was engineered to form a physical record of IEG *c-fos* activation, which can be labeled at multiple time-points by systemic administration of its different-colored fluorescent substrates (HaloTag ligands). This technology enables labeling of at least three distinct brain-wide neural ensembles, with a time resolution of approximately three hours and single-cell resolution. The tool opens the possibility of multi-timepoint global activity mapping at the single-cell level and provides a promising strategy for identifying the internal representations and connections of different brain states.

Disclosures: D. Lin: None. **X. Li:** None. **A.E. Cohen:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 1DP2GM146247-01

Title: Developing Optogenetic Nanobodies to Control Neuronal Signaling Proteins

Authors: *C. WOODS, J. ENGLISH;
Univ. of Utah, Salt Lake City, UT

Abstract: Optogenetic and chemogenetic tools permit the functional modulation of specific neuronal populations *in vivo.* Popular tools for this purpose include genetically expressed light-gated channels (Rhodopsins) or designer receptors exclusively activated by designer drugs (DREADDs). These tools allow manipulation of specific neuronal subsets within complex circuits. These tools do not directly modulate native signaling events, but instead introduce exogenous signaling proteins to impinge on native cell signaling. An improvement on these approaches would be to allosterically modulate native neuronal

signaling proteins during their native, physiological relevant activities. Through mammalian directed evolution with VEGAS (Viral Evolution of Genetically Actuating Sequences), our lab has developed nanobodies to modulate endogenous protein signaling. Nanobodies are small (~15 kDA) antigen binding fragments derived from heavy-chain-only antibodies found in camelids. Their small size and high specificity and affinity for an antigen make them ideally suited for use as an intrabody in living cells to endogenously control various protein functions. However, constitutive and unregulated expression of nanobodies is an undesirable tool for on-demand neuronal circuit control. Recently, Gil et al. (2020) inserted light-oxygen-voltage (LOV) domains into nanobodies, deemed OptoNBs, to enhance or inhibit nanobody binding to a protein of interest upon blue-light illumination. This photoswitchable control is the next step in fine-tuning nanobody research used thus far to dissect signaling pathways and circuits *in vivo*. Here, we generated optically-activatable LOV nanobodies targeting the human G-protein coupled receptor 5-HT_{2A} (serotonin 2A receptor). LOV domains were introduced at multiple positions of a nanobody previously evolved as a positive allosteric modulator of the 5-HT_{2A} receptor. These 5-HT_{2A}-LOV chimeric nanobodies were screened for their ability to optogenetically enhance 5-HT_{2A} signaling upon administration of serotonin. Our preliminary data indicate that these constructs can optogenetically modulate endogenous receptor activity. Using the VEGAS platform, we will develop additional nanobodies targeting neurologically important G-protein coupled receptors as candidates for OptoNB development. We believe our ability to control allosteric nanobody binding with light, in combination with our ability to evolve functional nanobodies against a broad range of cell signaling targets will prove to be essential tools for cell, developmental, and systems neuroscience.

Disclosures: C. Woods: None. **J. English:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Howard Hughes Medical Institute
Harvard University

Title: Pulse-chase HaloTag labeling of surface-exposed AMPA receptors reveals the spatial distribution of potentiated synapses in vivo

Authors: *D. KIM, X. LI, H. TIAN, J. D. WONG-CAMPOS, A. E. COHEN;
Chem. and Chem. Biol., Harvard Univ., Cambridge, MA

Abstract: Memories are formed by the strengthening of synaptic connections, predominantly via increases in the density of α-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in the post synaptic membrane. Increases in AMPAR density upon learning have been observed by *in vivo* 2-photon microscopy of a fusion between an AMPA receptor and a pH-sensitive fluorescent protein. This technique required registration of individual synapses at multiple time-points, and the imaging depth was limited by light scattering to superficial cortical layers. We developed an approach to labeling surface-

exposed AMPARs at different time-points via intracortical injection of membrane-impermeable HaloTag-ligand dyes, followed by *ex vivo* multi-color imaging. By separating the *in vivo* encoding from the *ex vivo* readout, this approach enables wide-area mapping of AMPAR dynamics in any brain region. We fused GluA1, a subunit of AMPAR, with the HaloTag, a self-labeling protein which forms a covalent bond to an exogenous ligand (HaloTag-ligand). We expressed HaloTag-GluA1 in mouse barrel cortex pyramidal neurons, and saturated the surface-exposed AMPARs via local injection of a membrane impermeable HaloTag-ligand dye. We stimulated the whiskers and then injected a different-colored HaloTag-ligand dye to label newly surface exposed AMPARs. High-resolution multicolor imaging of layer 2/3 pyramidal neurons in fixed brain slices revealed an increase in AMPAR density upon whisker stimulation. Pulse-chase HaloTag labeling of AMPARs can be a powerful tool to investigate the distribution and time-course of synaptic potentiation throughout the brain. We envision that this method will expand our knowledge of how memories are formed and stored.

Disclosures: D. Kim: None. **X. Li:** None. **H. Tian:** None. **J.D. Wong-Campos:** None. **A.E. Cohen:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Monitoring Neuromodulators by Fluorescence Lifetime Imaging of Neuromodulator Sensors

Authors: *P. MA, P. CHEN, E. TILDEN, Y. CHEN;
Dept. of Neurosci., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Monitoring the dynamics of neuromodulators is key to understand their functions. Engineering of G protein coupled receptor (GPCR)-activation-based neuromodulator optical sensors has enabled us to detect the neuromodulator changes based on the sensor fluorescence intensity changes. However, intensity-based measurement is only able reflect short-term and phasic changes of neuromodulators. In contrast, fluorescence lifetime measurement of the sensors, which is independent to the sensor expression levels, provides the possibility of measuring tonic activities, long-term chronic changes, and absolute concentrations of neuromodulators. Here using fluorescence lifetime imaging, we screened the commonly used GPCR-activation-based neuromodulator sensors and report that some neuromodulator sensors show changes of fluorescence lifetime. By simulation of the sensor fluorescence and autofluorescence of the bio-tissues, we found that autofluorescence contribution difference before and after sensor activation was not sufficient to induce as much fluorescence lifetime change as experimentally observed, indicating the authentic fluorescence lifetime change of the sensor. Using fluorescence lifetime measurement, we detected changes of neuromodulator in acute mouse hippocampus brain slices. Using fluorescence lifetime photometry combined with Electroencephalography (EEG) and Electromyography (EMG) recordings, we measured the long-term neuromodulator changes in the hippocampus along with sleep-wake cycles within 24 hours and across different days in mice. In summary, our study shows the

fluorescence lifetime changes of some GPCR-activation-based neuromodulator sensors and provide some proof-of-principle applications of fluorescence lifetime measurement in vitro and in vivo.

Disclosures: P. Ma: None. **P. Chen:** None. **E. Tilden:** None. **Y. Chen:** None.

Poster

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Program #/Poster #: P908.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH F32 MH120887-03
NIH R01 NS045193
H2020 Marie Skłodowska-Curie Fellowship: SicNet

Title: Temporal fidelity and integration of spike activity with the new jGCaMP8f calcium indicator

Authors: *G. J. BROUSSARD[1], F. J. URRA QUIROZ[2], G. DIANA[2], L. A. LYNCH[1], D. A. DIGREGORIO[2], S. S.-H. WANG[1];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Neurosci., Inst. Pasteur, Paris, France

Abstract: GCaMPs are indispensable for surveying action potential-associated calcium activity in populations of neurons. However, GCaMP6f and 7f exhibit slow fluorescence rise kinetics and a non-linear calcium-dependence, placing limits on their ability to read out spike timing and number. To compare how these GCaMP variants and the newer jGCaMP8f translate neural activity to fluorescence dynamics, we used stopped-flow fluorimetry of purified GCaMP protein and ex vivo recordings from parallel fiber boutons in brain slices which could be given controlled stimuli. GCaMP6f and 7f responses were largely explained by a slow, calcium-driven process with high cooperativity as indicated by their Hill coefficients (2.3 and 2.1). This cooperativity can account for ex vivo non-linearity of up to a three-fold increase in response to the second of two spikes applied 10 ms apart. In contrast, capturing the faster rise kinetics of jGCaMP8f required an additional fast calcium-dependent activation process, where each process displayed low cooperativity (Hill coefficients = 1.2 for fast and slow processes), and showed a near-linear response to paired spikes. However, jGCaMP8f also showed up to three-fold slower decay times in response to burst-rate (100 Hz) spiking, consistent with cumulative activation of the slow process. Despite this effect, jGCaMP8f's linearity and rapid rise time make it suitable for accurate spike inference using straightforward methods, even at high instantaneous firing rates. Taken together, this work identifies functional attributes of next-generation GCaMP variants that are suited for high-fidelity spike inference.

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Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.08

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Human Frontier Science Program #RGP0062/2019
Okinawa Institute of Science and Technology Graduate University
Government of Japan

Title: Dopamine distribution in time and space: effects of methylphenidate

Authors: *J. A. CHOUINARD[1], S. TAKAHASHI[1], N. KITAMURA[1], K. LIYANAGAMA[1], K. KURIMA[1], L. TIAN[2], J. R. WICKENS[1];
[1]Okinawa Inst. of Sci. and Technol., Onna-son, Japan; [2]Biochem. and Mol. Med., Univ. of California, Davis, Davis, CA

Abstract: Methylphenidate is the most widely prescribed treatment for attention-deficit hyperactivity disorder (ADSD). It inhibits the dopamine transporter (DAT) and, by reducing clearance, leads to increased and prolonged dopamine (DA) signal in the extracellular space, but its macroscopic effects are not completely understood. We first investigated the temporal dynamics of dopamine by fast-scan cyclic voltammetry (FSCV) using focal electrical stimulation. In the presence of the DAT blocker, a delayed concentration peak can be observed until after the end of the stimulation. This cannot be explained by a simple time delay due to diffusion time because there is no corresponding delay in onset of dopamine increase at the distant recording site. Diffuse optical stimulation was also used to assess if the initial increase in dopamine could result from an electrical current spread causing release at distant sites, while the delayed peak is due to diffusion delays. However, similar results to focal electrical stimulation were obtained. We finally explored if diffusing waves would occur on a much smaller spatial scale by combining simultaneous FSCV with pre or post-synaptic expression of the genetically encoded dopamine sensors dLight1.3b or dLight2.1 imaging to obtain more spatiotemporal information on dopamine release. A new type of Cre-dependent adeno-associated virus was also engineered to enhance the more sensitive dopamine sensor dLight2.1, which was found to provide bright, easy to locate sensor expression, with a better signal-to-noise ratio at 3 weeks post-injection. Results indicate that the clearance of dopamine is slow in all monitoring modalities used in the presence of DAT blockers, but the delayed peak can only be observed in voltammetry traces. We conclude that dLight reveals dopamine levels in the cell inner compartment - much closer to the source whether it is pre or post-synaptic - while FSCV is sensing diffusion way beyond the synaptic space. In the end, both FSCV and dLight imaging techniques provided different, but useful complementary information. The influence of methylphenidate on apparent diffusion distance of dopamine may be important for understanding its effects on processing of reward signals and its mechanisms of action in the treatment of ADHD.

Disclosures: J.A. Chouinard: None. **S. Takahashi:** None. **N. Kitamura:** None. **K. Liyanagama:** None. **K. Kurima:** None. **L. Tian:** None. **J.R. Wickens:** None.

Poster

P908. Biochemical and Molecular Techniques I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P908.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Cynthia and George Mitchell Foundation

Title: Development of multicolor fluorescent probes for heterogeneous Aβ deposits in Alzheimer's disease

Authors: *R. AL-LAHHAM, A. MUKHERJEE, C. SOTO;
UT Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Accumulation of Aβ into amyloid plaques and tau into neurofibrillary tangles are pathological hallmarks of Alzheimer's disease (AD). AD is also a mixed proteinopathy with α-synuclein, the pathological hallmark of Parkinson's disease, being detected in more than 50% of AD cases. However, there is a significant intra- and inter-individual variability with respect to coexistence, morphology and conformation of these aggregates, which may account for the extensive clinical heterogeneity observed in neurodegenerative diseases. In AD, Aβ can deposit in a spectrum of morphology from diffuse to fibrillar, and dense-cored plaques. The pathological relevance of these varied morphologies in AD is still unknown. In this study, we sought to develop an array of fluorescent dyes to specifically probe Aβ aggregates, in an effort to address their diversity. 10 µm-thick sections of paraffin-embedded frontal or temporal cortex from pathologically confirmed AD patients and healthy control as well as midbrain specimens from pathologically confirmed LBD patients were used for dyes staining, as well as 4G8, AT8, phospho-α-synuclein and α-synuclein immunostaining. APP/PS1 mice brain sections were also used for staining and immunostaining. We screened a small library of benzothiazole-coumarin fluorescent probes and identified three structurally similar fluorescent probes, PMDAM022, PMDAM006, and PMDAM015, that intensely stained Aβ plaques in frontal cortex AD brain sections, both parenchymal and vascular, with no apparent staining in healthy control brain. This was confirmed by immunostaining of mirror image sections with 4G8 antibody. Amyloid plaques in APP/PS1 mouse brain were also recognized by these probes. The set of these three dyes allowed the visualization of Aβ deposits in three different colors (blue, green and far-red). The triple-stained sections display a staining pattern that suggests they bind to different regions of the plaques, and therefore would be valuable to be used for different plaques morphologies. Interestingly, PMDAM0022 also stained NFTs in AD human brain temporal cortex sections and Lewy bodies in LBD human midbrain sections, while the PMDAM006 and PMDAM015 did not. Aβ aggregate-specific dyes identified in this study have the potential to be further developed into Aβ imaging probes for the diagnosis of AD. In addition, the far-red dye we developed in this study may serve as an imaging probe for small animal imaging of Aβ pathology. The present findings have several implications as they will not only facilitate the development of novel and refined diagnostic tools but also will help us address the clinical heterogeneity observed within AD.

Disclosures: R. Al-Lahham: None. **A. Mukherjee:** None. **C. Soto:** None.

Poster

P913. Genetic Techniques III

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P913.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Hock E. Tan and K. Lisa Yang Center for Autism Research at MIT
Poitras Center for Affective Disorders Research at MIT
NIH/NIMH Conte Center Grant (P50 MH094271)
NIH Office of the Director (U24 OD026638)

Title: Genome editing for non-human primates

Authors: *T. AIDA[1], J. J. WILDE[1], D. ROY[3], Y. ZHANG[1], R. C. DEL ROSARIO[3], M. WIENISCH[1], Q. ZHANG[1], G. FENG[1,2,3];
[1]McGovern Inst. for Brain Res., [2]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Many of the critical neural circuits and regional neuronal populations at the center of higher human cognitive function are not present in lower mammalian brains and can be studied only in nonhuman primate (NHP) brains. The recent emergence and rapid development of new genome editing technologies, such as the CRISPR/Cas system, have opened the door for generating genetically modified NHP models. These genetic NHP models are transforming our understanding of higher brain functions and facilitating the development of effective treatment for human brain disorders. We have developed a series of CRISPR technologies to specifically manipulate genomic sequences in NHP zygotes in an efficient, precise, and predictable manner for the generation of genetically modified NHPs. Importantly, these genetic NHP models can faithfully recapitulate symptoms of human psychiatric disorders. Finally, we show strategies empowering rapid homozygous animal production and direct in vivo genomic manipulation. Taken together, these genome editing technologies accelerate functional brain research using genetic NHP models.

Disclosures: T. Aida: None. **J.J. Wilde:** None. **D. Roy:** None. **Y. Zhang:** None. **R.C. Del Rosario:** None. **M. Wienisch:** None. **Q. Zhang:** None. **G. Feng:** None.

Poster

P913. Genetic Techniques III

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Program #/Poster #: P913.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH/NIDA P30 DA048736-01
NIH T32 DA07278-20

Title: Cell-specific genome editing in the mouse central nervous system utilizing a novel CRISPR/Cas9 technique

Authors: *M. A. QUINLAN[1], A. C. HUNKER[4], M. X. BERNSTEIN[2], M. E. SODEN[3], L. S. ZWEIFEL[1];
[1]Psychiatry and Behavioral Sci., [2]Neurosci., [3]Pharmacol., Univ. of Washington, Seattle, WA; [4]Allen Brain Inst., Seattle, WA

Abstract: Since the discovery of CRISPR/Cas9 (Clustered Regularly Interspaced Palindromic Repeats/CRISPR associated protein) as an effective means to modify the genomes of plants, animals, and bacteria it has emerged as the method of choice for genome editing and engineering. Although CRISPR/Cas9 methods have been broadly implemented in the *in* vitro setting at the single-cell level, their deployment in targeted gene modification within specific cell types of an intact multicellular organism has been limited by their efficiency in these contexts. Here, we sought to address this limitation by developing and optimizing a new technology for selective gene editing using a CRISPR/Cas9 method in combination with multiple copies of single-stranded DNA (msDNA) that acts as the homology donor template generated by a bacterial reverse transcriptase (RtEc86). Our method, dubbed DNA REplacemnt through AMplification (DREAM) is a viral-based system with the delivery of a cell-specific Cas9 and an RtEc86 that reverse transcribes our homology donor template *in vivo* in the central nervous system (CNS) in an adult mouse. To test the efficacy of this strategy, we targeted gene insertion in the mouse CNS by linking an EGFP coding sequence to homology arms flanking a Cas9-targeted sequence in the tyrosine hydroxylase (*Th*) gene. We previously demonstrated the efficacy of targeting mutagenesis of *Th* in the ventral tegmental area (VTA) utilizing our cell-specific CRISPR/Cas9 loss-of-function tool (Hunker et al. 2020). Using both immunohistochemistry and targeted sequencing, we validated the targeted insertion of EGFP into the TH locus and demonstrate that DREAM editing is highly efficient. We further assessed the minimal homology arm length for targeted insertion and tested the necessity of RtEc86 and Cas9. Based on this data, we conclude that targeted gene insertion *in vivo* in the adult CNS is highly efficient, rapid, and precise. The development of our DREAM technology will allow researchers to easily and precisely edit the genome *in vivo* and future experiments will assess the broad applicability of DREAM editing in other cell types and organisms. In addition to being a valuable molecular tool for basic research, we believe this strategy will have wide therapeutic potential.

Disclosures: M.A. Quinlan: None. **A.C. Hunker:** None. **M.X. Bernstein:** None. **M.E. Soden:** None. **L.S. Zweifel:** None.

Poster

P913. Genetic Techniques III

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Topic: I.01. Molecular, Biochemical, and Genetic Techniques

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NIH Grant MH120569
NIH Grant MH122414

NIH Grant MH123742

Title: Using CRISPR-dCas13 RNA editing technology for novel site-specific manipulations of ubiquitin-proteasome signaling during memory formation

Authors: *K. FARRELL[1], M. MUSAUS[2], T. J. JAROME[1];
[1]Dept. of Animal and Poultry Sci., [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: The ubiquitin-proteasome system (UPS) controls the majority of protein degradation in cells. This degradation process occurs through the regulatory protein ubiquitin, of which multiple can bind a target substrate and form polyubiquitin chains at 8 different linkage sites that each have unique functions. The most abundant polyubiquitin modifications are K48 and K63, the latter of which is thought to be independent of the degradation process while the former is preferentially targeted for degradation by the 26S proteasome, which is activated by phosphorylation of the RPT6 subunit at serine 120 (S120). Over the last decade, numerous studies have demonstrated that UPS-mediated protein degradation is necessary for memory formation in several brain regions. However, this evidence was obtained through broad manipulations of UPS signaling, such as proteasome inhibitors or knockdown of specific ubiquitin ligases. Due to this, the role of specific proteasome subunit phosphorylation sites and diverse polyubiquitin chains, especially those independent of the protein degradation process, in memory formation has never been directly tested. To address this gap in the field, we adapted the CRISPR-dCas13 (catalytically dead Cas13) system in which the dCas13 is fused with the deaminase protein ADAR (CRISPR/dCas13b-ADAR) to make site-specific modifications on the major ubiquitin coding gene, Ubc, and the RPT6 coding gene, Psmc5. We generated multiple guide RNAs (gRNAs) targeting the S120 codon of the Psmc5 transcript, converting it to glycine. In rat B35 cells we observed reduced levels of phosphorylated RPT6-S120 without any changes in total RPT6 levels (3 biological replicates, unpaired t-test, $P < 0.05$). Using the same experimental design, we targeted the lysine-63 (K63) codon in the Ubc gene to convert this lysine to glutamate and found reduced K63 polyubiquitination levels with no changes in the neighboring lysine-48 linkage site, indicating a site-specific codon edit. Next, we tested whether these plasmids could successfully control memory formation in vivo. We found that editing of K63 polyubiquitination in the amygdala impaired contextual fear memory in female rats ($n = 6$ per group, unpaired t-test, $P < 0.05$). Together, these data demonstrate the efficacy and specificity of this novel approach for generating single mismatches on RNA transcripts in vitro and in vivo, which provides a precise, endogenous method for elucidating the function of the proteasome and individual polyubiquitin linkage sites independently in the adult brain and during memory formation.

Disclosures: K. Farrell: None. **M. Musaus:** None. **T.J. Jarome:** None.

Poster

P913. Genetic Techniques III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P913.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: U19 MH114830

RF1MH121274
Paul G. Allen Foundation

Title: A transgenic toolkit for intersectional targeting and functional probing of mouse brain cell types

Authors: *T. L. DAIGLE[1], E. MORIN[1], J. L. BENDRICK[1], Z. YE[2], D. BIRMAN[2], P. BALARAM[1], K. TAKASAKI[1], J. ZHUANG[1], L. SIVERTS[4], M. WALKER[5], A. SEDENO-CORTES[3], B. OUELLETTE[1], G. LENZ[6], J. WATERS[1], N. A. STEINMETZ[2], H. ZENG[1], B. TASIC[1];
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Abstract: Single-cell transcriptomics approaches have unearthed a myriad of new cell types within the mammalian brain and have spurred interest in the study of their function. However, genetic access to many of these transcriptomically-defined cell types is limited because the available transgenic lines label relatively broad and heterogenous neuronal populations and the nascent cell types are often highly interrelated at the level of gene expression, making traditional single-gene-based approaches less tractable. To facilitate higher precision genetic access, we have generated a new suite of FlpO transgenic lines for intersectional genetics that are driven by marker genes for major inhibitory subclasses and select excitatory projection neuron types within neocortex. We characterize these lines systematically using a multi-modal approach and provide a roadmap for how the new tools can be combined with one another and existing transgenes or enhancer-driven adeno-associated viruses (AAVs; Graybuck, Daigle et al., Neuron 2021) to target specific transcriptomic cell types. In parallel, to compliment the FlpO driver lines, we have developed the TIGRE3.0 transgenic reporter platform that builds upon our previously published one (Daigle, Madisen et al., Cell 2018) and enables Cre- and Flp-dependent transgene expression in diverse neuronal populations. This new collection of conditional reporter lines includes tools for labeling (both cell-filling and nuclear), optical physiology, and optogenetics. TIGRE3.0 reporters offer several key advantages compared to published TIGRE2.0 reporters such as lower toxicity and functionally relevant levels of transgenes in a broader range of cell types. Together, these transgenic tools and strategies will enable explorations and better understanding of transcriptomic cell types in the mammalian brain.

Disclosures: T.L. Daigle: None. **E. Morin:** None. **J.L. Bendrick:** None. **Z. Ye:** None. **D. Birman:** None. **P. Balaram:** None. **K. Takasaki:** None. **J. Zhuang:** None. **L. Siverts:** None. **M. Walker:** None. **A. Sedeno-Cortes:** None. **B. Ouellette:** None. **G. Lenz:** None. **J. Waters:** None. **N.A. Steinmetz:** None. **H. Zeng:** None. **B. Tasic:** None.

Poster

P913. Genetic Techniques III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P913.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH grant R21MH118640
NIH grant R01NS104026
NIH grant R01NS069861

NIH grant R01NS097750
Hellman Foundation Fellowship

Title: Exbox: a simple boolean exclusion strategy to drive expression in neurons

Authors: *T. UBINA, T. VAHEDI-HUNTER, A. GUPTA, W. WONG, W. AGNEW-SVOBODA, V. SANTHAKUMAR, M. RICCOMAGNO;
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Abstract: The advent of modern single-cell biology has revealed the striking molecular diversity of cell populations once thought to be more homogeneous. This newly appreciated complexity has made intersectional genetic approaches essential to understanding and probing cellular heterogeneity at the functional level. Here we build on previous knowledge to develop a simple AAV-based approach to define specific subpopulations of cells and temporally control expression by Boolean exclusion logic (AND NOT). This Expression by Boolean Exclusion (ExBoX) system encodes for a gene of interest which is turned ON by a particular recombinase (Cre or FlpO) and turned OFF by another. ExBoX allows for the specific transcription of a gene of interest in cells expressing only the activating recombinase, but not in cells expressing both. We show the ability of the ExBoX system to tightly regulate expression of fluorescent reporters both *in vitro* and *in vivo*, and further demonstrate the powerful adaptability of the system by achieving expression of a variety of virally-delivered coding sequences in the mouse brain. This simple strategy will expand the molecular toolkit available for cell- and time-specific gene expression in a variety of organisms and systems.

Disclosures: T. Ubina: None. **T. Vahedi-Hunter:** None. **A. Gupta:** None. **W. Wong:** None. **W. Agnew-Svoboda:** None. **V. Santhakumar:** None. **M. Riccomagno:** None.

Poster

P913. Genetic Techniques III

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Program #/Poster #: P913.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: MEXT/JSPS KAKENHI Grant 19HP7002
MEXT/JSPS KAKENHI Grant 20H03345
MEXT/JSPS KAKENHI Grant JP18H05412
MEXT/JSPS ABiS JP16H06280
ROIS Challenging Exploratory Research Projects for the Future Grant

Title: Launching NeuroGT: a brain atlas of neurogenic tagging CreER drivers for birthdate-based classification and manipulation of mouse neurons

Authors: *T. HIRATA[1], Y. TOHSATO[2], H. ITOGA[3], G. SHIOI[3], H. KIYONARI[3], S. OKA[4], T. FUJIMORI[4], S. ONAMI[3];
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Abstract: Neuronal birthdates are commonly used to classify neurons. However, the current nucleotide-based birthdating method is retrospective in nature and does not allow the manipulation of classified neurons. To overcome this limitation, we developed neurogenic tagging mouse lines that can induce CreER-*loxP* recombination in the neurons with similar birthdates in living animals and enable various experimental manipulations of the classified subsets. To encourage the use of this resource, we constructed a brain atlas of the neurogenic tagging mouse lines (NeuroGT), which includes holistic sections and whole-mount image data of the *loxP*-recombined neurons and their processes across the entire brain that were tagged at each single day during the neurodevelopmental period. This image database is open to the public, offering people the opportunity to find specific neurogenic tagging driver lines and the stages of tagging appropriate for their own research purposes.
Visit NeuroGT database (https://ssbd.riken.jp/neurogt/), and explore the specific brain region of your interest. If you find a neurogenic tagging driver line promising for your research, you can advance your research using the mouse line deposited at RIKEN BDR after completion of MTA.
See also "Hirata et al, 2021, Cell Reports Methods 1, 100012"
https://doi.org/10.1016/j.crmeth.2021.100012

Disclosures: T. Hirata: None. **Y. Tohsato:** None. **H. Itoga:** None. **G. Shioi:** None. **H. Kiyonari:** None. **S. Oka:** None. **T. Fujimori:** None. **S. Onami:** None.

Poster

P913. Genetic Techniques III

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P913.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIMH-IRP

Title: Increased Efficiency of RapGEF2 Knockout in Drd1-Expressing Medium Spiny Neurons in Mouse Striatum by Cre Amplification

Authors: *H.-Y. ZHANG, W. XU, S. Z. JIANG, L. E. EIDEN;
Sec Molec Neurosci, NIH, NIMH-IRP, Bethesda, MD

Abstract: Cre-loxp technology was introduced in the 1980s (Sauer and Henderson 1988; Sternberg and Hamilton 1981). Many different Cre strains, each containing a Cre transgene under a different tissue-specific promoter, may be crossed with a loxP strain to allow the investigator to study a gene's effects in a tissue-specific manner. The Cre/loxP system is the most powerful tool and widely used to generate a tissue specific or inducible knockout mouse and has been particularly useful to help neuroscientists to study the brain functions within specific cell types and neural circuits. However, not every Cre driver mouse line will produce enough Cre to excise loxp-flanked gene elements to efficiently knock out the gene of interest. We generated a conditional RapGEF2 knockout mouse (Drd1Cre^{+}::RapGEF2$^{fl+/fl+}$cKO) in D1-MSNs by crossing Drd1cre mouse with our interest, RapGEF2 flox mice. No effect on RapGEF2 expression in the striatum of control mice and cKO mice, assessed by immunohistochemistry and Western Blot, was noted. In contrast, a significant decrease in RapGEF2 expression was detected in CA1

and DG subregion of hippocampus by crossing the Camk2α-Cre mouse with RapGEF2 flox mice to generate a RapGEF2 forebrain knockout mouse. These data suggest that the Drd1Cre mouse line does not provide enough Cre recombinase to functionally knock out RapGEF2. To solve this problem, we designed a Cre-dependent Cre (Syn-Flox-Stop-Cre-Venus) construct in C57Bl6 mice, to amplify the Cre expression under the Synapsin promotor, called for short 'Cre-Gone-Wild' (CGW) mice. First, the CGW mice were tested for leakage expression of Cre with Venus indicator by crossing CGW mice with Drd1Cre mice. Data showed that Venus expression was only detected in Syn-flox-stop-cre and Drd1-cre double positive mice, but not in Syn-flox-stop-cre+ only mice, indicating that CGW mice amplify low levels of Cre without non-specific breakthrough. Crossing the CGW mice with $Drd1Cre^{+}$::$RapGEF2^{fl+/fl+}$ mice to generate CGW::$Drd1Cre^{+}$::$RapGEF2^{fl+/fl+}$ cKO mice resulted in significant decrease in RapGEF2 mRNA (around 35%~45%) in both dorsal striatum and nucleus accumbens (NAc) of cKO mice, compared to control mice, by quantitative real-time PCR assay. Treatment of these mice with a single dose of cocaine (20 mg/kg, i.p) resulted in striking attenuation of phospho-ERK expression in the NAc in cKO mice, consistent with our previous reports using AAV-Cre-directed RapGEF2 knockout (Jiang, et al. JN 2021). These data support the successful employment of CGW mice to amplify Cre expression, which will be a useful tool to provide sufficient Cre recombinase to efficiently knockout target gene and knockout gene functions.

Disclosures: H. Zhang: None. **W. Xu:** None. **S.Z. Jiang:** None. **L.E. Eiden:** None.

Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.01

Topic: I.02. Systems Biology and Bioinformatics

Support: UM WISE Judith Cram Memorial Fund Research Award
NSF-1707316
NIH-RF1MH123402
NIH-RF1MH124611

Title: Integrated and extensible neuron morphology analysis in python with nGauge

Authors: *L. A. WALKER[1,2], J. S. WILLIAMS[3], Y. LI[4], D. H. ROOSSIEN, JR[6], N. S. MICHKI[1], D. CAI[4,1,5];
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Abstract: As more whole-brain-scale single neuron morphology reconstructions become accessible to the neuroscience community, robust and comprehensive methods to quantify the differences between neurons of different subtypes and animal species are highly desirable. Several software packages have been developed to analyze 3D neuron tracing results stored in the industry standard SWC format. However, they provide relatively simple quantifications and their non-extendable architecture prohibits these software packages from advanced data analysis and visualization. This limitation has arisen as a major

reason large projects opt for bespoke quantification pipelines which can be hard to reproduce and maintain between projects.
To address these challenges, we developed *nGauge*, a Python toolkit currently available in the Python software repositories. *nGauge* consists of tools to perform morphometry of individual neuron SWC files, plot 2D representations of neurons, as well as perform 3D visualizations and quantifications of multiple neurons. To ensure intercompatibility, *nGauge* implements nearly one hundred morphometrics using definitions from previously published studies. As an application programming interface (API), *nGauge* can be referenced by other popular open-source software to create custom informatics analysis pipelines and advanced visualizations. *nGauge* also defines an extendable data structure that handles volumetric constructions (e.g., soma), in addition to the SWC linear reconstructions, while remaining lightweight and capable of exporting to standardized SWC files. Here, we describe the development of *nGauge* through illustrations of the software's design and data structure. To demonstrate the power of the built-in visualization tools, we provide illustrated examples of reanalyzing published datasets. We envision that *nGauge*'s open-source and expandability nature will attract contributions from the community to its public repository to make it an important toolkit of neuroscience research.

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Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.02

Topic: I.02. Systems Biology and Bioinformatics

Support: K08MH122911
BX002395
BX004189

Title: Transcriptome Wide Association Study of Individually Imputed Genetically Regulated Gene Expression in the Million Veteran Program

Authors: *S. VENKATESH, W. ZHANG, G. HOFFMAN, P. ROUSSOS, G. VOLOUDAKIS;
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Abstract: Most neuropsychiatric disorders are moderately heritable but characterized by many genetic risk variants with weak effects. As such, it is difficult to point to direct causes or elucidate mechanisms of action. Despite the ease in gathering genetic data from humans, genetic data does not easily explain mechanistic effects. Gene expression on the other hand, can more easily explain mechanistic effects, but is harder to gather, especially in brain regions which are critical to the understanding of neuropsychiatric disease. To address this, we developed methods to impute genetically regulated gene expression (GREx) from genotypes and imputed GREx in over four hundred thirty thousand European individuals in the Million Veteran Program (MVP) for a wide variety of tissues and cell types. We use EpiXcan (based on PrediXcan) to develop machine learning models from training genotype, expression, and epigenetic data.

We use custom scripts to impute individual GREx and perform a variety of downstream association analyses, including Principal Component Analysis (PCA), GREx Phenome Wide Association Studies (PheWAS), and Transcriptome Wide Association Studies (TWAS). Results show an overlap in Schizophrenia genes identified by individual level TWAS and those identified by summary level TWAS informed by GWAS. TWAS also identifies genes involved in Major Depressive Disorder and Schizophrenia that are also implicated via other methodologies. Finally, correlation of targeted genes with COVID-19 severity reveals correlations seen in COVID-19 positive individuals. GREx presents a unique solution to integrate effects across the genome and increase sample size in gene expression analyses. We are pursuing the creation of additional EpiXcan models, improved statistical methods for downstream association analyses, and replication efforts across biobanks. We plan to perform these analyses in all ancestries, available EpiXcan and PrediXcan models, and relevant phenotypes.

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Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.03

Topic: I.02. Systems Biology and Bioinformatics

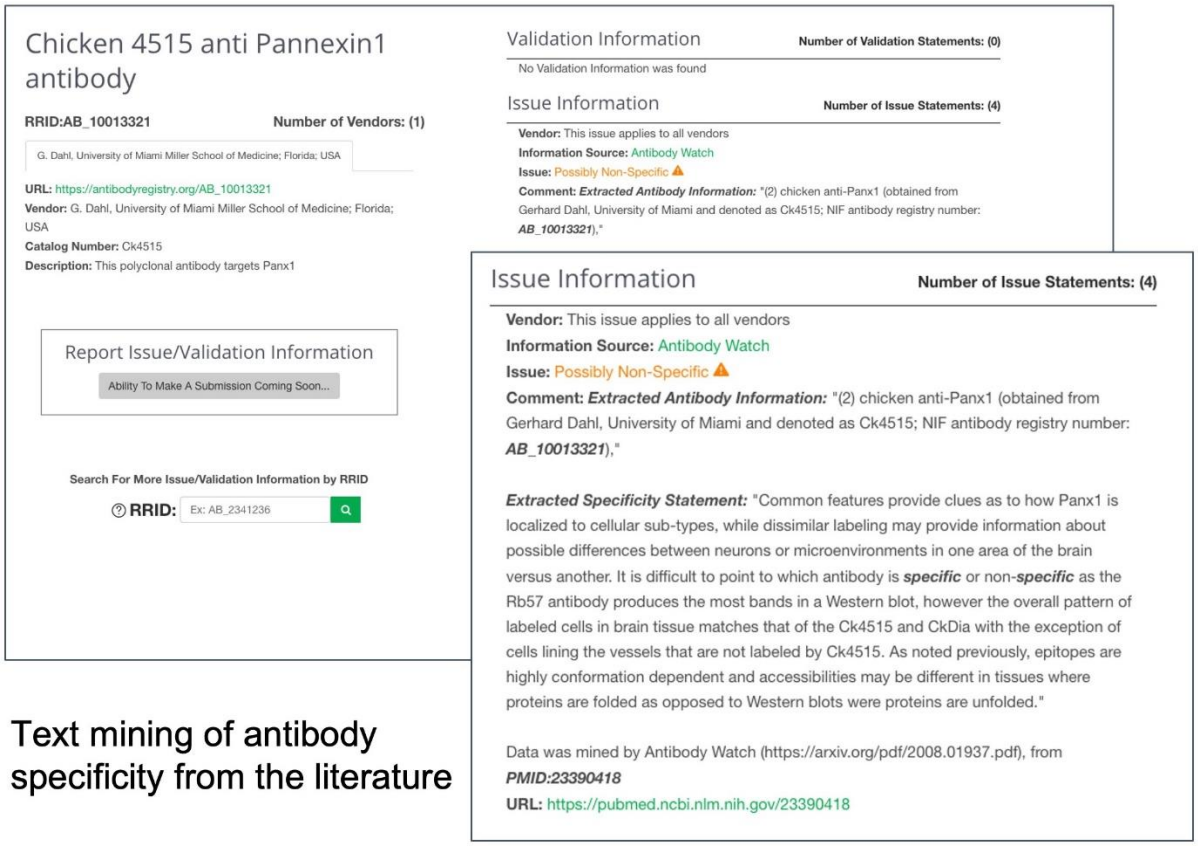
Support: NIH grant U24DK097771, which supports the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Information Network (dkNET, https://dknet.org)

Title: Resource Watch - Making Research Resource Issue, Characterization and Validation Information FAIR

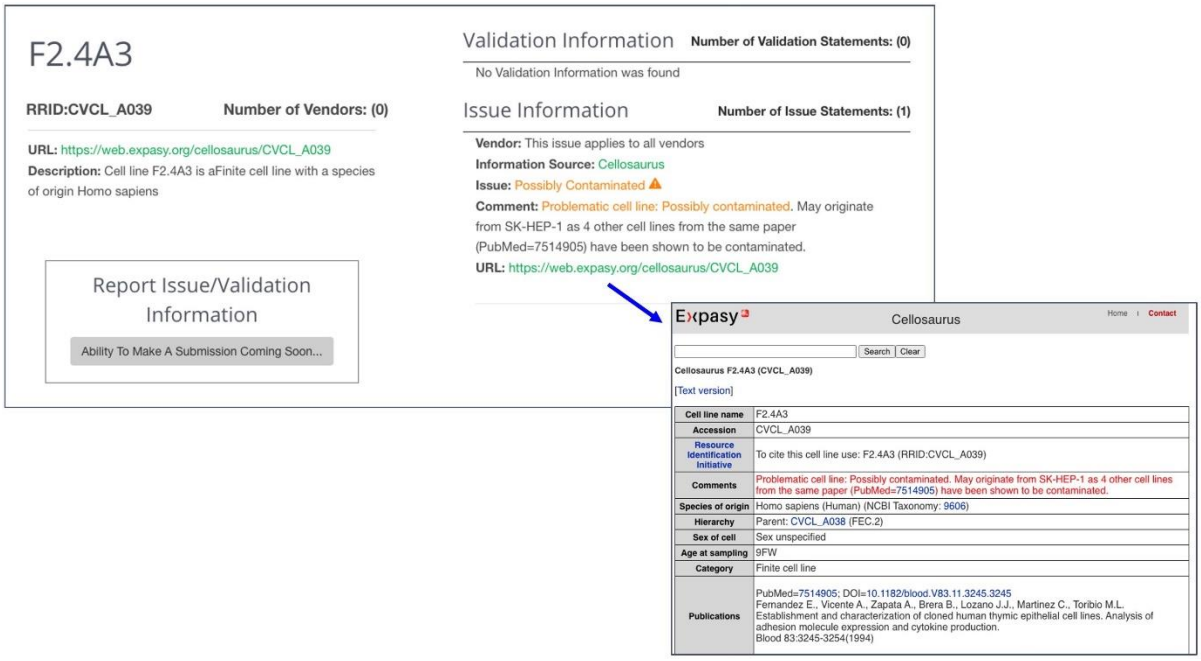
Authors: P. L. PASCUAL, K.-W. LIN, V. GUO, C.-N. HSU, A. E. BANDROWSKI, M. E. MARTONE, *J. S. GRETHE;
Dept. of Neurosciences, Univ. of California San Diego, Sch. of Med., La Jolla, CA

Abstract: Research resources, such as antibodies and cell lines, are a major source of variability in scientific experiments, and if they don't perform as expected, a major source of irreproducibility. Therefore, identifying and tracking the performance of these resources is important for maintaining the integrity of the scientific record. Resource Watch (https://scicrunch.org/ResourceWatch) serves this purpose as a hub for storing performance information (i.e. issues, characterization, and validation) about a variety of research resources within the biomedical domain. Resource Watch is built on the foundation of Research Resource Identifiers (RRIDs) as a means of uniquely identifying key research resources that underlie the findings of scientific studies in the literature. A core part of the content within Resource Watch comes from the community authorities that manage identifiers for specific resources, such as the Antibody Registry (antibodies) and Cellosaurus (cell lines). However, Resource Watch also enables aggregation of information from a number of other sources (e.g. Human Protein Atlas for antibody characterization information and the literature via natural language processing). In addition, the platform

also enables researchers to submit their own claims about a specific research resource. Resource Watch ensures that information on the performance of research resources is F.A.I.R. (Findable, Accessable, Interoperable, Reuseable) and is openly available to the biomedical community.



Text mining of antibody specificity from the literature



Disclosures: P.L. Pascual: None. **K. Lin:** None. **V. Guo:** None. **C. Hsu:** None. **A.E. Bandrowski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc.

Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.04

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF 1948181

Title: The OpenBehavior project: RRIDs, video repository, training workshops

Authors: *M. LAUBACH[1], A. V. KRAVITZ[2], L. M. AMARANTE[3], A. E. BANDROWSKI[4], K. CHAVEZ LOPEZ[1], W. FOBBS[1], J. FRIE[5], M. ISAACSON[1], J. KHOKHAR[5], S. R. WHITE[1]; [1]American Univ., Washington, DC; [2]Washington Univ., St Louis, MO; [3]Johns Hopkins Univ., Baltimore, MD; [4]SciCrunch Inc. and UCSD, La Jolla, CA; [5]Univ. of Guelph, Guelph, ON, Canada

Abstract: The OpenBehavior project disseminates information on open source tools and methods for research in the field of behavioral neuroscience. During the past year, the project has received funding from the National Science Foundation with three goals. First, we are creating a database of open source tools and, working with SciCrunch project, are issuing Research Resource Identifiers (RRIDs) for each tool. The initial database has been created based on more than 180 projects posted to openbehavior.com. The database will be used to create a factor for tracking the impact of open source tools, similar to the h factor. We also working with SciCrunch on the development of SciScore, a methods review tool for scientific articles. Second, we have created a repository of raw video files used for computer vision analysis in behavioral neuroscience experiments. The repository currently hosts 12 sets of videos covering a variety of common behavioral designs. The goal of the repository is to enable training on the use of some of the most currently popular open source tools in the field. In addition, we have hosted community conversations with leading developers and users of computer vision methods, and are actively working on a document to propose standards and increase rigor and reliability for the methods. Third, we are hosting training workshops on the most popular open source tools in the field. The first of the workshops is focused on hardware, specifically Arduino microcontrollers. We welcome interactions and discussions with the research community on these topics.

Disclosures: M. Laubach: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1948181. **A.V. Kravitz:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if

those funds come to an institution.; NSF 1948181. **L.M. Amarante:** None. **A.E. Bandrowski:** A. Employment/Salary (full or part-time):; Dr. Bandrowski is a co-founder of SciCrunch Inc, and it's CEO. **K. Chavez Lopez:** None. **W. Fobbs:** None. **J. Frie:** None. **M. Isaacson:** None. **J. Khokhar:** None. **S.R. White:** None.

Poster

P919. Bioinformatics I

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.05

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant R24 MH117295

Title: Dandi - a data archive and collaboration space for neurophysiology projects

Authors: *S. S. GHOSH[1], Y. O. HALCHENKO[2], R. CHOUDHURY[3], B. DICHTER[4], M. GRAUER[3], J. T. WODDER, II[2], D. CHIQUITO[3], J. NESBITT[3], B. HELBA[3], M. VANDENBURGH[3], D. JARECKA[1], S. A. ABRAHAM[1];
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Abstract: DANDI is a neurophysiology data archive and collaboration hub built to support multiscale, multispecies, and multimodal neuroscience research. The data and resources related to DANDI are supporting theoretical neuroscience, driving biological applications, helping develop new analytic tools through standardized annotation and dissemination. The DANDI infrastructure is built on opensource technologies and in the cloud, to support dissemination, search, visualization, computation, collaboration and coordination in neurophysiology research projects to promote FAIRness and efficiency. DANDI currently contains 32 TB of data from over 70 datasets, across 4 species, and multiple recording modalities spanning intracellular, extracellular, and behavioral timeseries from electrophysiology, optophysiology, and optogenetic experiments, as well as multimodal MRI, OCT and immunostaining data from human ex vivo brain tissue samples. DANDI aims to help make data and software for neurophysiology FAIR. DANDI currently provides neurophysiology data storage for the purposes of collaboration and dissemination of data, easy to use tools for data submission and access, a Jupyter-based computation hub to introspect data in the archive, and integration with other archives and analytic platforms. DANDI is a Web platform for scientists to share, collaborate, and process data from neurophysiology experiments using FAIR principles. DANDI is addressing challenges in standardization, data transfer, storage and access, and improving the culture of sharing through a community of practice. DANDI uses BRAIN Initiative community data standards such as NWB, and works closely with the BIDS and NIDM communities to expand those standards to neurophysiology and microscopy. DANDI has launched an application programming interface server to attract software developers to interact with the archive programmatically and has also contributed to community efforts to provide efficient access to larger datasets in the cloud. With DANDI, researchers can now share, collaborate on, and publish citable datasets, and thereby increase rigor and reproducibility of neurophysiology research.

Disclosures: S.S. Ghosh: None. **Y.O. Halchenko:** None. **R. Choudhury:** A. Employment/Salary (full or part-time):; Kitware Inc. **B. Dichter:** A. Employment/Salary (full or part-time):; Catalyst Neuro LLC. **M. Grauer:** A. Employment/Salary (full or part-time):; Kitware Inc.. **J.T. Wodder:** None. **D. Chiquito:** A. Employment/Salary (full or part-time):; Kitware Inc. **J. Nesbitt:** A. Employment/Salary (full or part-time):; Kitware Inc. **B. Helba:** A. Employment/Salary (full or part-time):; Kitware Inc. **M. VanDenburgh:** A. Employment/Salary (full or part-time):; Kitware Inc.. **D. Jarecka:** None. **S.A. Abraham:** None.

Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.06

Topic: I.02. Systems Biology and Bioinformatics

Title: Early prediction of neurodevelopmental disorders based on de novo coding variation

Authors: *J. CHOW[1], F. HORMOZDIARI[2];
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Abstract: The early detection and treatment of neurodevelopmental disorders (NDDs) can significantly improve affected patient outcomes. Whole exome and genome sequencing of families have identified rare coding variants, such as *de novo* variations, that are present at significantly higher rates in individuals with NDDs compared to unaffected controls. In particular, the enrichment of *de novo* likely gene-disruptive (LGD) variants in affected individuals relative to controls observed across multiple cohort studies has resulted in the identification of hundreds of NDD risk genes. The differential burden of non-synonymous *de novo* mutation that exists among NDD cases and controls indicates that *de novo* coding variation can be used to identify samples that will likely display an NDD phenotype. Thus, we have developed an approach for the accurate prediction of NDDs with a very low false positive rate (FPR) using *de novo* coding variation for a subset of affected cases.
We use a shallow neural net (SNN) with a custom loss function that specifically seeks to maximize TPR while minimizing FPR and incorporates LGD and missense *de novo* mutation, constraint, and conservation data. The SNN achieves a high (> 0.30129) true positive rate (TPR) at very low FPR (< 0.01) in comparison to traditional classification models (baseline models) such as random forest, support-vector machine (SVM), and logistic regression, corresponding to at least a 5% increase in TPR. The SNN also achieves a high precision recall - area under the curve (PR-AUC) (0.95050). As expected, an ensemble model that averages predictions among the SNN and baseline models is able to achieve increased TPR at FPR < 0.01 (0.30715) and PR-AUC (0.95176). The SNN itself is a major contributor to increased TPR at FPR < 0.01 and PR-AUC metrics observed in the ensemble model; an ensemble model that does not use SNN predictions yields decreased TPR at FPR < 0.01 (0.23347). Trained SNNs enable NDD risk gene ranking, revealing candidate NDD genes enriched in *de novo* non-synonymous mutations in NDD cases relative to controls.
In summary, the described SNN identifies NDD cases at high TPR while minimizing FPR with increased precision at lowered recall thresholds compared to traditional machine learning methods. Several factors contribute to the improved performance of the SNN, namely: the use of genic constraint and

conservation features in LGD-specific prediction, the architecture of the SNN, and the TPR-maximizing and FPR-minimizing custom loss function. The SNN trained on *de novo* coding variation additionally produces a ranked list of prioritized NDD risk genes for future clinical study.

Disclosures: J. Chow: None. **F. Hormozdiari:** None.

Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.07

Topic: I.02. Systems Biology and Bioinformatics

Title: Meta-analysis of neuron cell with single cell RNA-seq of human brain tissue

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Abstract: Introduction: In order to understand the development and role of the human brain, it is important to identify the cell types that compose the human brain tissue and the role of those cells. Recently, single-cell genomic analyses have been performed to human brain tissue, and revealed that there are various types of cells (interneuron, excitatory neuron, neuro precursor cell, microglia) in the human brain tissue. Generally, each cell type specifically express genes which are called cell marker. For example, GAD1 of interneuron and GFAP of astrocyte are well known cell markers. However, the cell markers used in each laboratory are different even for the same cell type. Thus, it is still unclear whether genes are available to use as a cell marker. The cell markers are often used to spatial analysis for human tissues to reveal distribution of each cell types. Likewise, it is important for cell differentiation technology to use cell type classification using cell marker. Above all, the cell markers of cell type in the fetal brain is good information, because ESC (embryonic stem cell) and iPSC (induced pluripotent stem cells) are known to be young cells. Over the past two years, several laboratories have been investigating single cell RNA-seq (scRNA-seq) data which are publicly available. In this study, we combined these data and used human brain single cell data to identify cell markers in fetal brain.Method: The scRNA-seq data which are gene expression data and metadata (cell types) of human brain tissue of fetuses were downloaded from publicly available database. Using these gene expression data and metadata (cell types) of each cells, we identified marker genes in each study to eliminate inter-study bias after that we integrated their gene lists. In addition, gene functional analysis was performed on marker genes.Results: The integration of data obtained from different laboratories revealed highly reproducible cell markers observed between different studies. Furthermore, it was revealed that several gene functions of the marker genes related to neuronal differentiation.

Disclosures: H. Watanabe: A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **W. Lin:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **Y. Kawashima:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **T. Hosoya:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd..

Poster

P919. Bioinformatics I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P919.08

Topic: I.02. Systems Biology and Bioinformatics

Support: NS111619
Austin's Purpose

Title: Three-dimensional missense tolerance ratio analysis

Authors: *R. E. PERSZYK[1], A. S. KRISTENSEN[2], P. N. LYUBOSLAVSKY[3], S. F. TRAYNELIS[4]; [1]Emory Univ., Atlanta, GA; [2]Univ. of Copenhagen, Copenhagen, Denmark; [3]Univ. of TexaS, Austin, TX; [4]Dept Pharmacol, Emory Univ. Sch. of Med., Atlanta, GA

Abstract: A wealth of genetic information is available describing single nucleotide variants in the human population that appear to be well-tolerated, and in and of themselves, do not confer disease. These variant datasets contain signatures about the protein structure-function relationship and provide an unbiased view of various protein functions in the context of human health. This information can be used to determine regional intolerance to variation, defined as the missense tolerance ratio (MTR), which is an indicator of stretches of the polypeptide chain that can tolerate changes without compromising protein function in a manner that impacts human health. This approach circumvents the lack of comprehensive data by averaging the data from adjacent residues on the polypeptide chain. We reasoned that many motifs in proteins are comprised of non-adjacent residues, but together function as a unit. We therefore developed an approach to analyze nearest neighbors in three-dimensional space as determined by crystallography, rather than on the polypeptide chain. We utilized members of the GRIN gene family that encode subunits of NMDA-type ionotropic glutamate receptors (iGluRs) to exemplify the differences between these methods. Our method, 3DMTR, provides new information about regions of intolerance within iGluRs, allows consideration of protein-protein interfaces in multimeric proteins, and moves this important research tool from one-dimensional analysis to a structurally-relevant tool. We validated the improved 3DMTR score by showing that it more accurately classified the functional consequences of set of newly measured and published point mutations of Grin family genes than existing methods.

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Poster

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Program #/Poster #: P919.09

Topic: I.02. Systems Biology and Bioinformatics

Support: DGAPA-UNAM grant IA203920

Title: A repertoire of nervous system related genes identified by literature mining showed unambiguous modular expression in brain tissues

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Abstract: Biological systems are inherently modular i.e. they have the ability to organize themselves into multiple sets of discrete individual units, that are relatively autonomous with respect to each other's functional tasks, but together drive specific physiological functions. The examples of discrete units could be sets of genes that execute glycolytic pathway and TCA cycle, which together are part of carbohydrate catabolic pathway. The discrete units of genes are referred to as functional or genetic modules since they have functional and genetic specificity. In the last two decades, several attempts have been made to predict genetic modules using a variety of datasets and techniques. However, our knowledge about genetic modules involved in various physiological functions and their interactions is largely incomplete. Literature databases such as PubMed provide a unique opportunity to mine research text, identify genes, and assemble genetic modules. In this study, I have successfully reconstructed genetic modules involved in nervous system related functions using 2,643,233 research articles published between 1801 to 2018 by querying nervous system related keywords in the PubMed database. Of them, 729,544 publications reported 62,250 unique genes. Hypergeometric distribution test was applied on each gene to assess its over-representation in nervous system related publications in the background of non-nervous system related publications. The 14,672 genes were significantly over-represented in the nervous system related publications at a p-value cutoff of 0.05 or less. In which, human encoded genes were 2,448, while remaining genes were from other species, which were mapped to human genes by best-bidirectional blast searches. This search identified additional 1,855 genes, which were not studied in humans with respect to the nervous system but in other species. In total 3,742 human genes were selected for further analysis, which were frequently reported in nervous system literature. Functional enrichment analysis confirmed their significant association with nervous system related functions, while 66% genes expressed exclusively in brain tissues. Astonishingly, most remaining genes showed a modular expression pattern in a few specific tissues such as blood, testis, and muscles. It indicates that these gene modules, though expressed in other tissues, are likely to form a communication bridge with the brain. Overall, this is a first ever study, which catalogues all genes that are scattered over millions of research articles on the nervous system at one place.

Disclosures: V.Y. Muley: None.

Poster

P932. Application of Optical Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P932.01

Topic: I.04. Physiological Methods

Support: NIMH (BRAIN) Grant RF1 MH114276-01

Title: Do arousal fluctuations alter functional connectivity?

Authors: *S. SHAHSAVARANI[1,2], D. N. THIBODEAUX[1], C. J. NWOKEABIA[1], W. XU[1], F. LODGHER[1], D. A. HANDWERKER[2], J. GONZALEZ-CASTILLO[2], P. A. BANDETTINI[2], E. M. C. HILLMAN[1];
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Abstract: In functional Magnetic Resonance Imaging (fMRI), researchers often rely on dynamic Functional Connectivity (FC) to investigate ongoing fluctuations in the correlation structure of neural activity. To fully leverage this non-invasive neuroimaging approach, it is imperative to first characterize what drives the underlying neural phenomena that induce the dynamics of functional connectivity as observed in fMRI data. As a first step in that direction, here we asked whether spontaneous changes in neuronal patterns of FC could be explained by behavioral or physiological variables in the awake, behaving mouse. Simultaneous neuronal calcium and hemodynamic signals were recorded from five thinned-skull adult Thy1-jRGECO1a mice, using Wide Field Optical Mapping (WFOM). The mice were free to move on a rotating wheel while their heads were fixed. Concurrently with brain imaging, we monitored the mice's locomotion and whisking patterns to measure changes in behavior. We also recorded pupillometry to measure physiological arousal. Applying pairwise Pearson's correlation coefficient on all temporal segments overlapping with each behavior of interest, we created neuronal FC maps for five distinct behavior and physiological states: (1) locomotion onset, (2) locomotion, (3) locomotion offset, (4) high arousal level right after locomotion offset, and (5) low arousal level 40 seconds after locomotion offset. Next, to predict the temporal evolution of behavioral states during the experimental sessions, we modeled every FC frame as a linear combination of these representative FC brain states. Our results revealed systematic shifts between high and low arousal states when the mouse was not running. Low arousal states were correlated with smaller pupil size and less whisking compared with the high arousal states. Further, our network analyses showed that during the low arousal state, the lateral frontal network and a sensory network, including the barrel cortex, were less synchronized with other brain regions. Additionally, when comparing rest with running, we noted distinct interhemispheric correlations in our brain networks. Specifically, the frontal network and the barrel network exhibited higher interhemispheric correlations during rest, whereas the visual network showed higher interhemispheric correlations during running. Our findings provide evidence that dynamic fluctuations in FC estimated from neuronal data directly relates to our measures of behavior, especially fluctuations in arousal. Future work will assess the hemodynamic correlates of these findings.

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Poster

P932. Application of Optical Methodologies

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Topic: I.04. Physiological Methods

Support: USA NIH Grant U01EB027005
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Title: Decoding the identities of naturalistic movie clips from human brain hemodynamics using high-density diffuse optical tomography

Authors: *Z. E. MARKOW[1], K. TRIPATHY[3], J. W. TROBAUGH[2], A. M. SVOBODA[4], M. L. SCHROEDER[5], S. M. RAFFERTY[6], E. J. RICHTER[2], A. T. EGGEBRECHT[6], M. A. ANASTASIO[7], J. P. CULVER[8];
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Abstract: In the last decade, functional MRI (fMRI) has achieved remarkable success at decoding the identity and content of a wide range of stimuli experienced by human subjects, using their brain activity and machine learning methods. Unfortunately, fMRI employs bulky equipment that cannot be used at the bedside, cannot image many patients with metal implants, and is difficult in young children. More-lightweight non-invasive tools have not accomplished the decoding performance of fMRI. High-density diffuse optical tomography (HD-DOT) non-invasively images blood oxygen fluctuations related to brain activity, like fMRI, but with near-infrared light. HD-DOT is an alternative in fMRI-incompatible patients and settings, and has spatial resolution between fMRI and more-lightweight non-invasive technologies such as NIRS and EEG. To evaluate feasibility of decoding naturalistic movie stimuli with HD-DOT, we first evaluated how well an HD-DOT system could identify which of four 90-second movie clips was being viewed based on imaged brain dynamics. During each session, each clip was viewed 4-8 times (trials) total. For the first half of each session (training set), the brain responses to each clip were averaged to form a "template" response for each clip. For each remaining trial (testing set), our simple decoder guessed that the clip shown was the clip whose template had the highest correlation with the measured response. These guesses were over 80% accurate across 16 sessions from 4 subjects, well above chance (25%) in terms of effect size and statistical significance ($p<0.001$). Next, we attempted to identify clips outside a decoder's training set. To do this, we relabeled two clips and their responses as training trials, and we used these to fit a linear model for predicting the imaged response from wavelet motion energy features in any clip. The model was used to predict the responses to the other two (test) clips and to two "lure" clips never viewed by subjects. This decoder guessed that the clip viewed in each trial was the clip whose predicted response had the highest correlation with the measured data. Across subjects and sessions, average accuracy exceeded 60% and statistically exceeded chance (25%, $p<0.05$). Accuracy

remained above chance even with up to 40 lure clips. Future work will attempt to decode more types of stimuli.

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Poster

P932. Application of Optical Methodologies

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Program #/Poster #: P932.03

Topic: I.04. Physiological Methods

Support: NRF- 2020R1A2C3010304
NRF-2019R1I1A1A01060660

Title: A New Monitoring Method for Detection of Stimulation Regions during HD-tDCS using Effective Connectivity Analysis: An fNIRS Study

Authors: *Y.-H. KIM[1,2,3], G. LEE[1], J. LEE[1], J. KIM[1,2], H. KIM[1,2], S. SHIN[1];
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Abstract: Transcranial direct current stimulation (tDCS) has been gaining increasing interest as a potential therapeutic treatment in rehabilitation. Although there have been many studies for the effects of tDCS, there are insufficient studies on real-time monitoring methods to give information on the exact location of stimulation personalized to the individual patient for improving the effect of tDCS. In this study, we propose a new method based on functional near-infrared spectroscopy (fNIRS) that can detect the location of stimulation in real-time to provide accurate stimulation location of high-definition tDCS (HD-tDCS) to the functional region of interest of the individual patient. The subjects wear both fNIRS and HD-tDCS devices, which are NIRScout® system (NIRx Medical Technologies, Germany) and Starstim 8 (Neuroelectrics®, Spain). The fNIRS signals around the HD-tDCS electrodes are measured in real-time and the phase-locking values (PLV) are calculated for each fNIRS channel. The PVL has information about not only the connectivity between fNIRS channels, but also the direction of stimulation transmitting by phase analysis. Using this information, the stimulus region can be accurately detected by estimating the location where the stimulus is the most applied. The proposed detection method was loaded into *ActiVeiw*®, which is a real-time brain activity monitoring toolbox, and an experiment was performed with 1 mA HD-tDCS. Real-time responses were observed by calculating the PLV using the fNIRS channels located on the top, bottom, left, and right with the anode of tDCS. Four vectors were created with the magnitudes which were calculated from PLV and the directions estimated from the four positions to each other. Then the summation of the four vectors was represented as the flow of the stimulus transition from the center. This stimulus flow is transmitted from the location of the maximum stimulations to the surroundings by HD-tDCS and the maximum stimulus location can be estimated.

Effectiveness of the proposed method was confirmed by observing the stimulus region according to changes of the cathodal array of HD-tDCS in real-time. Using the proposed method, it was possible to check whether or not the tDCS is being accurately stimulated to the desired regions in real time and was able to give a feedback for correction of the HD-tDCS protocol. This method may be able to improve HD-tDCS effect by providing a personalized stimulation protocol for individual patients**.**

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Poster

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Topic: I.04. Physiological Methods

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Whitehall Foundation 2017-12-94

Title: Optical resting state reveals cortical connectivity with columnar resolution in monkeys

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Abstract: Spontaneous modulations in brain activity (i.e., resting state) reveal fundamental features of brain organization. Measuring resting state with fMRI has gained considerable traction as a non-invasive approach to studying cortical connectivity in humans and animals. Although resting state connectivity (RSC) corresponds with structural connectivity (SC) at the macroscale, it is unclear whether RSC can reveal granular elements of SC. Addressing this problem requires 2 provisions: (1) measuring RSC at cortical column resolution (<200 um), and (2) comparing RSC and SC in the same animal and hemisphere. To meet both provisions, we investigated RSC and SC in motor and somatosensory cortex in 2 squirrel monkeys. We used intrinsic signal optical imaging (ISOI, 630 nm illumination) to measure spontaneous hemodynamic fluctuations under isoflurane anesthesia. High resolution optical images (1312 x 1082 pixels, ~19 um/pixel) were acquired in >12 experiments/animal (15 min/run, 10 frames/s) over 14-16 months. Optical images were processed, temporally filtered (bandpass 0.01-0.1 Hz), then used in cross-correlation analyses between pixels. The field-of-view (~26 x 22 mm) included motor and somatosensory areas, which we mapped extensively (>400 sites/hemisphere) with microstimulation and multi-unit recordings. We used a clustering approach and a seed-based approach to examine spatial patterns in resting state activity. For clustering we applied principal component analysis and k-means to define functionally-related cortical zones. Clustering maps corresponded well with microelectrode maps, which contained anatomical and functional features as they included cortical borders and somatotopic zones. In the seed-based approach, 48 seeds were examined in frontal motor areas (M1, PMd, PMv) and somatosensory areas 3b, 1, and 2. In separate imaging sessions, we used microstimulation + ISOI at the same sites to investigate effective connectivity (EC). Finally, we injected retrograde tracers in 5 of those sites to reveal SC. Thus, for every seed there were 2 connectivity maps (RSC and EC) and 5 of those seeds also had SC maps. All connectivity maps were spatially quantified according to cortical area and

somatotopic zone. Direct comparison of the maps showed excellent correspondence between RSC, EC, and SC. Collectively, the clustering and seed-based approaches showed that resting state ISOI can reveal embedded cortical networks at cortical column resolution. We are now leveraging resting state ISOI to investigate rules that govern connectivity in motor and somatosensory cortex.

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Poster

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Topic: I.04. Physiological Methods

Support: RO1-NS102870
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R01NS094692
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McDonnell Center for Systems Neuroscience

Title: Simultaneous, wide-field optical imaging of neural, metabolic and hemmodynamic activity in awake mice

Authors: *X. WANG, A. BICE, Z. ROSENTHAL, J. PADAWER-CURRY, J.-M. LEE, A. BAUER; Washington University, St. Louis, Saint Louis, MO

Abstract: In the healthy brain, local changes in blood flow and brain energy utilization are coupled to changes in local neural activity, phenomenon described as neurovascular coupling (NVC) and neurometabolic coupling (NMC). NVC and NMC evolve during development, abd are altered under anesthesia, and other conditions affecting the central nervous system disrupt individual or multiple pathways involved in NVC. Understanding how different central nervous system. diseases affect different components of NVC will enable linking of changes in neural or metabolic dysfunction to changes in hemodynamic signaling upon which functional neuroimaging methods rely. Genetic engineering techniques in mice have provided new opportunities for extending wide-field optical imaging methods to direct measures of neural activity. Fluctuations in calcium concentration can be imaged and visualized using fluorescent, genetically encoded calcium indicators (GECIs). However, the excitation/emission spectra of commonly used GECIs (e.g. GCaMP) overlap with those of flavin adenine dinucleotide (FAD), an endogenous measure of oxidative metabolism. Red-shifted GECIs allow for parallel imaging of calcium and FAD events and have advantages for in vivo imaging due to reduced tissue scattering and absorption. In addition, unlike GCaMP, excitation spectrum of red-shifted GECI does not overlap with Channelrhodopsin-2(ChR2) spectrum, which makes optogenetics targeting possible. Six mice (7-8 months of age) expressing the red-shifted GECI jRGECO1a with cranial window were used for experimentation. A custom light engine consisting of 470nm, 530nm and 625nm LEDs illuminated the skull. Diffuse reflected light for optical intrinsic signal imaging and fluorescence emission were collected

by a lens, split by a 580nm dichroic and sampled by two CMOS cameras. We developed a dual-fluorophore, wide field imaging system for rapid, simultaneous mapping of calcium, metabolic and hemodynamic activity in awake mice. As a proof-of-concept, we report stimulus-evoked and spontaneous patterns of activity across hemoglobin, FAD and jRGECO1a in awake and anesthetized animals. Contrast-specific patterns of activity differ across state and frequency range examined, providing complementary information along the NVC pathway. This flexible hardware platform allows for integrating optogenetic stimulation for all optical neural circuit interrogation and readout, and for examining the interaction between multiple cell populations. This system can be used to determine how glucose challenge and stroke recovery change the NVC.

Disclosures: X. Wang: A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health. **A. Bice:** A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health, McDonnel Center for SYstems Neuroscience. **Z. Rosenthal:** A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health. **J. Padawer-Curry:** A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health. **J. Lee:** A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute of Health. **A. Bauer:** A. Employment/Salary (full or part-time):; Washington University in Saint Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Health of Institute, McDonnell Center for Systems Neuroscience.

Poster

P932. Application of Optical Methodologies

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Program #/Poster #: P932.06

Topic: I.04. Physiological Methods

Support: NIH Grant R01 NS111028
NIH Grant R61/R33 NS115089
NIH Grant P30 DA048742

Title: Activity-dependent segmentation of wide-field imaging data using spatial independent component analysis (sICA) reveals stable cerebral cortical maps

Authors: *A. K. NIETZ, M. L. STRENG, L. S. POPA, Mr, E. FLAHERTY, R. CARTER, J. D. ARONSON, T. J. EBNER;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Recent advances in cranial windows in conjunction with genetically-encoded calcium indicators have allowed chronic, wide-field optical access to non-contiguous brain structures. However, analysis of the (often large) neuroimaging datasets is challenging due the complexity and variability of activation patterns. A fundamental issue is the method used to functionally segment the region imaged, including the stability of that segmentation over different time scales. We implemented spatial Independent Component Analysis (sICA) using the blind source separation algorithm JADER to extract spatial independent components (sICs) on cortex-wide mesoscale calcium imaging data in six mice expressing genetically-encoded GCaMP6f (Thy1-GCaMP6f), a calcium indicator. Spatial ICA segments the cerebral cortex by identifying regions with statistically independent activity based on minimizing mutual information. A surgically implanted transparent polymer skull allowed extensive optical access to the dorsal cerebral cortex. Imaging was performed with the mice head-fixed on a freely moving disk treadmill, allowing for free limb and body movements that included locomotion and grooming. Mice were imaged multiple times over several months, with datasets of approximately 5.5 to 14.5 hours.First, we performed a spatial segmentation of each mouse cortex based on the entire data set, the template map. In all mice, the segmentation showed minimal overlap between sICs and extensive coverage of the imaged cortex. Second, we repeated the analysis using different length time windows of data and compared the resulting sICs with the sICs obtained from the template map using both Gaussian mixture model clustering and a 2D correlation coefficient with a cutoff threshold for similarity. Both methods revealed remarkably similar ICs, in shape and location, across the time windows analyzed. However, not all sICs from the template map were present within the finer time windows, suggesting that certain regions are engaged only at specific times. Intriguingly, ICs from the template map, can split into two components in the finer time windows.These observations argue for two hypotheses. First, the stability of the sICs over different time scales suggests that neural populations in well-defined areas operate in a highly coherent manner, potentially providing the computational building blocks of cortical function. Second, the observation that not every sIC in the template map has a counterpart in finer time windows suggests a temporal dynamic underlies sIC processing and their engagement in behaviors.

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Poster

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Topic: I.04. Physiological Methods

Support: Bill and Melinda Gates Foundation OPP1184813

Title: Naturalistic stimuli for human brain mapping using high-density diffuse optical tomography

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Abstract: The study of early brain development is challenging due to limitations in both imaging modalities and stimulus protocols. While considered the gold-standard, functional magnetic resonance imaging (fMRI) presents challenges in pediatric populations as the loud, confined space in the bore of the magnet, away from a caregiver, can be frightening for children. Alternatively, high-density diffuse optical tomography (HD-DOT) is an emerging method that uses a dense array of overlapping light measurements to improve image quality over traditional functional near-infrared spectroscopy (fNIRS) as validated against fMRI in adults. The open-air environment of HD-DOT, along with the development of a child-sized imaging cap, makes our preschooler age HD-DOT system conducive for studying childhood brain development. Movie viewing is an increasingly popular naturalistic stimulus as it can reduce head motion and increase engagement in young children. Movies also drive reproducible brain activity despite their complexity and can be used to map multiple processing pathways in parallel using feature regressor analysis. These regressors are time courses for certain features in the movie including low-level features, such as luminance, as well as high-level features like speech or faces, which can be either manually or automatically coded. Movie features often covary, for example speech and faces, prompting the need for a multivariate general linear model (GLM) -based processing approach. To validate the movie regressor maps we compared the maps from speech feature regressors to activation maps from a well-characterized word hearing task. The maps from movies vs isolate maps displayed considerable similarities. However, manually coding these high-level features is a time-consuming and subjective process that severely limits our library of movie clips. Alternatively, a Faster Region-based Convolutional Neural Network (R-CNN) was trained and implemented to detect faces in animated movie clips and automatically code the face regressor. Maps were compared between the automatically and manually coded face regressors and displayed a high degree of similarity based on the Pearson correlation coefficient across the entire field of view. Overall, the establishment of an engaging child-friendly, naturalistic stimuli lays the groundwork for future developmental neuroscience studies in preschool age children.

Disclosures: M. Fogarty: None. **K. Tripathy:** None. **A. Svoboda:** None. **M. Schroeder:** None. **S. Rafferty:** None. **P. Mansfield:** None. **R. Ulbrich:** None. **M. Booth:** None. **E. Richter:** None. **C. Smyser:** None. **A.T. Eggebrecht:** None. **J. Culver:** None.

Poster

P932. Application of Optical Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P932.08

Topic: I.04. Physiological Methods

Support: JST-CREST, Grant No. JPMJCR1651

KAKENHI, Grant No. 18H03780

Title: Observing the Activity of Serotonergic Neurons After Acute Pain Stimulation Using Implantable CMOS Imaging Device and Microdialysis in Freely Moving Mice

Authors: *L. AKBAR, Y. OHTA, M. KAWAHARA, H. TAKEHARA, M. HARUTA, H. TASHIRO, K. SASAGAWA, J. OHTA;
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Abstract: Visualizing neural activity using imaging method is recently becoming an intriguing trend in neuroscience. However, current available devices are relatively larger and weightier, make it difficult to employ in a deeper brain region. Furthermore, multiple sites of imaging or combination with other systems to gather valuable information is still limited. In fact, neurons are working within numerous network connections, for instance, acute pain involves diverse neural projections. Serotonin is a neurotransmitter firmly related with pain. Dorsal raphe nucleus (DRN) serves as the major source of serotonergic neurons in the brain which innervates various parts including central amygdala, particularly the capsular-lateral subsection (CeLC), and anterior cingulate cortex (ACC). CeLC and ACC are extensively associated with the affective dimensions of pain. Nevertheless, direct observation of these three different areas concurrently on a living animal remain unexplored. In this study, we aim to demonstrate the design and utility of integrated system of implantable imaging device with microdialysis. Our device is thin and lightweight (~0.2 gram), composed of CMOS image sensor and micro-LED (λ=470 nm) embedded on the flexible printed circuit (FPC) substrate. The absorption filter is applied above the image sensor. The device is coated by Parylene-C for biocompatibility and waterproofing. The design of our device avoids bulky optical compartment while retaining its crucial function for observing neural activity. The imaging device was implanted to DRN, and microdialysis probes in CeLC and ACC. We subcutaneously injected 2% paraformaldehyde (PFA) to the mouse hindpaw to induce acute pain condition. The microdialysis sample were collected every 15 minutes and measured by high-performance liquid chromatographic column-electrochemical detector (HPLC-ECD). Using GCaMP6 transgenic mice, our device was able to detect neural activity. The results suggested that fluorescence intensity increased in DRN after 2% PFA stimulation. Serotonin concentration also elevated both in CeLC and ACC, observably higher in the first 15 minutes after the stimulation which in line with a massive licking behavior in the injected hindpaw. By this experimental scheme, we revealed that our device is feasible for multi-site implantation with less invasiveness and did not hinder the mice movement, an important consideration for *in vivo* investigation. The streamlined structure of our device can be safely combined with other systems, and it also enables us to conduct triple implantation, opening possible way to monitor neural circuits in many locations simultaneously.

Disclosures: L. Akbar: None. **Y. Ohta:** None. **M. Kawahara:** None. **H. Takehara:** None. **M. Haruta:** None. **H. Tashiro:** None. **K. Sasagawa:** None. **J. Ohta:** None.

Poster

P932. Application of Optical Methodologies

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Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P932.09

Topic: I.04. Physiological Methods

Title: Effective correction of physiological noise and head motion artifacts with resting-state fNIRS data

Authors: *P. LANKA[1], T. HUPPERT[2], H. BORTFELD[1];
[1]Univ. of California, Merced, Merced, CA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Resting-state functional connectivity (RSFC) with functional near-infrared spectroscopy (fNIRS) is an effective tool to study cortical connectivity across development. However, the presence of motion artifacts (MA) and systemic physiology (SP), including cardiac, respiration, and blood pressure, in the fNIRS signal can lead to incorrect statistical conclusions due to increased false positives (FP) and lowered sensitivity to the underlying neural activity. For example, shared SP between fNIRS channels may lead to spurious correlations due to increased covariance between channels. Moreover, the hemodynamic response (HR) and SP combined with the high sampling rate of fNIRS can lead to temporal autocorrelation of the time series, also producing spurious correlations. Finally, motion corrupted timepoints, whether as spike or shift artifacts, have higher signal intensity than neural activity and thus may also lead to false conclusions. It is imperative for fNIRS researchers to correct for these issues to obtain statistically valid RSFC measures using this technique. Previous studies have shown that pre-whitening and the use of robust methods are effective in reducing temporal autocorrelation and motion artifacts respectively, while the use of short separation (SS) channels that capture signal changes originating in the scalp offers a solution to ameliorate some of the problems with SP in fNIRS data. However, questions remain about the effectiveness of principal component analysis (PCA) for removing shared SP, and the effectiveness of these methods for time-lagged connectivity metrics such as Granger causality (GC) is not well understood. In the current study, we used simulated data with a known covariance structure to mimic the HR associated with neural activity and added shared physiological noise along with spike and shift artifacts to mimic motion artifacts. We used FP rate plots and receiver operating characteristic (ROC) curves to assess the effectiveness of these methods. Our results using simulated data corroborate the use of robust statistics and pre-whitening as effective methods to correct for MA and autocorrelation in fNIRS time series. More importantly, we found that using principal components extracted from SS channels as covariates in partial correlations between channels was effective in reducing spurious correlations due to shared SP. Finally, while our approach is also applicable to GC metrics, it is not as effective in reducing the FP rate as with the zero-lag connectivity metrics. We recommend a combination of pre-whitening, robust methods, and partial correlation for obtaining statistically valid connectivity metrics with fNIRS.

Disclosures: P. Lanka: None. **T. Huppert:** None. **H. Bortfeld:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.01

Topic: I.06. Computation, Modeling, and Simulation

Support: DC 009977-10.

Title: Working with Wilfrid Rall: Origins of computational neuroscience

Authors: *G. M. SHEPHERD;
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Abstract: John Moore (2010) has provided a valuable "personal view" of the early development of computational neuroscience with recollections of his work with Kacy Cole in 1950, carrying out the first computer calculations of the Hodgkin-Huxley equations for the action potential on the SEAC, the first "truly functional electronic computer in the US". A decade later I joined Wilfrid Rall when he was creating the compartmental method for representing integration of synaptic activity in neurons. The first application of the Rall method to motoneuron dendrites became a classic of the founding of computational neuroscience (Rall, 1964). The second application was in our work on olfactory bulb neurons, characterized by Moore as a "computational breakthrough; the prediction of the possibility of dendrodendritic synapses (Rall and Shepherd, 1968)." This work, together with Tom Reese and Milton Brightman, has been summarized in "The Theoretical Foundation of Dendritic Function" (Segev et al, 1995). Here I provide background with unpublished documentation for how we extended the Rall method to brain neurons and microcircuits. The Rall method adapted the metabolic approach of Mones Berman describing the movement of tracers through large body compartments to the biophysical representation of synaptic potentials spreading in fine dendritic processes of individual neurons. In our model he added the first representation of simplified HH equations for analysis of active dendritic properties. The antidromically driven mitral cells and synaptically activated granule cells were analyzed as electric dipoles generating successive time periods of extracellular potentials, which served to constrain the interpretation of active vs passive properties of the neurons. My proposed local circuit wiring diagram facilitated testing for the interactions between mitral and granule cells; the model rejected axon collaterals and predicted a sequence of dendrodendritic activation of granule cell dendrites which then inhibit the mitral cell dendrites. Rall recorded our discussion as we created this prediction in his notebook Vol. 4 (August 24, 1964, p.56). The prediction was confirmed by electron microscopy (Rall et al, 1966) as recorded in correspondence between the four investigators at the time. This was a novel brain microcircuit based on neuroanatomy, electrophysiology, electronmicroscopy, and a realistic computational biophysical model. Rall's lab notebooks and our correspondence describing this and other early unpublished work on computational models are openly accessible to scholars at https://medicine.yale.edu/lab/shepherd/.

Disclosures: G.M. Shepherd: None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.02

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant P01 AG054407
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The Michael J Fox Foundation
The ALS Association

Title: Super-human cell death detection with biomarker-optimized neural networks

Authors: *J. LINSLEY[1], D. LINSLEY[3], J. LAMSTEIN[1], G. RYAN[1], K. SHAH[4], N. CASTELLO[1], V. OZA[1], J. KALRA[1], S. WANG[1], Z. TOKUNO[2], A. JAVAHERIAN[1], T. SERRE[3], S. FINKBEINER[1];
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Abstract: Many of the cellular events that underlie neurodegenerative disease are best captured by continuously imaging live neurons over time with microscopy. The advent of robot-assisted microscopy has helped scale longitudinal live microscopy to high-throughput regimes with the statistical power to detect transient events. Yet analysis of these experiments still relies on time-intensive human annotation. Cell death in particular is a fundamental biological process commonly found in live microscopy but that is difficult to automatically detect without perturbing experiments with stains, dyes or biosensors that can bias experimental outcomes, lead to inconsistent results, and reduce the number of processes that can be simultaneously labelled. We address this fundamental limitation of live microscopy with biomarker-optimized convolutional neural networks (BO-CNN): interpretable computer vision models trained directly on biosensor activity. We demonstrate the ability of BO-CNNs to detect cell death with super-human accuracy and speed by learning to identify important subcellular morphology associated with cell vitality, despite receiving no explicit supervision to rely on these features. Importantly, these models also uncover novel intranuclear morphology signal that is difficult to spot by eye and has not yet been linked to cell death, but reliably indicates death. BO-CNNs are broadly useful for analyzing any live microscopy and essential for interpreting high-throughput robotic-aided experiments.

Disclosures: J. Linsley: None. **D. Linsley:** None. **J. Lamstein:** None. **G. Ryan:** None. **K. Shah:** None. **N. Castello:** None. **V. Oza:** None. **J. Kalra:** None. **S. Wang:** None. **Z. Tokuno:** None. **A. Javaherian:** None. **T. Serre:** None. **S. Finkbeiner:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.03

Topic: I.06. Computation, Modeling, and Simulation

Title: Mathematical simulation predicts hyperexcitability of axotomized neurons through decrease in the membrane capacitance (C_m)

Authors: *E. PETROFF, V. SNITSAREV;
Montclair State Univ., Montclair, NJ

Abstract: Axotomy induces considerable changes in the electrophysiological characteristics of sensory neurons and leads to hyperexcitability, which in case of nociceptive neurons may cause chronic pain. We

used a Simulink implementation of nodose neuron action potential firing model developed by Schild et al. *J Neurophysiol* 71, 2338-2358, 1994, and further updated in Schild & Kunze *J Neurophysiol* 78, 3198-3209, 1997, to model changes that may lead to hyperexcitability. In the mathematical simulation of an A-type neuron [https://www.mathworks.com/matlabcentral/fileexchange/18812-nodose-neuron-action-potential-firing], the resting membrane potential (MP_{rest}) settles to -56.0 mV upon initialization. In response to progressively increasing current injections from 0.025 to 0.045 nA with 0.005 nA increments, the model generates 0, 1, 2, 4, and 6 APs, and adapts within 1 second to the membrane potentials of -48.0, -46.4, -44.6, -42.6, and -40.5 mV, respectively. The model behaves similar to an A-type neuron. For example, elimination of conductance of the fast tetrodotoxin-sensitive voltage-gated Na^+ channel, similar to the experimental application of tetrodotoxin, leads to elimination of action potentials in the model. We paid particular attention to the parameter shifts that could increase neuronal excitability, a model of chronic pain elicited by nociceptive neurons after injury and following tissue regeneration. Because C_m is directly proportional to the plasma membrane surface area, we hypothesized that a decrease in C_m may lead to an increase in excitability. A decrease in C_m by 10% from its default value of 32.5 pF results in 0, 1, 4, 10 APs and adaptation to -48.0, -46.4, -44.6, and -42.8 mV in response to 0.025, 0.03, 0.035, and 0.04 nA current injection, respectively; while in response to 0.045 nA a non-adapting train of APs at 25 Hz was elicited. Conversely, an increase in C_m by 10% from its default value of 32.5 pF results in 0, 1, 2, 2, and 3 APs and following adaptation to -48.0, -46.4, -44.6, -42.6, and -40.3 mV in response to 0.025, 0.03, 0.035, 0.04 and 0.045 nA current injection, respectively. Notably, these changes in excitability were not directly related to the changes in the level of depolarizing membrane potentials in response to current injections (model of the receptor potential). This simulation could potentially contribute to further understanding of neuronal hyperexcitability and pain during inflammation, injury and following tissue regeneration to develop tools for pain reduction.

Disclosures: E. Petroff: None. **V. Snitsarev:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.04

Topic: I.06. Computation, Modeling, and Simulation

Title: A conductance-based model of intrinsic firing activity in human induced pluripotent stem cell-derived dopaminergic neurons

Authors: *A. L. HANES[1], D. PRE[2], A. WOOTEN[2], A. G. BANG[2], J. M. GEARHART[3];
[1]On contract to AFRL 711 HPW/RHBBA, UES, Inc., Beavercreek, OH; [2]Prebys Ctr., Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA; [3]On contract to AFRL 711 HPW/RHBBA, Henry M. Jackson Fndn., Dayton, OH

Abstract: Human induced pluripotent stem cell (hIPSC)-derived neurons are an in vitro platform for high-throughput screening that measures the effect of neuroactive compounds in terms of altered firing activity, but not mechanisms. To complement this screening platform, we developed an in silico conductance based model of the intrinsic properties of hISPC-derived dopaminergic (DA) neurons using

the NEURON modeling software, with the intention to later expand the model to simulate small networks. Our objective is to identify hypothetical mechanisms of action for neuroactive compounds by tuning model parameters to reproduce the altered activity caused by those compounds. Ion channels were selected for inclusion in our model via literature search, and the presence of these channels in hIPSC-derived DA neurons was confirmed through RNAseq. The channels' voltage-dependence and kinetic parameters were selected via literature search; a single-cell model was created with representations of these ion channels, as well as intracellular calcium buffering and efflux, and volume transmission and reuptake of dopamine. A simulation of multiple non-networked neurons was created by generating replicates of the single cell model in which the maximal conductances and some kinetic parameters were randomly varied. To obtain the data for model validation, neurons were cultured on microelectrode array plates in the presence of synaptic blockers, such that the resulting firing activity represented the cells' intrinsic pacemaking activity rather than synchronized network bursts. These data were then analyzed via spike-sorting, yielding the spiking activity and firing rates of individual firing units. This process was repeated with neuronal cultures treated with verapamil and gabapentin, which have a known pharmacological effect on some of the ion channels in the cultures. By tuning the model parameters according to these compounds' mechanisms of action, we were able to create simulations that reproduced the approximate range of firing rates seen in all three treatment conditions, indicating that our model is an accurate reproduction of the cellular mechanisms underlying the intrinsic neuronal properties observed in vitro.

Disclosures: A.L. Hanes: None. **D. Pre:** None. **A. Wooten:** None. **A.G. Bang:** None. **J.M. Gearhart:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.05

Topic: I.06. Computation, Modeling, and Simulation

Support: samsung science and technology foundation under project number SSTF-BA1602-11

Title: Aging Lévy walk with rest model for Arc and β-actin mRNA transport in neurons

Authors: *H. AHN[1], X. DURANG[2], J. SHIM[1], G. PARK[1], J.-H. JEON[2], H. PARK[1];
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Abstract: Localization of mRNA in neurons is crucial for regulating gene expression for long-term memory formation. mRNAs are recruited to messenger ribonucleoprotein (mRNP), which are packages of mRNAs and proteins, and transported to their target location by motor proteins along cytoskeletons. However, the mechanism by which mRNPs find their target site is not understood well. Here, using the MS2/PP7 mRNA labeling system, we observed endogenous Arc and β-actin mRNA in living neurons as they are known to be localized to activated synapses. After investigating the statistical properties of mRNA movements, we modeled the mRNA movement as an aging Lévy walk which has two dynamic

phases: the motor-involved ballistic run and static localization. This study suggests a theoretical model for the mechanism of neuronal mRNP transport and provides a quantitative comparison between the model and experimental data for the two different mRNAs.

Disclosures: H. Ahn: None. **X. Durang:** None. **J. Shim:** None. **G. Park:** None. **J. Jeon:** None. **H. Park:** None.

Poster

P946. Cellular Models I

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Program #/Poster #: P946.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CAREER 1844762

Title: Computational modeling of blocking afferent neural transmission by sub-kilohertz electrical stimulation of dorsal root ganglia

Authors: *N. SHALABY, B. FENG;
Dept. of Biomed. Engin., Univ. of Connecticut, Storrs, CT

Abstract: Chronic visceral pain is a debilitating medical condition that leads to decreased quality of life. Its multifaceted nature and vague identifiable symptoms make it a challenge to treat by conventional pharmacological approaches. Neuromodulation techniques, such as spinal cord stimulation and peripheral nerve stimulation, have emerged as non-drug alternatives to chronic pain management. We recently provided compelling experimental evidence to indicate that dorsal root ganglion (DRG) stimulation can block action potential transmission in peripheral nerves, which potentially alleviates pain without evoking paresthesia. To gain mechanistic insights into DRG stimulation, we report in this abstract computational models of myelinated and unmyelinated sensory afferent neurons and systematical assessment of the effect of extracellular DRG stimulation on action potential transmission and conduction block. NEURON simulation environment is used to build models of sensory afferent neurons consisting of a soma in the DRG, a stem axon, and its bifurcation at the T-junction into a peripheral axon projecting to the target tissue and a central axon projecting to the spinal cord. Action potentials are evoked in the distal end of the peripheral axon and extracellular electrical stimulation is delivered close to the DRG soma. Myelinated A-fibers are modeled with regions of Nodes of Ranvier connected by passive internodal segments. Unmyelinated C-fibers are assumed to have homogeneous ion channel densities in axonal regions. We used the models to assess the following potential mechanisms responsible for the blocking effect by DRG stimulation: activation of calcium-activated potassium channels at the T-junction, increase of intracellular sodium and extracellular potassium concentrations, axonal membrane hyperpolarization by elevated sodium potassium ATPase, and soma membrane hyperpolarization. This preliminary modeling study will not only advance our mechanistical understanding of sub-kilohertz DRG stimulation in afferent conduction block, but also guide the design of new stimulation protocols that target the DRG and other regions of the afferents to effectively attenuate peripheral drives to the central nervous system.

Disclosures: N. Shalaby: None. **B. Feng:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.07

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CAREER Award 1653080

Title: Computational modeling of extracellular microelectrode recordings from A-delta neurons in the dorsal root ganglia

Authors: *L. R. MADDEN[1,2], R. D. GRAHAM[1,2], S. F. LEMPKA[1,2,3], T. M. BRUNS[1,2];
[1]Biomed. Engin., [2]Biointerfaces Inst., [3]Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Dorsal root ganglia (DRG) are discrete recording targets for closed-loop peripheral neuromodulation, due to the presence of sensory neurons that innervate specific dermatomes. DRG contain pseudounipolar neurons, which have a stem axon protruding from the soma that splits into a peripheral axon that extends out to the body and a central axon that enters the spinal cord. A-type DRG neurons occasionally contain a long, tortuous, unmyelinated axonal pathway at the initial segment, known as a glomerulus. The electrophysiological effects of potential ephaptic coupling - the phenomenon that the electric field generated by a firing axon can influence the firing properties of adjacent axons - has yet to be explored in these neurons. Additionally, in vivo DRG recordings with penetrating microelectrodes can have distinctive “W”-shaped waveforms whose origin is not understood. Here, we built a computational model of an A-delta neuron within a DRG to investigate how the extracellular voltage waveform recorded by a penetrating microelectrode array can be influenced by the neuron’s structure (the trajectory of the glomerulus), electrophysiological properties (ephaptic coupling within the glomerulus), and its location relative to the recording electrode. We built a finite element method model that included general thorax tissue, bone, intraforaminal space, a dural sheath, white matter peripheral and spinal nerve roots, a grey matter DRG, and a penetrating multi-site microelectrode array. We built a multi-compartment double cable model that contained a myelinated stem axon, peripheral and central axon branches, an unmyelinated glomerulus section, and a 40-µm diameter soma. We used a reciprocity-based approach to simulate extracellular recordings at multiple sites on our microelectrode array. Our model demonstrated how the location of the recording contact relative to different components of the neuron influenced the peak-to-peak voltage amplitude and multiphasic properties of the recorded waveform. The results of this model may be used to provide context for in vivo neural recordings, identify features to improve the accuracy of spike sorting algorithms, and give insights into the electrophysiological function of glomeruli in DRG A-type neurons.

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Poster

P946. Cellular Models I

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Program #/Poster #: P946.08

Topic: I.06. Computation, Modeling, and Simulation

Support: Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (No. 2017-0-00451)
2021 Joint Research Project of Institutes of Science and Technology

Title: Effects of electric field on neuromodulation in transcranial direct current stimulation

Authors: *H. CHUNG[1], C. IM[1], H. SEO[2], S. C. JUN[1];
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Abstract: Noninvasive brain stimulation (NIBS) has increasingly attracted attention from many researchers as a neuromodulation technique because of its application in brain research and treating neurologic and psychiatric disorders. One of the ways to apply NIBS is transcranial direct stimulation (tDCS), which modulates cortical neurons' activities by delivering weak electric currents through two or more electrodes attached to the scalp. However, the results of tDCS are highly variable depending on the inter-subjects and there remains uncertainty about the affected brain areas as well as its cellular mechanisms. In particular, there has been a controversy around the deterministic factors of cortical neurons' response to tDCS. Some studies reported that the orientation of stimulation, which is represented as the radial field (RF), is a crucial factor, while others insisted that electric field (EF) magnitude itself is the key factor. In the midst of this controversy, we aimed to investigate the deterministic factor for neuronal response to conventional (C)-tDCS and high-definition (HD)-tDCS in a computational study by constructing a multi-scale model. We integrated anatomically detailed head models and morphologically detailed multi-compartmental models of three types of cortical neurons. Our neuron models were modified versions of neuron models from the blue brain project and had an anatomically detailed morphology from dendrites to arborized axons. With a multi-scale model, we quantified the neuronal response to the C-/HD-tDCSs and investigated the effects of EF and RF magnitudes on the excitation threshold of neurons. We found that EF was more highly correlated to neuronal response than RF in both C-/HD-tDCSs. In a comparison between C-/HD-tDCSs, the latter's EF and RF had a higher correlation on neuronal response. This is possibly because, as reported by other studies, HD-tDCS has higher EF and RF focalities, compared to C-tDCS. We concluded that EF was a deterministic factor for the excitation threshold. However, RF also had a noticeable impact on the cortical neuronal response to tDCS, even though it is relatively weak. This result might suggest that the strength and orientation of the electric field should be taken into consideration when tDCS is applied. This work allowed us to quantify the effect of EF and RF in the cases of both C-/HD-tDCSs by combining morphologically realistic neurons and an anatomically realistic head model. Further, this work should be helpful in getting us one step closer to settling the controversy surrounding the deterministic factor of the cellular mechanisms of NIBS and cellular mechanisms per se.

Disclosures: H. Chung: None. **C. Im:** None. **H. Seo:** None. **S.C. Jun:** None.

Poster

P946. Cellular Models I

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Program #/Poster #: P946.09

Topic: I.06. Computation, Modeling, and Simulation

Support: UKRI grant EP/S02431X/1

Title: Combining neural ODEs and incomplete ODE systems to model complex under-parameterised biochemical networks

Authors: *D. LINKEVICIUS[1], A. CHADWICK[1], M. STEFAN[2], D. STERRATT[1];
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Abstract: Complex biochemical networks that contain on the order of a thousand unique protein species [3] underpin synaptic function. Such biochemical networks can be modelled as systems of ordinary differential equations (ODEs). However, to date, a detailed dynamical model of synaptic biochemistry contained at most 55 unique proteins [2]. This large discrepancy is due to the dearth of knowledge on the structure and reaction rates of synaptic biochemical networks, making only partial models of the synapse possible. Therefore, there is a need to develop alternative approaches to model synaptic biochemical networks, which are agnostic to the full structure and parameterisation of the biochemical system.
In this exploratory work we propose a method of combining an existing partial ODE model with a powerful novel machine learning approach - neural ODEs [1]. We restrict some of the derivatives in the Neural ODEs to be a partial ODE model of a biochemical system. Our approach can then learn the remaining dynamics necessary to reproduce given physiological data in an efficient, data-driven manner and requires less data on the biochemical reaction structure and rates. By using a synthetic example we demonstrate how the resulting model is more powerful than traditional approaches, yet is partially interpretable via the encoded partial ODE system which represents real biochemical species.
Most dynamical models of synaptic activity are constructed in order to investigate a very limited number of phenomena. Since such models only include a small fraction of the protein species existing within a synapse [2], it is unclear how they would perform in reproducing a broader range of synaptic dynamics. Given our exploratory work, we believe that our semi-black box hybrid approach could ultimately produce a dynamical model that is powerful enough to reproduce a much larger set of empirical studies on synaptic dynamics. Such a model could be an invaluable tool to further both theoretical and empirical understanding of synapses.
References:[1] Chen, R. T. et al. *Advances in Neural Information Processing Systems 2018-Decem* (2018), 6571-6583.[2] Heil, K. F. et al. *bioRxiv* (2018).[3] Sorokina, O. et al. *Scientific Reports 11*, 1 (2021), 1-9.1

Disclosures: D. Linkevicius: None. **A. Chadwick:** None. **M. Stefan:** None. **D. Sterratt:** None.

Poster

P946. Cellular Models I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P946.10

Topic: I.06. Computation, Modeling, and Simulation

Support: GR36716

Title: A graph neural network approach to neuron classification

Authors: *E. A. SMITH, R. C. GERKIN;
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Abstract: The morphology of neurons determines their functional processing capabilities and their role in neural circuits. Constructing biologically realistic computational models of neural circuits will require accounting for a diversity of morphologies -- including from the same nominal neuron type -- and then generating statistically equivalent diverse neuron types in silico. In order to construct a framework for classification and generation of diverse morphologies, we used a graph neural network (GNN) architecture, a deep learning architecture that accounts for connectivity relationships in predicted elements; specifically we used the actual neuronal morphology as the "graph", with reconstructed neuritic segments as nodes and edges. We trained models of this type using complete reconstructions of mammalian olfactory bulb neurons from NeuroMorpho, and evaluated the ability of these models to correctly classify specific cell types. Simulation results indicate that the model performance is comparable to conventional methods of classifying neurons from structure. Because these GNN models develop an internal representation of the relationship between the low-level morphological details and neuron types, future work will allow the operation to be reversed: creating novel neuron morphologies from provided types, while respecting observed variability within and across types.

Disclosures: E.A. Smith: None. **R.C. Gerkin:** None.

Poster

P978. Electrical Methods to Modulate Neural Activity II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P978.01

Topic: I.08. Methods to Modulate Neural Activity

Title: Characterizing the TMS-evoked EEG responses of the leg, hand, and face areas in the primary motor cortex

Authors: *E. KALLIONIEMI[1,2], S. MÄÄTTÄ[2], L. SÄISÄNEN[2,4,5], J. HYPPÖNEN[2], P. KOSKENKORVA[3], J. SAARI[2,5];
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Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method. When combined with simultaneous electroencephalography (EEG), TMS-evoked EEG potentials (TEPs) can be applied to evaluate the excitability, connectivity, and oscillatory characteristics of the stimulated cortical

area. So far in the motor cortex, TEPs have been described mainly in the hand motor area. No research exists on whether TMS applied to cortical representation areas for different muscle groups induce similar TEPs to that of the hand TEPs or whether the TEPs are unique for the specific functional area being stimulated. Thereby, we aimed to characterize the TEPs measured from the cortical leg, hand, and face area. The cortical representation area for the leg is near the vertex, the hand slightly more lateral, and the face the most lateral in the primary motor cortex. The study included 9 healthy right-handed subjects (38±11 years, 5 females). First, the cortical representation areas for the right leg (tibialis anterior), hand (first dorsal interosseous), and face (mentalis) were mapped, and the resting motor threshold (rMT) from these areas were measured as the % of maximum stimulator output (%MSO). In total, 150 TEPs from each area were measured using single-pulse TMS at an intensity of 90% of the area-specific rMT. In the analyses, the TEPs for each representation area were averaged. The subject-specific TEP peaks were characterized by their mean latency and polarity (negative, N; positive, P) at the Cz electrode. rMT of the hand was lower than that of the face and leg (p=0.001). The mean ± standard deviations were 56.0 ± 14.0 %MSO (leg), 38.0 ± 4.7 %MSO (hand) and 63.7 ± 19.3 %MSO (face). For leg, the most consistently identifiable peak latencies at single-subject level had a group mean ± standard deviation of P33 ± 5ms, N53 ± 7ms, P66 ± 10ms, N77 ± 10ms, P133 ± 8ms, N178 ± 8ms, and P225 ± 3ms. For hand, the peaks were P30 ± 5ms, N58 ± 5ms, N100 ± 5ms, P154 ± 4ms, and N175 ± 5ms. For the face, the latencies were N20 ± 5ms, P32 ± 5ms, N60 ± 6ms, P78 ± 6ms, N113 ± 7ms, P166 ± 6ms, and N215 ± 5ms. TEPs in all muscle groups had a similar initial waveform, but after about 66 ms after the TMS-pulse, the TEP peaks started to differ, especially that of hand differed from others. Both the hand and face TEPs exhibited the N100 peak, which was not visible in the leg TEPs. Alternatively, the leg N100 could have appeared earlier than in the other muscles, as the leg TEPs involved an additional negative peak at 77 ms after the TMS-pulse. These results suggest that TEPs might be unique to each muscle group.

Disclosures: E. Kallioniemi: None. **S. Määttä:** None. **L. Säisänen:** None. **J. Hyppönen:** None. **P. Koskenkorva:** None. **J. Saari:** None.

Poster

P978. Electrical Methods to Modulate Neural Activity II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P978.02

Topic: I.08. Methods to Modulate Neural Activity

Support: NIMH T32MH115886
University of Minnesota's Medical Discovery Team (MDT) on Addiction
Minnesota’s Discovery, Research, and InnoVation Economy (MnDRIVE)

Title: Neurocognitive biomarkers of TMS response: Modeling the trajectories of change in cognitive control in response to TMS for depression.

Authors: *S. T. OLSEN, C. R. P. SULLIVAN, D. C. COOPER, S. WILSON, A. I. SONMEZ, S. C. ALBOTT, S. C. OLSON, Z. NAHAS, C. B. PETERSON, B. R. RITTBERG, A. HERMAN, A. S. WIDGE;
Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Transcranial magnetic stimulation (TMS) of the prefrontal cortex (PFC) is an effective treatment for depression, though it is time consuming and costly, and only 40-70% of patients respond. TMS suffers from a lack of biomarkers of target engagement that are scalable to general practice. Further, there is a lack of mechanistic understanding; it is unknown how activation of the PFC leads to improvement in depressive symptoms. Cognitive control has been linked to both PFC function and the symptoms of depression, as well as having been shown to improve with TMS. In this way, changes in cognitive control with TMS could be a potential target engagement biomarker, as well as elucidating the mechanism of action of TMS response. Additionally, better (and earlier) prediction of patient response, could further improve treatment outcomes and potentially shorten the number of necessary treatments. We are combining a trajectory modeling approach (latent class mixture modeling) with a battery of cognitive control tasks, measured longitudinally throughout the course of TMS for treatment resistant depression (TRD). We have conducted a replication of the trajectory modeling of clinical response using a naturalistic sample of 155 patients who received TMS for TRD. Results of that retrospective analysis indicated a non-response, and lower and higher baseline symptom response trajectories, partially replicating previous research using this approach. However, it remains unclear whether this modeling can be used to accurately predict response prior to completion of treatment. We have begun data collection on the cognitive battery study, with 6 patients currently enrolled. Tasks are performed at two baseline visits, once weekly throughout treatment, and at a one-month follow-up. Tasks measure different aspects of cognitive control and include: Bandit, Two-Step, Dot-Probe Expectancy, and WebSurf. Additionally, a questionnaire assessing depression symptoms (Patient Health Questionnaire-9, PHQ-9) is taken daily as a part of normal clinical care. For each run of the task, we use established modeling (e.g., drift diffusion, or logistic regression assessing model-based versus model-free learning) to extract a measure of the patient's decision making, which can then be tracked across time using the trajectory modeling approach. We predict that changes in cognitive control will precede changes in depression symptoms, providing evidence of cognitive control as a viable biomarker of TMS response.

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Poster

P978. Electrical Methods to Modulate Neural Activity II

Location: Virtual Only

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Program #/Poster #: P978.03

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS088674
NIH Grant R01NS117405
NSF DGF 1106401

Title: Rapid estimation of neuronal activation by transcranial magnetic stimulation using convolutional neural networks

Authors: *A. S. ABERRA[1], A. LOPEZ[2,3], W. M. GRILL[1,2,4,5], A. V. PETERCHEV[1,2,5,6];
[1]Biomed. Engin., [2]Electrical and Computer Engin., [3]Mathematics, [4]Neurobio., [5]Neurosurg., [6]Psychiatry and Behavioral Sci., Duke Univ., Durham, NC

Abstract: Transcranial magnetic stimulation (TMS) can modulate neural activity by evoking action potentials in populations of cortical neurons. The TMS-induced electric field (E-field) can be simulated in subject-specific head models derived from MRI data, but the spatial distribution of the E-field alone does not predict the neuronal response. Coupling E-field models to populations of biophysically realistic neuron models has yielded insights into the direct activation mechanisms of TMS (Aberra et al. 2020), but the significant computational cost associated with non-linear neuronal models limits their widespread use and eventual translation to clinical applications. Our objective was to use machine learning approaches to develop computationally efficient estimators of the activation thresholds of multi-compartmental cortical neuron models in response to TMS-induced E-fields. We used a multi-scale model combining anatomically accurate finite element method (FEM) E-field models with layer-specific models of cortical neurons adapted from the Blue Brain library to approximate the properties of human neurons (Aberra et al. 2018). We calculated activation thresholds of model pyramidal cells (PCs) in layers 2/3 and 5 and large basket cells in L4, and we used these data to train 3D convolutional neural networks (CNNs) to predict the thresholds for specific model neurons given their local E-field distribution sampled on a cubic grid. We compared this CNN estimator to an approach using the uniform E-field approximation to estimate thresholds in the non-uniform TMS-induced E-field. Using training and test datasets from different head models, the 3D CNNs were substantially more accurate than the uniform E-field approach, with mean absolute percent error (MAPE) on the test dataset below 2.5% compared to 5.9 - 9.8% MAPE with the uniform E-field approach. Further, there was a strong correlation between predicted and actual thresholds ($R^2 > 0.96$) for all cell types vs. 0.62 - 0.91 R^2 for the uniform E-field approach. The CNNs estimated thresholds with 2 - 4 orders of magnitude computational speedup over the multi-compartmental neuron models. We found a 3D CNN architecture can estimate rapidly and accurately the activation thresholds of biophysically realistic neuron models for TMS using sparse samples of the local E-field, enabling simulation of the response of large neuron populations on a personal computer.

Disclosures: A.S. Aberra: None. **A. Lopez:** None. **W.M. Grill:** None. **A.V. Peterchev:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Rogue Research, Tal Medical/Neurex Therapeutics, MagVenture. F. Consulting Fees (e.g., advisory boards); Tal Medical/Neurex Therapeutics.

Poster

P978. Electrical Methods to Modulate Neural Activity II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P978.04

Topic: I.08. Methods to Modulate Neural Activity

Support: MH114877
AG063775
Philanthropic support

Title: Does transcranial alternating current stimulation modulate cognition? A systematic review and meta-analysis.

Authors: *R. FAYZULLINA[1], S. GROVER[1], B. M. BULLARD[2], V. LEVINA[3], R. M. REINHART[1]; [1]Dept. of Psychological & Brain Sci., Boston Univ., Boston, MA; [2]Dept. of Psychology, The Univ. of California, Berkeley, Berkeley, CA; [3]Dept. of Psychiatry, Yale Univ., New Haven, CT

Abstract: In the past decade research in non-invasive brain stimulation has become more prevalent, drawing attention not only to the opportunity to study causal relationships between brain and behavior but also to the potential of stimulation to improve cognition. A growing body of studies examines the effects of transcranial alternating current stimulation (tACS) on cognitive performance. We aimed to evaluate the evidence accumulated in existing research and quantify the effects of tACS on various cognitive domains. We performed a random-effects meta-analysis of 90 studies (266 experiments) that used tACS to modulate attention, memory, executive control, learning, fluid intelligence, and decision-making, or to improve clinical symptoms. The effect sizes were synthesized using the robust variance estimation method separately for performance and reaction time outcomes. We further performed the moderator analysis that investigated the effects of various parameters of stimulation by the means of meta-regression. Quality assessment, testing for heterogeneity, evaluation of the publication bias, and sensitivity analysis were performed to ensure the robustness of the results. Total sample size included 2656 participants (1159 males, average age 31.4 (SD =16.5)). The results showed a small, but statistically significant overall effect of tACS on performance across all cognitive domains (Hedges' $g = 0.29$, 95% CI [0.2, 0.38], $p < 0.0001$), and an even smaller, yet significant, effect of tACS on reaction time (Hedges' $g = 0.20$, 95% CI [0.08, 0.32], $p = 0.002$). We found significant effects of tACS on performance in executive control ($g = 0.52$), attention ($g = 0.32$), long-term memory ($g = 0.28$), and working memory ($g = 0.26$), but not fluid intelligence or motor learning. Moderator analysis showed a statistically greater offline effect of tACS on cognitive performance compared to the online effect. Exploratory analysis revealed significant interaction of the timing of stimulation effects with the use of current-flow modeling and manipulation of the current phase. No other parameters of stimulation significantly affected the magnitude of the effect size. Our work presents the largest existing meta-analysis of tACS effects on cognition so far, yet it also shows the heterogeneity present in existing research - a typical feature of a young developing field. While the results of the meta-analysis showed a robust effect of tACS on cognitive performance, the optimal features of stimulation setup remain less clear. More research is needed to evaluate an effective combination of stimulation parameters to guide future studies and interventions.

Disclosures: R. Fayzullina: None. **S. Grover:** None. **B.M. Bullard:** None. **V. Levina:** None. **R.M. Reinhart:** None.

Poster

P978. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: P978.05

Topic: I.08. Methods to Modulate Neural Activity

Support: KNRF Grant 2020M3C1B8081319
KNRF Grant IITP-2020-2016-0-00464
KNRF Grant 2019R1I1A1A01061545

Title: Fronto-occipital phase shift in EEG cross-frequency coupled phase-dependency during working memory performance

Authors: M.-H. AHN[1], H.-S. KIM[2], ***B.-K. MIN**[3];
[1]Lab. of Brain & Cognitive Sci. for Convergence Med., Hallym Univ., Anyang, Korea, Republic of; [2]Biomed. Engin. Res. Ctr., Asan Med. Ctr., Seoul, Korea, Republic of; [3]Dept. of Brain & Cognitive Engin., Korea Univ., Seoul, Korea, Republic of

Abstract: Transcranial current stimulation is a potent neuromodulation technique used to enhance human cognitive function in a non-invasive manner. In this study, we investigated whether a cross-frequency coupling (CFC), after transcranial alternating current stimulation (tACS), was observed differently in the frontal and occipital areas during working-memory performance. Eighteen healthy participants were recruited in this study: nine for a tACS-treated group and nine for a sham group of age-gender-matched controls. Participants were instructed to perform a modified Sternberg task, where a combination of letters and digits (7 items to be encoded) was presented before and after the tACS or sham stimulation. The stimulation group was treated with CFC-tACS for 20 minutes (input channel: F3, return channels: Fp1, Fz, F7, and C3). We analyzed delta-phase/high-gamma-amplitude CFC of electroencephalographic data to find neural correlates for the enhancement of working-memory performance by tACS-treatment. We observed phase-shifts between the frontal and occipital CFC phase-dependency in the second half of the retention period along with tACS-mediated improvement in working-memory performance. This finding implies that their CFC neurodynamics reflect a long-range communication between the frontal and occipital areas during working-memory performance. Our observations provide CFC-mediated neural correlates for working-memory performance.

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Poster

P978. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: P978.06

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant EY0113588
NIH Grant EY012576
2018 NARSAD Young Investigator Grant to EA

Title: Differential Effects of Unilateral and Bilateral tDCS on Scalp EEG Power Spectra

Authors: ***S. SEIDL**[1], C. RANGANATH[1,2], G. R. MANGUN[3,2,4], W. M. USREY[1,4,5], E. G. ANTZOULATOS[1,2,5];

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Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has shown promise in improving cognitive functioning and as a therapy for neurological disorders. Recent studies have shown that it can modulate widespread neural activity; yet, these effects are highly variable and depend on the areas being stimulated (montage) and the type of stimulation (polarity and intensity). We tested two tDCS stimulation montages (unilateral and bilateral) targeting the nonhuman primate prefrontal cortex (PFC), and examined their influence on spectral power in scalp-recorded EEG and intracranial field potentials. The effects of polarity (anodal or cathodal) and intensity (0.5-1.5mA) were also examined. We found changes in EEG power at parietal scalp sites during tDCS stimulation in the lower frequency bands (<4 Hz). These effects were larger when using the bilateral tDCS montage. No effects of polarity were seen, but intensity of stimulation showed a roughly linear effect on power. Changes in scalp EEG power in parietal recordings did not persist post stimulation, and tended to show decreases in power. Although frontal scalp EEG was not recorded during stimulation, increases in power were seen post stimulation. These results highlight the importance of tDCS electrode placement in order to target specific brain areas. Furthermore, these data allow us to better understand the underlying mechanisms of tDCS and can help translate findings across experimental studies.

Disclosures: S. Seidl: None. **C. Ranganath:** None. **G.R. Mangun:** None. **W.M. Usrey:** None. **E.G. Antzoulatos:** None.

Poster

P978. Electrical Methods to Modulate Neural Activity II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:00 AM - 10:00 AM

Program #/Poster #: P978.07

Topic: I.08. Methods to Modulate Neural Activity

Title: Modulation of Motor Sequence Learning with 4mA tDCS

Authors: *G. HSU[1], A. D. SHEREEN[2], L. C. PARRA[1];
[1]Biomed. Engin., City Col. of New York, New York, NY; [2]Advanced Sci. Res. Ctr. at the Grad. Ctr., New York, NY

Abstract: Direct current stimulation (DCS) reliably boosts synaptic plasticity in vitro, but requires fields stronger than those produced in vivo in humans at 2mA with transcranial direct current stimulation (tDCS), the effects of which are still in contention. Through a well established motor sequence learning task, we hypothesize that concurrent tDCS at an increased intensity of 4mA reliably improves task performance. Furthermore, we expect the boosting effect to last at least an hour after initial training and be specific to the trained hemisphere and sequence. Functional magnetic resonance imaging (fMRI) of healthy participants (N = 10) executing simple finger movements was used in a current flow model to formulate a generalized 4x4 focal high definition tDCS (HD-tDCS) electrode montage targeting the hand knob on the contralateral primary motor cortex (M1). In a single-blind design, 72 healthy right-handed adult participants received either anodal (N = 36) or cathodal (N = 36) HD-tDCS while they performed a

sequential finger tapping task (FTT) using their non-dominant hand for 12 minutes. A 1-hour follow-up session measured retention of task performance and included two control tasks with unfamiliar sequences on both the contralateral and ipsilateral hands. Two-sample t-tests of the mean tapping speed and sequence completion indicate a significant difference in performance between the anodal and cathodal groups on the trained sequence. Unexpectedly, we also find a polarity effect on task performance that carries over to the untrained hand as well as an untrained sequence. Discomfort at various time points during the procedure was measured using a visual analog scale (VAS). In both groups the mean VAS values did not exceed moderate levels of discomfort. These results suggest that 4mA HD-tDCS targeted to M1 has a non-specific effect on motor sequence learning. Furthermore, 4mA HD-tDCS is well tolerated.

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Poster

P021. Axon Growth and Guidance

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.01

Topic: A.05. Axon and Dendrite Development

Support: Research Grants Council GRF 14113618
CUHK direct grant scheme
United College endowment fund

Title: The roles of the neuronal adaptor FE65 in neurite outgrowth

Authors: *K.-F. LAU, W. CHAN, W. LI;
The Chinese Univ. of Hong Kong, Shatin, NT, Hong Kong

Abstract: Neurite outgrowth is a crucial process in developing neurons for neural network formation. Neurite damage is often observed after brain injuries and in the early stages of many neurodegenerative diseases and in the case of age-related neural degeneration. Understanding the regulatory mechanisms of neurite outgrowth is essential for developing strategies to stimulate neurite regeneration after nerve injury and in neurodegenerative disorders. We have shown that the neuronal adaptor FE65 activates neurite outgrowth by recruiting the small GTPase ARF6 and the Rac1 GEF ELMO1 by its PTB1 domain and N-terminal region, respectively. Interfering with the formation of the multimeric signaling complex attenuates both ARF6-ELMO1-mediated Rac1 activation and neurite elongation. The plasma membrane trafficking of ELMO1 is markedly decreased in cells with suppressed expression of either FE65 or ARF6. Moreover, FE65 is shown to increase the amount of ELMO1 in the recycling endosome, an organelle responsible for returning proteins to the plasma membrane. In conclusion, FE65 potentiates ARF6-Rac1 signaling by orchestrating ARF6 and ELMO1 to promote the plasma membrane trafficking of ELMO1 via the endosomal recycling pathway, and thus, potentiates Rac1-mediated neurite outgrowth.

Disclosures: K. Lau: None. **W. Chan:** None. **W. Li:** None.

Poster

P021. Axon Growth and Guidance

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.02

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant R01GM129374

Title: Dystonia Mutation in TorsinA Impairs Neurite Formation in Hippocampal Neurons

Authors: D. C. MENDEZ[1], G. W. G. LUXTON[2], *T. W. BASTIAN[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. of California - Davis, Davis, CA

Abstract: Dystonia is the third most common neurological movement disorder and is characterized by sustained muscle contractions resulting in involuntary twisting of the extremities and abnormal posturing. The most common and severe inherited form is DYT1 dystonia, caused by a loss-of-function mutation ΔE302/303 (ΔE) in the conserved luminal AAA+ protein, torsinA. Brain imaging studies show that mouse and human carriers of ΔE mutation display reduced axonal integrity and coherence in pathways that modulate the sensorimotor cortex, suggesting that DYT1 dystonia is a neurodevelopmental circuit disorder. However, the mechanisms underlying torsinA-dependent neurodevelopment are unclear. Therefore, we asked if torsinA is required for axon and dendrite initiation and/or elongation using developing mouse primary hippocampal neuron cultures. Cells were nucleofected at plating with plasmids expressing EGFP alone or conjugated to 1) wild type torsinA (torsinA^{WT}); 2) torsinA$^{\Delta E}$ (dystonia mutation); or 3) torsinA^{E171Q} (ATP-hydrolysis defective). At 2 days *in vitro* (DIV), when axon specification is complete, neurons were stained for axons (Tau) and dendrites (MAP2). EGFP-positive neurons were imaged and the morphology of their axons and dendrites were analyzed (18-22 neurons per group). Neurons expressing torsinA$^{\Delta E}$ had significantly decreased total neurite length when compared with neurons expressing torsinA^{E171Q} and exhibited a decreasing trend in total neurite number by 2DIV when compared to EGFP alone or torsinA^{WT}. No significant change in total neurite length or number was observed in neurons expressing torsinA^{E171Q} at 2DIV. Together, these data suggest that the expression of torsinA$^{\Delta E}$inhibits neurite extension in polarizing hippocampal neurons, while expression of the ATP-hydrolysis defective torsinA^{E171Q} has no impact on this process. Since localization of the centrosome is necessary and sufficient for the polarization of cultured hippocampal neurons, we hypothesize that torsinA may promote proper neurite development and neuronal polarization in hippocampal neurons by controlling the subcellular localization of their centrosome which will be tested in future work. Here, we provide experimental evidence supporting a role for torsinA in neurite development in developing hippocampal neurons. Elucidating how torsinA functions during this process can help explain how neurons develop functional domains (one axon, multiple dendrites). We are currently assessing effects on axonal and dendritic morphology. This can lay the foundation for developing novel therapies for the treatment of dystonia and other diseases caused by torsinA mutations.

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Poster

P021. Axon Growth and Guidance

Location: Virtual Only

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Program #/Poster #: P021.03

Topic: A.05. Axon and Dendrite Development

Support: R01 MH 112669
UM Rackham Merit Fellowship
T21RS La Caixa Fellowship

Title: Interactions between the Down syndrome-related genes Dscam and Appl in axon patterning during neurodevelopment

Authors: *S. PIZZANO[1,2], M. VELING[1,3], G. STERNE[1,2], B. YE[1,3,4];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Neurosci. Grad. Program, Ann Arbor, MI; [3]Dept. of Cell and Developmental Biol., Ann Arbor, MI; [4]Life Sci. Inst., Ann Arbor, MI

Abstract: Down syndrome (DS) is a neurodevelopmental disorder caused by trisomy of human Chromosome 21 (HSA21). In patients, the extra chromosome results in higher expression of many of the triplicated genes, including *Down syndrome cell adhesion molecule (DSCAM)* and *Amyloid Precursor Protein (APP)*. 99% of DS patients present with intellectual disability (ID) and DS models show that trisomy causes atypical morphology and connectivity in CNS neurons. Despite the high rate of ID, no single region of HSA21 has been isolated as causal. This could suggest that ID has multiple causal regions or that interactions exist between HSA21 casual genes. However, it is technically challenging in mammals to test the hypothesis that HSA21-genes interact. We used the *Gal4/UAS* system along with other *Drosophila* genetics to model the increased expression of multiple DS-gene homologues during development. This allowed for cell-type specific and temporally-controlled expression. Our work suggests that the *Drosophila* homologs of *DSCAM* and *APP* interact to regulate axon morphology in neurodevelopment. We found that Appl up-regulation or loss of function increases or decreases Dscam expression respectively; This causes axonal overgrowth or restriction in Class IV Dendritic Arborization Neurons (C4Da). Furthermore, Appl regulates Dscam protein but not mRNA, indicating a post-transcriptional regulatory mechanism. We are identifying the underlying mechanisms of this interaction for future study in DS mouse models. This work will 1) provide insight into the mechanisms underlying the neurodevelopmental interactions of Down syndrome-related genes and 2) elucidate the potential link between atypical neurodevelopment and a well-characterized, Alzheimer's-linked gene (*APP*).

Disclosures: S. Pizzano: None. **M. Veling:** None. **G. Sterne:** None. **B. Ye:** None.

Poster

P021. Axon Growth and Guidance

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.04

Topic: A.05. Axon and Dendrite Development

Support: NIH R01-NS98372
NIH R01-NS115400
UW Madison SciMed GRS

Title: The F-BAR protein CIP4 regulates neurite dynamics and cortical neuron migration

Authors: *L. A. ENGLISH[1], R. J. TAYLOR[2], C. J. CAMERON[2], E. J. DISTLER[2], *K. TAYLOR[2], E. W. DENT[2];
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Abstract: Neurite initiation from newly born neurons is a critical step in neuronal differentiation and migration. Additionally, neuronal migration in the developing cortex is accompanied by dynamic extension and retraction of neurites as neurons progress through bipolar and multipolar states. However, there is a relative lack of understanding regarding how the dynamic extension and retraction of neurites is regulated during neuronal migration. In recent work we have shown that CIP4, a member of the F-BAR family of membrane bending proteins, inhibits cortical neurite formation in culture. CIP4 knockout neurons initiate neurites earlier than wild-type controls, while CIP4 overexpression results in protrusion of lamellipodia-like veils, which inhibit filopodia formation and neurite initiation. Moreover, CIP4 is predominantly expressed prenatally in cortical tissue. These results beg the question of how CIP4 functions in radial neuron migration and differentiation *in vivo*, including the timing and manner of neurite repression. To examine the effects of modulating expression of CIP4 *in vivo*, we used *in utero* electroporation, in combination with our newly published Double UP technique, to allow for comparison of experimental (knockdown or overexpression) and control cells within the same tissue. We show that either knockdown or overexpression of CIP4 results in the marked disruption of radial neuron migration, by increasing or decreasing neurite number and length, respectively. Further experiments will determine if CIP4 both inhibits extension and promotes retraction of neurites in early developing cortical neurons. Together these results will provide insight into the function of F-BAR proteins in cortical neuronal migration.

Disclosures: L.A. English: None. **R.J. Taylor:** None. **C.J. Cameron:** None. **E.J. Distler:** None. **K. Taylor:** None. **E.W. Dent:** None.

Poster

P021. Axon Growth and Guidance

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.05

Topic: A.05. Axon and Dendrite Development

Support: NIMH Grant U19 MH107367

Title: Neuron Navigator 1 contributes to neuron morphogenesis via regulation of the cytoskeleton and the plasma membrane

Authors: *R. POWERS, E. DESAI, T. LICHTENBERG, B. CALABRESE, S. HALPAIN;
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Abstract: Proper regulation of the cytoskeleton is essential for neurodevelopment. Cytoskeleton associated proteins integrate extra- and intracellular signals to influence actin and microtubule dynamics in the developing neuron. These cytoskeleton dynamics are necessary for later circuit integration and brain development, but many of the proteins involved have yet to be elucidated. Neuron Navigator 1 (Nav1) is a microtubule +TIP protein highly expressed during brain development. Nav1 is necessary for neuritogenesis, but the underlying mechanisms are relatively unknown. Using RNAi and knockout strategies in primary neurons and cell lines along with live and fixed microscopy techniques, we found that Nav1 is important for coordinating the cytoskeleton of the cell periphery for accurate cell morphogenesis. This includes an unexpected role in regulating F-actin dependent membrane ruffles and endocytosis in the growth cone, as well as a novel role in regulating actin-membrane coupling. These data highlight the importance of Nav1 in cell morphogenesis, as well as reveal new roles of this +TIP protein in regulating actin and plasma membrane to organize the cell periphery.

Disclosures: R. Powers: None. **E. Desai:** None. **T. Lichtenberg:** None. **B. Calabrese:** None. **S. Halpain:** None.

Poster

P021. Axon Growth and Guidance

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.06

Topic: A.05. Axon and Dendrite Development

Support: NINDS Grant 5R01NS104026

Title: Cas adaptor proteins are required for cortical axon tract fasciculation

Authors: *J. ESTEP[1], W. WONG[2], M. RICCOMAGNO[3];
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Abstract: Proper neural circuit organization requires individual neurons to project to their targets with high specificity. While several guidance molecules have been shown to mediate axonal fasciculation and pathfinding, little is understood regarding how neurons intracellularly integrate these cues. Here we provide genetic evidence that the Crk-Associated Substrate (Cas) family of intracellular adaptor proteins are required in a non-neuronal autonomous manner for proper fasciculation and guidance of several cortical white matter tracts, including external capsule (EC) and thalamocortical axon (TCA) projections. These findings build on a growing literature implicating Cas proteins as key mediators of cell motility and adhesion signaling.

Disclosures: J. Estep: None. **W. Wong:** None. **M. Riccomagno:** None.

Poster

P021. Axon Growth and Guidance

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Program #/Poster #: P021.07

Topic: A.05. Axon and Dendrite Development

Support: NRF 2019M3C7A1032601
NRF 2021R1A2C1005395
NRF 2021M3E5D9021902

Title: Interaction of SPIN90, SH3 protein interacting with Nck, 90 kDa, with miR-135a in neocortical neuronal migration

Authors: *S.-O. HUH, J.-E. KANG, H. PARK, A. SADRA;
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Abstract: Precise coordination of cytoskeleton is required for newly born neocortical neurons to migrate through multiple laminar layers and form normal connections with other neurons. As such, defects in the expression of genes related to cytoskeleton dynamics can lead to detrimental effects in neural proliferation, migration and neural connectivity, which in turn could lead to developmental neural migration disorders including autism spectrum disorder. Here, we investigated roles of SPIN90 (SH3 protein interacting with Nck, 90 kDa) in radial migration. Silencing of SPIN90 expression using RNAi was performed via in utero electroporation. We found down-regulation of SPIN90 resulted in abnormal termination of the neuronal migratory process. New born neurons with reduced expression of SPIN90 failed in reaching their final destination with neocortex and remained and accumulated in IZ. Furthermore, the morphology of these cells exhibited multipolar. In addition, SPIN90-silencing also caused reduction of the numbers of dendrites and neurites, as well as shortening of axon length. In contrast, overexpression of SPIN90 induced a significant increase in the number of migrating cortical neurons, as revealed by transwell assay. To elucidate key regulatory gene networks involved in neocorticogenesis, we sought to identify any regulatory miRNAs modulating the levels of SPIN90, and found that microRNA-135a is capable of regulating SPIN90 message. This microRNA also promoted neuronal migration and axonal elongation in neuronal processing as part of a gene expression regulatory network thought to be active in neocorticogenesis. Together, our observations suggest an essential role of SPIN90 in the neocortical neuronal migration.

Disclosures: S. Huh: None. **J. Kang:** None. **H. Park:** None. **A. Sadra:** None.

Poster

P021. Axon Growth and Guidance

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P021.08

Topic: A.05. Axon and Dendrite Development

Support: NINDS Intramural Research Program

Title: Trio interacts with CRMPs and plays a role in the Semaphorin3A pathway

Authors: *E. FINGLETON[1], J. D. PASKUS[2], K. W. ROCHE[3];
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Abstract: The RhoGEF Trio contains tandem GEF domains capable of activating both Rac1 and RhoA, positioning it as a bidirectional modulator of cytoskeletal dynamics in key neuronal processes, such as neuronal migration, axon guidance, dendrite arborization, and structural long-term potentiation. Additionally, de novo mutations in some regions of Trio are highly associated with Autism Spectrum Disorder, suggesting an important role for Trio in early stages of neurodevelopment. In a recent affinity purification/mass spectrometry screen for Trio interactors, collapsing response mediating proteins (CRMPs) 1-4 were identified as Trio-interacting proteins. CRMPs are most well known for their role in mediating Semaphorin3A (Sema3A) induced axon repulsion, but also play key roles in neuronal migration, dendrite arborization, and some forms of synaptic plasticity. Due to their roles as bidirectional modulators of the cytoskeleton and their phenotypic overlap with Trio, we hypothesize that CRMP binding may modulate the activity of either or both of Trio's GEF domains. Here we present data verifying that Trio and CRMP interact in vivo. Additionally, we present new data suggesting that Trio mediates Sema3A-induced neurite retraction in vitro. Additional experiments are necessary to fully dissect the nature of this interaction.

Disclosures: E. Fingleton: None. **J.D. Paskus:** None. **K.W. Roche:** None.

Poster

P021. Axon Growth and Guidance

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Program #/Poster #: P021.09

Topic: A.05. Axon and Dendrite Development

Support: NIH P20GM103650
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P20GM103440
R01MH112669
R01NS104299

Title: Dual leucine zipper kinase regulates Dscam expression through a non-canonical function of the cytoplasmic poly(A)-binding protein

Authors: *M. SINGH[1], J. KIM[2], B. YE[3];
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Abstract: Dual leucine zipper kinase (DLK) plays essential role in the development, degeneration, and regeneration of neurons. DLK can regulate gene expression post-transcriptionally, but the underlying mechanism remains poorly understood. *Drosophila* DLK, Wallenda (Wnd) regulates the expression of Down syndrome cell adhesion molecule (Dscam) by the 3' untranslated region (3'UTR) of *Dscam* mRNA. We speculated that Wnd may require an RNA binding protein (RBP) for this regulation, because being a protein kinase, it unlikely affects the 3'UTR of mRNAs directly. In this study, using an unbiased cell-based RNAi screen in cultured *Drosophila* Schneider 2 (S2) cells, we identified, pAbp —*Drosophila* ortholog of cytoplasmic PABP (PABP-C) as an RBP that is required for Wnd-mediated upregulation of Dscam. Subsequent studies showed that pAbp mutations abrogated the increased expression of Dscam as well as the exuberant presynaptic arbor growth by Wnd. PABP-C acts as a general translation activator by interacting with the poly(A) tails of mRNA. Interestingly, pAbp interacts with a non-canonical binding site on *Dscam* 3'UTR. Removing this region significantly reduced Wnd-induced increase in Dscam expression. These suggest that a non-canonical interaction of PABP with the 3'UTR of target transcripts is essential for DLK functions.

Disclosures: M. Singh: None. **J. Kim:** None. **B. Ye:** None.

Poster

P021. Axon Growth and Guidance

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Program #/Poster #: P021.10

Topic: A.05. Axon and Dendrite Development

Support: CIHR
NSERC
NIH Grant R01NS097161

Title: Structural basis and function of Kirrel3 homophilic adhesion in axonal targeting.

Authors: *N. VADDADI[1], J. WANG[2], J. S. PAK[2], Y. PARK[3], S. QUILEZ[4], C. A. ROMAN[2], E. DUMONTIER[4], J. W. THORNTON[3], E. OZKAN[2], J.-F. CLOUTIER[4];
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Abstract: The Kirrel3 receptor has been implicated in the regulation of multiple processes during the development of nervous system circuitry, including the targeting and coalescence of axons within synaptic fields and the formation of synapses. The function of Kirrel3 in these processes has been proposed to rely on homophilic adhesion between Kirrel3 molecules, but the physiological importance of Kirrel3 homophilic interactions in circuit development remains to be established. To assess the requirement of homophilic adhesion in Kirrel3 function, we first visualized the molecular basis of the homophilic adhesion by solving the crystal structure of the mouse Kirrel3 homodimer complex. These analyses identified the first immunoglobulin domain as the mediator of Kirrel3 homophilic adhesion and identified specific residue substitutions within this region that abolish the interaction. To examine the

importance of Kirrel3 homophilic adhesion in circuit formation *in vivo*, we used the CRISPR-Cas9 technology to edit the *Kirrel3* gene in mice to encode a Kirrel3 protein lacking homophilic adhesion capabilities (*Kirrel3-Q128A*). An analysis of axonal targeting in the accessory olfactory system of *Kirrel3Q128A* mice revealed alterations in the formation of the glomerular map, which phenocopy defects observed in *Kirrel3* null animals. Taken together, our results uncover the homophilic adhesion of Kirrel3 receptors as a key mechanism to regulate axonal targeting during development of the nervous system.

Disclosures: N. Vaddadi: None. **J. Wang:** None. **J.S. Pak:** None. **Y. Park:** None. **S. Quilez:** None. **C.A. Roman:** None. **E. Dumontier:** None. **J.W. Thornton:** None. **E. Ozkan:** None. **J. Cloutier:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P102.01

Topic: B.06. Synaptic Transmission

Support: NIH Grant R35NS097362
NIH Grant R01MH061876
HHMI Investigator Grant

Title: Indirect modulation of synaptic transmission in mouse striatal neurons by synaptotagmin-9

Authors: *M. J. SEIBERT, K. STANLEY, J. BRIGUGLIO, E. R. CHAPMAN;
Howard Hughes Med. Inst. & Dept. of Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: In many CNS synapses, synaptotagmin-1 (syt1) (NCBI Gene ID# 20979) serves as a calcium sensor that triggers fast, synchronous neurotransmitter release. A closely related but relatively uncharacterized isoform, synaptotagmin-9 (syt9) (NCBI Gene ID# 53420), is also expressed in CNS neurons and has been shown to be a calcium sensor for dense-core vesicle (DCV) exocytosis and neuropeptide secretion in neuroendocrine cells. In this work we attempt to characterize the role of syt9 in neuronal cell biology and synaptic physiology. We use male and female syt9 KO mice and cultured P0-1 mouse neurons - sex differences were not assessed. We show, via quantitative immunoblotting, that endogenous syt9 is expressed in cortical, hippocampal, and striatal neurons at levels that are ~25-fold lower than syt1. We conducted whole-cell voltage clamp experiments and observed that loss of syt9 has no effect on evoked neurotransmitter release in any of these three neuronal cell types. However, upon significant overexpression, we confirmed that syt9 can rescue some degree of fast, synchronous neurotransmitter release in syt1 KO cortical neurons, but this is an artifact due to up-regulation of this protein. Consistent with this observation, immunocytochemistry (ICC) experiments indicated that overexpressed syt9 had a high degree of colocalization with the synaptic vesicle marker, synaptophysin. We went on to observe that miniature inhibitory postsynaptic current (mIPSC) frequency was lower in cultured syt9 KO striatal neurons compared to WT neurons; this effect was striatum specific, as mIPSCs were unchanged in syt9 KO cortical and hippocampal neurons. To begin to elucidate the role of syt9 in regulating mIPSCs in striatal neurons, we used ICC and found that endogenous syt9 colocalized with

Substance P (SP), a neuropeptide that is packaged into DCVs, is enriched in striatal tissue, and is an agonist to the neurokinin 1 receptor (NK1R). To determine whether SP secretion contributes to mIPSC frequency, we supplemented the culture media with this peptide and found that it fully rescued the decreased mIPSC frequency in syt9 KO striatal neurons. Additionally, when WT striatal neurons were treated with the NK1R antagonist SR140333, we observed a decrease in mIPSC frequency that appeared to phenocopy the syt9 KO phenotype. These results suggest that syt9 may serve as a calcium sensor for SP secretion from striatal neurons, thereby indirectly regulating aspects of synaptic transmission. This work posits a novel role of syt9 in neurons and underscores a gap in our understanding of this protein's function in hippocampal and cortical neurons.

Disclosures: M.J. Seibert: None. **K. Stanley:** None. **J. Briguglio:** None. **E.R. Chapman:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.02

Topic: B.06. Synaptic Transmission

Support: NIH grant GM130722
NIH grant GM058055

Title: Isoflurane reduces brain-derived neurotrophic factor release leading to inhibition of glutamate exocytosis

Authors: R. WILLIAMS[1], K. W. JOHNSON[2], H. C. HEMMINGS, Jr.[1], *J. PLATHOLI[1];
[1]Anesthesiol., [2]Pharmacol., Weill Cornell Med., new york, NY

Abstract: Inhibition of glutamate release is one of many ways general anesthetics depress excitatory synaptic transmission, but the underlying cellular and molecular targets remain unclear. We hypothesized that isoflurane, a common general anesthetic, reduces brain-derived neurotrophic factor (BDNF) release, resulting in decreased presynaptic glutamate release. Dissociated hippocampal neurons from wild-type and loss-of-function BDNF Val66Met knock-in mice with reduced BDNF secretion were used to test this. Isoflurane-induced changes in BDNF release were measured using the genetically encoded biosensor BDNF-pHluorin. Neurons in culture with varying levels of BDNF secretion were used to determine the effect of reduced endogenous BDNF amounts on glutamatergic synaptic vesicle exocytosis using vGlut1-pHluorin. Our results show that isoflurane attenuates BDNF release contributing to inhibition of glutamate release and that this inhibition may be long-lasting in neurons with reduced endogenous BDNF (Val66Met).

Disclosures: R. Williams: None. **K.W. Johnson:** None. **H.C. Hemmings:** None. **J. Platholi:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.03

Topic: B.06. Synaptic Transmission

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VKSZ 14-1-2015-0155
Frontline - Research Excellence Programme KKP 19 (KKP 129961)
National Program in Brain Sciences (2017-1.2.1-NKP-2017-00002)

Title: Synaptic cannabinoid signaling in the absence of endocannabinoid-synthesizing enzymes

Authors: *B. BARTI[1], K. KENESEI[3], M. LEDRI[5], M. KISFALI[3], B. TÓTH[6], V. MICZÁN[3], G. HORVAI[6], S. E. VIZI[4], I. KATONA[2];
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Abstract: Retrograde endocannabinoid signaling via presynaptic cannabinoid (CB_1) receptors plays an essential role in the calibration of neurotransmitter release probability in both phasic and tonic manner. However, the role of the major endocannabinoid messengers [2-arachidonoylglycerol (2-AG), anandamide (AEA)] and their predominant synthesizing enzymes [diacylglycerol lipase-α (DAGLα), N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD)] in tonic endocannabinoid signaling has remained elusive. We utilized patch-clamp electrophysiology with combination of Stochastic Optical Reconstruction Microscopy (STORM), two-photon imaging and liquid chromatography/tandem mass spectrometry to address potential cell-type specific physiological and molecular changes in mice with chronic absence of DAGLα. Despite the reduced basal 2-AG levels, our results demonstrate unaltered morphology and CB_1 receptor expression with unchanged baseline synaptic transmission between inhibitory basket cells and CA1 pyramidal cell pairs in the hippocampus. Pharmacological blockade of CB_1 receptors in both DAGLα- and NAPE-PLD knockout mice revealed elevated inhibitory synaptic transmission, therefore unaltered cannabinoid tone. These findings highlight a ligand-independent persistent cannabinoid signaling which maintained synaptic function at homeostatic levels.

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Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.04

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH107435-06

Title: Endocannabinoid Modulation of Synaptic Transmission in the Lateral Habenula

Authors: *N. D. WINTERS[1], M. ALTEMUS[2], K. D. JOHNSON[2], S. PATEL[2];
[1]Pharmacol., [2]Psychiatry, Vanderbilt Univ., Nashville, TN

Abstract: The lateral habenula (LHb) is an epithalamic brain structure critically involved in the processing of aversive stimuli. Despite the increasingly evident role of the LHb in neuropsychiatric disease, the molecular regulators that orchestrate synaptic transmission within this brain structure are poorly understood. Among the plethora of neuromodulatory systems that have been described within the LHb is the endocannabinoid (eCB) system, a lipid-derived retrograde signaling system that dynamically regulates a variety of functions in the brain. Data from other labs have demonstrated the presence of functional CB1 receptors at LHb synapses, that LHb eCBs are recruited by stress, and that intra-LHb CB1 inhibition can produce anxiolytic and antidepressive-like effects, suggesting the hypothesis that eCB signaling within the LHb may serve an activity-promoting function. To mechanistically test this hypothesis, we have begun to examine how eCB signaling modulates synaptic transmission within the LHb. We have found that CB1 activation or blockade produces unexpected effects on excitatory vs. inhibitory spontaneous release. We have begun testing a hypothesis involving an indirect endocannabinoid signaling mechanism and have generated data mechanistically supporting these paradoxical findings. Ongoing studies are aimed at further dissecting the role of this indirect endocannabinoid mechanism in regulating LHb synapses and examining the function of eCBs in regulating evoked release from key stress-related inputs to the LHb.

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Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.05

Topic: I.04. Physiological Methods

Support: DA04041513

Title: Activation of the serotonin 2A receptor Inhibits claustrum neurons projecting to anterior cingulate cortex and modulates cognitive flexibility performance

Authors: *T. L. ANDERSON, P. I. ORTINSKI;
Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: The claustrum (CLA) has long been speculated to be fundamental in a variety of brain functions such as attention salience and cognitive flexibility. The CLA also boasts being the most densely innervated structure in the brain and has the highest expression of the serotonin 2A receptor (5HT2AR), the main excitatory G protein-coupled receptor subtype for serotonin (5HT), and the major site of action for psychedelic hallucinogens. The CLA, as well as 5HT and the 5HT2AR, have recently been implicated for playing a role in cognitive flexibility, the ability to adapt behavior to environmental changes, though these relationships remain largely uninterrogated. Because cognitive flexibility is emerging as a testable metric relevant to drug use research, as many drugs of abuse, including cocaine negatively affect cognitive flexibility, we observed the effects of both cocaine, and the potent 5HT releasing agent, MMAI, on rat cognitive flexibility performance using a set-shifting task. We also use whole cell electrophysiological slice recordings to observe effects of serotonin on neuronal activity in the claustrum, first targeting general claustrum neurons, and then using retrograde labeling, to record from CLA neurons projecting to the anterior cingulate cortex (ACC) in the presence of 5HT and the 5HT2AR antagonist, Ketanserin. Spontaneous excitatory post-synaptic current (sEPSC) frequency and amplitude were analyzed, as well as other cell properties such as resting membrane potential, action potential firing rate, and spontaneous inhibitory post-synaptic currents (sIPSCs). Significant decreases in sEPSC frequency and amplitude were observed in both indiscriminate CLA neurons and CLA-ACC labeled neurons after application of 5HT to the slice. Similarly, robust increases in sIPSC frequency and amplitude were observed. Blockade of the 5HT2AR with Ketanserin eliminated the synaptic effects of 5HT, indicating a regulatory role of the 5HT2AR in claustrocortical signaling. Our behavioral preliminary experiments included testing rat cognitive flexibility under the influence of either cocaine, MMAI, or saline in set-shifting tasks to receive sugar pellets. Our results showed that both cocaine and MMAI had profound negative effects on cognitive flexibility performance. These findings provide the first physiological evidence that the large population of CLA-ACC neurons are under strong inhibitory control from 5HT and the 5HT2AR. Our behavior data also confirms that disruption of serotonergic brain signaling can negatively affect cognitive flexibility performance.

Disclosures: T.L. Anderson: None. **P.I. Ortinski:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P102.06

Topic: B.06. Synaptic Transmission

Support: NIH Grant DA035714
NIH Grant DA041932

Title: Hiv-1 tat protein exacerbates methamphetamine-dysregulated dopamine uptake into vesicular monoamine transporter-2 and potentiates methamphetamine conditioned place preference in hiv-1 tat transgenic mice

Authors: *J. ZHU[1,2], M. J. STRAUSS[1], S. E. DAVIS[1], J. P. MCLAUGHLIN[2];
[1]Drug Discovery and Biomed. Sci., Col. of Pharmacy, Univ. of South Carolina, Columbia, SC;
[2]Pharmacodynamics, Univ. of Florida, Gainesville, FL

Abstract: Methamphetamine (METH) abuse has been shown to increase the incidence of HIV-1 associated neurocognitive disorders (HAND). Perturbation of dopamine (DA) transmission has been demonstrated as a mediating factor in HAND and METH abuse. Our published work has demonstrated that the HIV-1 regulatory protein, transactivator of transcription (Tat), decreases DA transport via the DA transporter (DAT) and vesicular monoamine transporter-2 (VMAT-2). The VMAT-2 transports cytosolic DA into synaptic vesicles and plays a critical role in DA homeostasis. Therefore, this study examined the synergistic effects of Tat and METH on DA uptake through VMAT-2 and associated METH reward through the following three experiments. *Experiment-1*: *in vitro* incubation of isolated mouse whole brain vesicles with recombinant Tat_{1-86} or METH displayed a concentration-dependent inhibition of vesicular [^{3}H]DA uptake, in which a combination of Tat and METH induced an additive reduction of DA uptake via VMAT-2 compared to Tat or METH alone. *Experiment-2*: we determined whether the *in vitro* effect of Tat and METH on VMAT-2 uptake can be replicated in an inducible Tat transgenic (iTat-tg) mouse model. This model recapitulates many aspects of the neurocognitive impairments observed in HIV infected individuals. iTat-tg and G-tg (Tat null) mice were given saline or doxycycline (Dox, 100 mg/kg/day, i.p.) for 21 days, and on day 8 after starting injection of saline or Dox, mice were given saline or METH (3 mg/kg, i.p.) daily until day 21. 24 hours after last injection, all mice were subjected to kinetic analysis of [^{3}H]DA uptake into whole brain vesicles. Results show that 21-day Dox-induced Tat expression caused a 57% decrease in the maximal velocity (V_{max}) value, which was attenuated in G-tg mice. 14-day METH alone induced a 35% and 52% reduction of V_{max} in iTat-tg and G-tg mice, respectively, whereas a greater decrease (66%) in V_{max} was observed in iTat-tg mice of Dox-METH group. Considering that both Tat and METH interact with DAT and VMAT-2, these results provide evidence that Tat and METH could disrupt DA transmission by inhibiting both DAT and VMAT-2 function. *Experiment-3*: following 14-day treatment of Dox, the iTat-tg mice potentiated METH-conditioned place preference 6-fold over saline-treated mice, suggesting that Tat expression potentiates the rewarding effect of METH. The current findings suggest that Tat and METH synergistically inhibit VMAT-2-mediated DA uptake, leading to dysregulation of DA transmission and raises the exciting possibility of a potential therapeutic strategy by targeting VMAT-2 for METH abuse in HIV infected individuals.

Disclosures: J. Zhu: None. **M.J. Strauss:** None. **S.E. Davis:** None. **J.P. McLaughlin:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.07

Topic: B.06. Synaptic Transmission

Support: 5R01DA011289-21

Title: Somatodendritic release of cholecystokinin regulates VTA local circuitry and mouse behavior

Authors: *V. MARTINEZ DAMONTE[1], M. B. POMRENZE[2], R. C. MALENKA[2], J. A. KAUER[1]; [1]Dept. of Psychiatry and Behavioral Sci., [2]The Pritzker Laboratory, Dept. of Psychiatry and Behavioral Sci., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Ventral tegmental area (VTA) dopamine (DA) neurons participate in circuits that underlie diverse behaviors, including motivation, learning, aversion, and locomotion. Somatodendritic DA release is a notable feature of DA cells and decreases spontaneous firing mediated by D2R autoreceptors. Most DA neurons also express the neuropeptide cholecystokinin (CCK), but its role in the VTA has remained elusive.GABAergic inputs are essential for controlling the firing pattern of VTA DA neurons. In electrophysiological recordings in horizontal midbrain slices, we recently found that somatodendritically-released CCK potentiates inhibitory postsynaptic currents (IPSCs) onto VTA DA neurons. This potentiation is triggered by a mild depolarization of the DA neuron, is blocked by the CCK2R antagonist LY225910, and occurs only at specific subsets of inhibitory synapses on DA cells. Here we explore CCK release and its impact on VTA-related behaviors.First, we examined the mechanisms underlying CCK release. Since depolarization of DA neurons releases CCK, we tested whether optogenetic activation of DA neurons alone might release CCK. We found that this also potentiated IPSCs in DA cells. Our preliminary data suggest that ELISA assays confirm this.As Ca2+ chelation prevents CCK-induced LTP, we next explored whether blocking L-type voltage-gated calcium channels, generally associated with dense core vesicle release, prevents depolarization-induced LTP. We bath applied NiCl2 (50μM) and found that depolarization no longer triggered LTP. We are currently evaluating the involvement of other cellular proteins that may be required to support CCK release.Finally, we studied CCK effects on the excitability of DA neurons and on VTA-related behaviors. We infused either CCK or saline bilaterally into the VTA of fasted mice and measured food intake. We found that in the first hour after CCK infusion, food consumption was reduced. However, we also observed in an open field test that CCK delivery decreased the total distance traveled and time spent in the field center, suggesting that locomotor deficits or anxiety could contribute to the food intake results.Our work in VTA DA neurons reveals a novel role for CCK somatodendritic release as an overlooked modulator of the local circuit and its behavioral consequences.

Disclosures: V. Martinez Damonte: None. **M.B. Pomrenze:** None. **R.C. Malenka:** None. **J.A. Kauer:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P102.08

Topic: B.06. Synaptic Transmission

Support: 5R01DA040630
T32 GM07628

Title: Stress sensitive kappa opioid receptor modulation of excitatory drive onto nucleus accumbens fast-spiking interneurons

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Abstract: The dynorphin/kappa opioid receptor (KOR) system within the nucleus accumbens (NAc) contributes to negative affective states following withdrawal from illicit drugs, pain, and stress. In the NAc, parvalbumin fast-spiking interneurons (PV-FSIs) receive similar excitatory input as neighboring medium spiny neurons (MSNs) and robustly inhibit MSN activity via feedforward inhibition, critically regulating NAc circuit dynamics. KORs have been shown to presynaptically inhibit glutamate release onto MSNs, but dynorphin/KOR regulation of excitatory drive onto PV-FSIs remains unknown. To address this gap, here we characterize KORs at glutamatergic synapses onto PV-FSIs in the NAc core (NAcc). Using male and female PV-cre/Ai9(tdTom) mice and whole cell electrophysiology, we show that activation of KORs induces long-term depression (LTD) of excitatory drive onto PV-FSIs. Further characterization shows that the depression is expressed postsynaptically and is mediated by PKA and calcium/calcineurin dependent endocytosis of AMPARs. We also report that KORs preferentially modulate midline nuclei of the thalamus afferents and not prefrontal cortex afferents onto NAcc PV-FSIs. To determine the potential involvement of this mechanism in the response to stress, mice were subjected to restraint stress for one hour, a manipulation shown to increase NAc dynorphin. In stressed animals the KOR agonist no longer elicited LTD. Interestingly, the LTD is rescued by administration of the KOR antagonist, nor-BNI, prior to the stress. This work provides a novel mechanism and synaptic locus by which KORs modulate NAc circuit activity and provides evidence for the recruitment and/or dysregulation of this mechanism following stress.

Disclosures: B.C. Coleman: None. **K.M. Manz:** None. **B.A. Grueter:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.09

Topic: B.06. Synaptic Transmission

Support: NIH R01 HL098602
R01 HL128454 (DDK)

Title: Corticotropin-releasing hormone and oxytocin augments synaptic activity in the nucleus tractus solitarii of rats subjected to chronic intermittent hypoxia.

Authors: *P. BARCELLOS-FILHO, D. D. KLINE;
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Abstract: Hypertension is one consequence in individuals with obstructive sleep apnea. Chronic intermittent hypoxia (CIH) in rodents mimics the hypoxia-induced hypertension seen in sleep apnea. Alterations in synaptic activity within the nucleus tractus solitarii (nTS), the central integration site of sensory afferent, are involved in the CIH-induced hypertension. The paraventricular nucleus of the hypothalamus (PVN) has a modulating role in controlling nTS activity to influence blood pressure and respiration. The PVN sends direct neuronal projections containing oxytocin (OT) and/or corticotropin-

releasing hormone (CRH) to the nTS, and these neuropeptides alter nTS synaptic signaling. During hypoxia, there is an increase in the production of these neuropeptides, yet their contribution to nTS activity is not completely understood. We hypothesized OT and CRH (individual and combined) modulates nTS synaptic activity in normoxia and their influence is enhanced after CIH. Male Sprague-Dawley rats (3-4 weeks) were exposed to 10 days normoxia (21% O_2) or 10 days CIH (30-40 sec of 6% oxygen, 10 episodes/h, 8 h/day). Horizontal brainstem slices were generated, and using whole-cell patch-clamp recordings, we examined synaptic neurotransmission and electrophysiological properties of monosynaptic nTS neurons. Excitatory postsynaptic currents (EPSCs) and current-evoked action potential discharge (APD) were examined during sequential aCSF control, OT (600 nM) alone, CRH (300 nM) alone, and the combination of OT (600 nM) and CRH (300 nM). In normoxia, compared to aCSF baseline, OT alone had no effect on afferent (TS)-evoked EPSC amplitude, spontaneous (s)EPSC amplitude or frequency, or APD. CRH alone tended to increase TS-EPSC amplitude yet decreased APD. sEPSCs were not affected. Co-application of OT and CRH did not alter EPSCs but reversed the CRH-induced depression of discharge. Conversely, after CIH, the response to neuropeptide activation was enhanced. While OT had a tendency to increase TS-EPSCs, CRH alone and its combination with OT significantly augmented TS-EPSC amplitude evoked in response to 0.5 and 20Hz stimulation. The characteristic frequency-dependent depression of TS-EPSCs in the nTS was not altered by any drug combination, suggesting pre-synaptic release was not altered. sEPSCs and discharge were relatively unaffected. In summary, these data show that following CIH, CRH and OT synergistically enhanced afferent-driven neurotransmission to nTS neurons via an increase in their postsynaptic receptors.

Disclosures: P. Barcellos-Filho: None. **D.D. Kline:** None.

Poster

P102. Synaptic Transmission: Modulation by Neurotransmitters and Peptides I

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Program #/Poster #: P102.10

Topic: B.06. Synaptic Transmission

Support: IBRO Travel Grant Award for Participation in SFN 2021 Ref.No. TG2021JulDec-15
Dr. Pratibha Thakur Recipient of Senior Research Fellowship (SRF) from Indian Council of Medical Research (ICMR), Govt. of India, Ref. No. 45/37/18-PHA/TRANS/BMS

Title: The neuropeptide oxytocin: search for its possible neuromodulatory action of dopamine & serotonin in different region of the brain

Authors: *P. THAKUR[1], R. SHRIVASTAVA[2], V. K. SHRIVASTAVA[1];
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Abstract: The neuropeptide oxytocin has been implicated in social behavior and being evaluated as a possible treatment for neurodegenerative disorders *i.e.* schizophrenia, autism spectrum disorders, anxiety, and depression etc., but the neural mechanisms how oxytocin modulates social behavior is unknown. Dopamine and serotonin are important neurotransmitter in central nervous system and disruption in dopaminergic and serotoninergic neurotransmission have been found in the patients of neuropsychiatric

disorder *i.e.* autism, depression etc. Here, we have explored the influence of exogenous oxytocin in the neurotransmission of dopamine and serotonin level in various regions of the brain. Experimental animal, were exposed intraperitoneally (i.p.) to oxytocin 0.0116mg/kg for 30, 60, and 90 days while control animals were treated with normal saline. After the completion of different duration, all the animals of different groups were sacrificed by cervical dislocation; the brains were carefully removed, washed in normal saline, and frozen tissue was divided into seven regions, the medulla oblongata, midbrain, cerebellum, cerebral cortex, striatum, hippocampus, and hypothalamus, adopting the methodology of (Glowinski & Iversen, 1966) for the estimation of dopamine and serotonin in different region of the brain. In the present study we found that, there is significant increase ($p<0.001$, one way analysis of variance [ANOVA]) in dopamine level in hypothalamus, cerebral cortex, and midbrain of the brain region of the animals treated upto 90 days, which indicates the stimulation of dopamine mesocorticolimbic pathway. Furthermore, dopamine level significantly decreased in cerebellum of 30 days oxytocin treated group, while the level of dopamine increased after 60 and 90 days of treatment with oxytocin, which may be due to dose and duration dependent factor of oxytocin. However, oxytocin treatment upto 90 days results significantly increase in the level of serotonin in selected seven region of the brain. This finding is consistent with the effect of exogenous oxytocin on neuromodulation of serotonergic system in different region of the brain and regulates appetite social cognition, homeostasis, and energy metabolism and further paves the way for the identification of novel neurodegenerative drug target.

Disclosures: P. Thakur: None. **R. Shrivastava:** None. **V.K. Shrivastava:** None.

Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P156.01

Topic: B.11. Glial Mechanisms

Title: Properties of astrocyte polarity

Authors: *J. D. ELLIOTT, M. MATHEW, G. ZHANG, J. L. FUCHS;
Univ. of North Texas, Denton, TX

Abstract: Astrocytes are often considered relatively unpolarized, in keeping with the meaning of astrocytes as “star cells.” In this respect, astrocytes contrast with neurons, which are a paragon of polarity, sending action potentials down a single axon from the neuron’s basal pole and receiving dendrites located apically. However, astrocytes do exhibit polarity in the distribution of the intermediate filament glial fibrillary acidic protein (GFAP) and the location of the primary cilium. These features may be polarized beginning with the birth of astrocytes, when newly born pairs of daughter cells are mirror images of each other with the most distant poles having both the primary cilium and the highest concentration of GFAP. The present study is a systematic analysis which addresses these aspects of astrocyte polarity: heterogeneity across brain regions; orientation with respect to migration or region-specific architecture; developmental changes; and influence of cilia deficiency. We developed measures to quantify polarity strength, polarity orientation with respect region-specific architecture, and the occurrence of GFAP polarity relative to the primary cilium location. Polarity strength was the ratio of the distance between the

centers of mass of GFAP concentration and the soma, to the radius of the soma along the same axis. These measures were evaluated in prefrontal and somatosensory cortices, hippocampal CA1, caudate putamen, and corpus callosum of Aldh1L1-EGFP astrocyte reporter mice on postnatal days P30 and P1. On P30, GFAP polarity showed main effect of brain region ($p<0.001$). Mean polarity ratio for the five regions was 0.75 ± 0.01 SEM, ranging from 0.71-0.83. Selective polarity orientation was evident in prefrontal cortex, hippocampus, and corpus callosum only. GFAP polarity strength was greater on P1 than on P30 ($p<0.001$), with polarity ratios of 0.83 ± 0.01 and 0.75 ± 0.01, respectively. GFAP and primary cilia were both located in the same pole of the soma in 94.4% of P30 astrocytes compared to 82.4% on P1. Astrocytes lacked primary cilia in cilium-deficient $Tg737^{orpk}$ mutant mice on P31 and the average GFAP polarity was greater than Aldh1L1-EGFP mice (0.77 ± 0.01 and 0.75 ± 0.01, respectively, $p=0.045$). Our study suggests (1) Polarity via GFAP and primary cilium location is a general feature of brain astrocytes; (2) Polarity strength and orientation vary with brain region; and (3) Polarity may be present in newly born astrocytes and is maintained throughout development. The results lead to questions about the implications of polarity and its potential relationship to the dual role of astrocytes in communicating with both neurons and the circulatory system.

Disclosures: J.D. Elliott: None. **M. Mathew:** None. **G. Zhang:** None. **J.L. Fuchs:** None.

Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P156.02

Topic: B.11. Glial Mechanisms

Title: Regulation of astrocytic glutamine synthetase expression through extracellular glutamine

Authors: *Y. NASU[1,2], K. TABETA[2], M. TERUNUMA[1];
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Abstract: <META NAME="author" CONTENT="那須 優介">Astrocytes, one of the major glial cells in the central nervous system, is the only cell types that express glutamine synthetase (GS) to protect neurons against neurotoxicity induced by excess amount of ammonia and glutamate. An increasing number of studies have indicated that GS levels in astrocytes is associated with several brain disorders including Alzheimer's disease, schizophrenia, mesial temporal lobe epilepsy and depression. However, the detailed mechanism regulating astrocytic GS expression remains unclear. According to a recent report, GS expression in the liver is regulated by extracellular glutamine (Nguyen TV et al. *Mol Cell*. 2016). In this study, we investigated whether GS expression in astrocytes is regulated in response to the extracellular glutamine concentration.We used primary cultured astrocytes prepared from rat embryo in this study. We first removed glutamine for 36 hours and then increased extracellular glutamine concentration to 4 mM. We observed a time-dependent reduction in total GS expression. The gene encoding GS, *glul*, was not reduced, suggesting the possible mechanism of enhanced GS degradation in this condition. GS in liver has been reported to be ubiquitylated and subsequently degraded by the proteasome along with extracellular glutamine levels (Nguyen TV et al. *Mol Cell*. 2016). Thus, we used

proteasome inhibitor MG132 and found that glutamine-induced GS down-regulation was attenuated when proteasome degradation pathways are inhibited. In contrast, glutamine-deprived astrocytes dramatically increased GS expression. Interestingly, the application of glutamate and NH_4Cl, the sources of glutamine, in glutamine-deprived astrocytes did not increase GS as much as that of glutamine-deprived astrocytes, suggesting that the amount of intracellular glutamine may be the determinant of GS expression in astrocytes. We are currently investigating the mechanism of GS up-regulation in glutamine-deprived astrocytes.

Disclosures: Y. Nasu: None. **K. Tabeta:** None. **M. Terunuma:** None.

Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: NIH R01 NS120746
Virginia Tech Start Up Funds

Title: Dna methylation regulates trkb isoform expression in cns

Authors: *X. WEI[1], M. L. OLSEN[2];
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Abstract: The tropomyosin receptor kinase B (TrkB), the canonical receptor of Brain-Derived Neurotrophic Factor (BDNF), is broadly expressed in developing and mature brain. Studied for nearly three decades, BDNF/TrkB signaling has been shown to play critical roles in central nervous system (CNS) development, neuronal cell growth, differentiation, synaptogenesis and synaptic plasticity. While dysregulated BDNF/TrkB signaling is implicated in a growing list of neurodevelopmental and neuropathological disorders. TrkB is encoded by the *Ntrk2* gene, a complex gene approximately 330kb in length. TrkB has two main isoforms expressed in the CNS, the full length TrkB (TrkB.FL) receptor and the truncated TrkB (TrkB.T1) receptor. We recently demonstrated that TrkB.T1 is the predominant isoform in the rodent cortex, is almost exclusively expressed in astrocytes, and appears critical for astrocyte morphological maturation. In contrast TrkB.FL is the main isoform expressed in neurons. Given the critical role for this signaling pathway in healthy brain development and mature CNS function, we aim to identify the molecular underpinnings for the cell type specific expression of each TrkB isoform. We isolated astrocytes and neurons from p28 WT male mice cortex with magnetic isolation method and high molecular weight DNA was extracted to construct libraries for four biological replicates of astrocytes and neurons. Using nanopore sequencing, which enables direct, quantitative analysis of the methylation status of Ntrk2 in its entirety, preliminary data indicates marked differences in neuronal and astrocyte methylation. Notably, the majority of differentially methylated sites between astrocytes and neurons were found in intron located after the first coding exon expressed in both TrkB.FL and TrkB.T1 and in regions which flank a unique TrkB.T1 exon, which indicated that DNA methylation may regulate

TrkB isoform expression. Future work is aimed at investigating and manipulating these unique differentially methylated regions to determine in DNA methylation patterns in Ntrk2 regulate cell-type specific expression patterns in unique CNS cell populations.

Disclosures: X. Wei: None. **M.L. Olsen:** None.

Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Program #/Poster #: P156.04

Topic: B.11. Glial Mechanisms

Support: NIH Grant RO1-NS-065201
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Title: Uptake of biotinylated spermine in astrocytes: effect of Cx43 siRNA, HIV-Tat protein and polyamine transport inhibitor on polyamine uptake.

Authors: *C. J. MALPICA-NIEVES[1], Y. RIVERA[2], D. E. RIVERA-APONTE[3], O. PHANSTIEL[5], R. W. VEH[6], M. J. EATON[3], S. N. SKATCHKOV[4];
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Abstract: Polyamines (PAs) are polycationic biomolecules containing multiple amino groups. Patients with HIV-associated neurocognitive disorder (HAND) have high concentrations of the polyamine N-acetylated spermine in their brain and cerebral spinal fluid (CSF) and have increased PA release from astrocytes. These effects are due to the exposure to HIV-Tat protein since it produces conversion of SPM in astrocytes to N-acetylated-SPM (Ac-SPM) which has been found to be a novel biomarker predicting the severity of HAND in HIV-infected individuals. In healthy adult brain, PAs are accumulated, but not synthesized in astrocytes suggesting that PAs must enter astrocytes to be N-acetylated and released. Therefore, we tested if Cx43 hemichannels (Cx43-HCs) are pathways for PA flux in control and HIV-Tat treated astrocytes. We used biotinylated spermine (b-SPM) to examine polyamine uptake in cells bathed in a solution containing 2.5 mM Ca^{2+} and 2 mM Mg^{2+}. We found that control astrocytes and those treated with siRNA-Cx43 took up b-SPM similarly suggesting that PA uptake under these conditions is via a transporter/channel other than Cx43-HCs. Surprisingly, astrocytes pretreated with both HIV-Tat and siRNA-Cx43 showed increased accumulation of b-SPM. Using a novel polyamine transport inhibitor (PTI), trimer 44NMe, we blocked b-SPM uptake showing that PA-uptake is via the PTI-sensitive transport mechanism such as organic cation transporters. Our data suggest that Cx43 HCs are not a major pathway for b-SPM uptake in the condition of normal extracellular calcium concentration but may be involved in the release of PAs to the extracellular space during viral infection.

Disclosures: C.J. Malpica-Nieves: None. **Y. Rivera:** None. **D.E. Rivera-Aponte:** None. **O. Phanstiel:** None. **R.W. Veh:** None. **M.J. Eaton:** None. **S.N. Skatchkov:** None.

Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: NIH-NINDS NS089791
NIH-NINDS NS105742

Title: Activity-dependent regulation of astrocyte expressed synapse-modulating genes

Authors: *I. FARHY-TSELNICKER[1,2], M. M. BOISVERT[1,3], H. LIU[1], C. DOWLING[1], G. ERIKSON[1], E. BLANCO-SUAREZ[1,4], C. FARHY[5], M. SHOKHIREV[1], J. R. ECKER[1,6], N. J. ALLEN[1]; [1]The Salk Inst., La Jolla, CA; [2]Biol., Texas A&M Univ., College Station, TX; [3]Neurol., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Neurosurg., Thomas Jefferson Univ., Philadelphia, PA; [5]Sanford Burnham Prebys medical discovery institute, La Jolla, CA; [6]Howard Hughes Med. Inst., La Jolla, CA

Abstract: Astrocytes are important regulators of neuronal synapse development and function. In the rodent cortex neurons are arranged in layers, each with stereotyped synaptic connectivity. Cortical astrocytes produce several synapse promoting factors, however, what regulates their regional and temporal expression during development is unknown. Here we use RNA sequencing, genetic mouse models, immunohistochemistry and in situ hybridization to determine the expression profile of astrocyte synapse promoting genes, and their regulatory mechanisms in the developing mouse visual cortex. This analysis identified astrocyte signals that show differential temporal and layer-specific expression. The observed expression changes occurred mainly between post-natal days (P) 7 and 14, a time between synapse initiation and maturation. We focused on factors that promote expression of AMPA receptors (AMPARs), crucial components of active excitatory synapses, such as glypican 4 (Gpc4) and chordin like 1 (chrdl1). AMPAR subunit composition undergoes a developmental switch, whereupon GluA1 is prevalent in immature synapses, while GluA2 marks a mature synapse. Gpc4, which promotes expression of GluA1 is highly expressed at P7, and is downregulated at P14 specifically in layer (L) 1, suggesting a role in synapse initiation. Chrdl1, which promotes synapse maturation by regulating expression of GluA2, peaks at P14 in the upper layers. These temporal and regional changes are regulated by visually evoked neuronal activity, as they are absent in mice lacking glutamate release from thalamo-cortical projections, resulting in delayed synapse maturation. Further, expression of synapse regulating genes and synaptic development are also altered when astrocyte signaling is blunted by diminishing calcium release from intracellular stores, as evident from mice lacking the Ip3r2 gene. Single nucleus RNA sequencing identified astrocytic genes from various functional categories, that are regulated by neuronal and astrocyte activity, along with multiple genes that show layer-specific enrichment. These findings provide insight into neuron-astrocyte interaction as it occurs at the level of the distinct cortical connections, and constitute an important frame work for future studies of astrocyte and synapse development in the cortex.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: University of Louisiana at Lafayette Minigrant for Undergraduate Research
University of Louisiana at Lafayette Graduate Student Association
McNair Scholars Program

Title: Fibroblast Growth Factor Receptor 1 interacts with diet to impact tanycyte morphology and physiology

Authors: *K. SMITH[1,2], N. A. ESTEVE[2], G. NORA[2], L. HUVAL[2], T. ADOUN[2], H. MAYEUX[2];
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Abstract: Fibroblast Growth Factor Receptor 1 (FGFR1) is expressed by most astrocytes in the Central Nervous System, including strong expression in hypothalamic tanycytes. Tanycytes are a specialized subtype of astrocyte of the hypothalamus. The cell bodies of tanycytes are located in the ventral wall of the 3rd ventricle, alongside ependymal cell bodies. Tanycytes have long radial projections into the hypothalamus, and previous studies have indicated that the radial morphology of tanycytes aids in their functions of transferring metabolic signals and hormones from the 3rd ventricle and blood stream to the hypothalamic nuclei controlling physiological processes such as appetitive behaviors. Tanycytes are in a privileged position between the CSF in the 3rd ventricle, the blood supply via fenestrated capillaries in the median eminence, and metabolism-influencing nuclei in the hypothalamus. In this study, we utilized a Nestin-Cre Recombinase transgenic adult mice line that conditionally deleted FGFR1 in neural stem cells (NSCs), to investigate the impacts that FGFR1 has in tanycyte morphology and physiology. We also explored differential impacts upon the dentate gyrus (DG) of the Hippocampus. We placed 7-11 mice per group on a one-month long high fat diet to investigate differences in body homeostasis and tanycyte morphology between FGFR1 flox allele controls and Cre+ FGFR1 deficient mice. We found that FGFR1 is a vital contributor to tanycyte morphology and quantity, and a partial promotor of NSC maintenance. Although tanycyte morphology was disrupted in regular diet (RD) KO mice, glucose physiology and body weight was unperturbed relative to RD WT mice. With a combination of FGFR1's deletion and a high fat diet (HFD), NSCs were greatly reduced in both the 3rd ventricle and the dentate gyrus. Although a HFD has be proven to promote a low-grade pro inflammatory environment, microglia were not drastically activated in the HFD mice compared to RD mice; however, they were reduced in number in the DG of HFD mice.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: NIH Grant NS113499
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Title: Neuronal activity drives pathway-specific depolarization of astrocyte distal processes

Authors: M. ARMBRUSTER[1], S. NASKAR[2], J. GARCIA[2], M. SOMMER[2], E. KIM[2], Y. ADAM[3], P. G. HAYDON[4], E. S. BOYDEN[6], A. E. COHEN[7], ***C. G. DULLA**[5];
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Abstract: Astrocytes are glial cells with elaborate morphological complexity, allowing close physical and functional interactions between nanometer-scale distal astrocyte processes (DAPs) and neuronal synapses. Excitatory amino acid transporters (EAATs), including GLT1 and GLAST, are concentrated in DAPs where they remove extracellular glutamate, providing spatiotemporal control of excitatory neurotransmission. The inward rectifying potassium (K^+) channel Kir4.1 is also present in DAPs, where it mediates K^+ buffering by allowing K^+ influx when extracellular levels are high. Astrocytes have low membrane resistance (R_m, ≈ 5 MΩ) and hyperpolarized membrane potentials (V_m) (≈ -80 mV), near the K^+ reversal potential, thanks to their expression of a cadre of K^+ channels. This has led to the assumption that astrocytes are electrically passive and undergo only very small changes in V_m. Whole cell recordings from astrocyte soma show that astrocyte V_m changes by only a few mVs during neuronal activity and returns to baseline over the course of seconds. Because of low astrocyte R_m and DAP morphological complexity, there is minimal spatial propagation of depolarization in astrocytes. Therefore, measurements made at the soma at best represent a heavily filtered and attenuated version of changes in V_m (ΔV_m) in DAPs. Short bursts of neuronal activity rapidly and reversibly inhibit EAAT function with synapse specificity. Because EAATs are voltage-dependent, we suspected that DAP depolarization may contribute to activity-dependent EAAT inhibition. To address this possibility, we expressed genetically encoded voltage indicators in astrocytes to image astrocyte V_m. Using this approach, we report that neuronal activity induces large, rapid, focal, and pathway-specific depolarization of astrocyte DAPs. These depolarizations are mediated by elevated extracellular K^+ during presynaptic activity, with an additional contribution from EAAT-mediated currents. These depolarizations lead to voltage-dependent inhibition of EAATs which enhances synaptic NMDA currents. This represents a novel form of astrocyte-neuron communication mediated by rapid, spatially specific DAP depolarization and has important implication for understanding the role of astrocytes in shaping extracellular glutamate and K^+ dynamics.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Program #/Poster #: P156.08

Topic: B.11. Glial Mechanisms

Support: AFOSR ASTRONIR to VB
AFOSR 3DNeuroglia to VB
AFOSR AstroDyn to WL VB GPN KMO
AFOSR MURI to WL

Title: Dynamic actin waves in astrocytes sense environmental cues and cluster into hotspots of activity

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Abstract: Astrocytes are recognized as the brain cells that maintain homeostasis and, more recently, as modulators of synaptic transmission. *In vivo* studies have shown that astroglial homeostatic regulation and synaptic modulation occur mainly at the endfeet of astrocytes, in so called “microdomains”. While the effects of transmembrane flux of ions and water molecules on these processes have been deeply investigated, the role of cytoskeleton dynamics has not been explored. Here, we investigate the dynamic function of actin in live astrocytes in response to chemophysical changes to the extracellular environment. To this end, we use confocal microscopy to capture actin dynamics in live primary neocortical rat astrocytes that have been transduced with actin-GFP. We perturb the cells chemically by changing the imaging media from a standard external solution (the control) to a “triggering” solution - either an isotonic high potassium solution (“high K+”; [K+] = 40 mM) or a hypotonic solution (“hypotonic”; ΔOsm = 60 mOsm). We also culture astrocytes on two different surfaces: poly-D-lysine- (PDL-) coated glass as a control or on hydrotalcite nanoparticle films (HTlc), the latter of which is a validated, biocompatible nanotopography that causes astrocytes to differentiate and become more *in vivo* like in morphology and function. We employ an optical flow analysis method to analyze how actin dynamics change after chemical perturbation and how the characteristics of actin dynamics are altered in distinct mechanical environments, specifically investigating the magnitude, probability, and persistence of dynamics. We also identify small regions of especially high activity, which we call “hotspots”. Chemical perturbations (both high K+ and hypotonic) strengthen actin dynamics compare to paired controls, and high K+ causes more dynamics near the boundary of the cell compared to paired controls. Of note, when analyzing actin dynamics within “hotspot” regions, we find that the relative strength of actin dynamics within hotspots compared to the whole cell increases for the high K+ condition but not for the hypotonic condition. We also compare actin dynamics in undifferentiated astrocytes grown on PDL to differentiated astrocytes grown on HTlc substrates, finding that PDL cells display stronger actin dynamics but that HTlc cells display more frequent actin dynamics. Taken together, our results suggest that actin dynamics are a local manifestation of the cellular homeostatic response to chemical and physical changes in the extracellular microenvironment.
* O'Neill & Saracino co-first; # Benfenati & Losert co-corresponding.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P156.09

Topic: B.11. Glial Mechanisms

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Title: A large portion of the astrocyte proteome is dedicated to the perivascular endfeet, including critical components of the electron transport chain

Authors: *B. SHIM[1], J. A. STOKUM[1], W. HUANG[2], M. KANE[2], J. A. SMITH[1], V. GERZANICH[1], J. SIMARD[3];
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Abstract: Perivascular astrocyte endfeet are specialized, diffusion-limited subcellular compartment that completely envelop the cerebral vasculature. Despite significant efforts to characterizing the structural aspects of the astrocyte endfeet, a clear understanding of the endfoot physiology remains elusive, in part due to the limited studies on the endfoot proteome which may be distinct to the proteome of the greater astrocyte body. To address this, we developed a novel technique to isolate the perivascular endfeet from brain tissue, which we further utilized to identify and compare the proteomes of the endfoot and somata. In our protocol, we isolated the astrocyte endfeet by dissociating these processes from freshly isolated brain microvessels, which have previously been reported to retain the endfeet. The endfeet were further purified using the ACSA-2-based sorting procedure, a method previously reported to isolate ultrapure astrocyte somata from the adult rodent brain. Results from the proteomics study expand the previously known set of proteins enriched at the endfeet from 10 to 516, which comprised more than 1/5th of the entire astrocyte proteome. Importantly, a number of critical electron transport chain proteins was identified to be exclusive to the endfeet while enzymes involved in glycogen storage were localized to the somata, thus suggesting compartmentalization of subcellular metabolic functions. Furthermore, the endfoot proteome also revealed a number of proteins that were previously understood to contribute to maintaining the blood-brain barrier but not known to localize to the endfeet. Our findings in this study identify a number of key astrocyte endfoot-specific proteins, which may extend to a better understanding of the physiological and/or pathophysiological role of the endfeet.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

Location: Virtual Only

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Program #/Poster #: P156.10

Topic: B.11. Glial Mechanisms

Title: Astrocytic nanostructure and organization in the brain

Authors: *C. K. SALMON[1], J. B. KACEROVSKY[1], T. SYED[2], N. ALIVODEJ[1], M. P. PRATTE[1], A. L. SCHOBER[1], M. ROSEN[1], M. GREEN[1], A. CHIRGWIN-DASGUPTA[1], H. VALI[3], C. A. MANDATO[4], K. SIDDIQI[2], K. K. MURAI[1];
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Abstract: Astrocytes have many essential roles in brain function. Underpinning these roles is an elaborate cellular architecture based on frequent, extremely fine, but seemingly haphazard branches, as well as prominent features including tripartite synaptic complexes and perivascular endfeet. How these astrocytic structures combine to form a unified cellular architecture that supports their complex functions in the CNS is unclear. This is largely due to a dearth of high quality, high resolution datasets that reveal these nanoscopic structures, and robust computational approaches that effectively interrogate astrocyte morphology and organization. Here, we produced and analyzed three, high-resolution datasets using focused ion beam serial electron microscopy and computer vision approaches to provide a principled, quantitative analysis of astrocytic ultrastructure. Analysis of changes in process thickness and surface curvature across the astrocytic volumes allowed for the decomposition of the astrocytes into fundamental 'parts.' Network analysis of these connected parts demonstrates the existence of centralized, but infrequent hubs that give rise to many simple branches, as well as large loops in the structure of astrocytes. Interestingly, tripartite synapses were not distributed evenly across these parts. We also directly measured distances through the convoluted astrocytic volumes using fast marching wavefront propagation. This allowed us to define spatial relationships between tripartite synapses, the astrocyte surface, and astrocytic mitochondria. Using these relationships, we found that astrocytes partition the surrounding synaptic population into clusters that are distinct from synaptic clusters defined simply by direct synapse-synapse spatial relationships. Furthermore, astrocytic mitochondria appear to be positioned preferentially closer to specific synaptic clusters, but not to specific classes of synapses. This study reveals that astrocytes have complex anatomical adaptations and provides deployable computational resources to systematically and quantitatively resolve astrocyte nanostructure and architecture in the CNS.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

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Title: Storm super-resolution imaging of molecules in the fine processes of mouse hippocampal astrocytes

Authors: *M. ZÖLDI[1], K. KENESEI[2], Z. LÁSZLÓ[2], I. KATONA[1];
[1]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [2]Inst. of Exptl. Medicine, HAS, Budapest, Hungary

Abstract: Astrocytes are now recognized as key players in shaping synaptic signaling between neurons. However, our understanding of how the expression and distribution of astrocytic molecules exert their regulatory control over synapses is still limited owing to the difficulties to localize them inside astrocytes. As the thin astrocytic processes are beyond the diffraction limit and many of the astrocytic proteins are expressed in low copy numbers, the traditionally used confocal and electron microscopic techniques suffering from low resolution and low labeling density, respectively, can not be used to tackle the above questions. As a potential alternative approach, STochastic Optical Reconstruction Microscopy (STORM), a recently developed fluorescence-based super-resolution imaging method, could bridge the gap between resolution and labeling density. The simultaneous visualization of astrocytic plasma membranes along with a target protein in their native tissue context in a way compatible with STORM imaging, however, is still a very difficult task. Therefore, we aimed to develop and present a labeling, imaging and analysis pipeline with which we can better study the nanoscale arrangement of astrocytic molecules and fine processes in relation to synapses. To sparsely label hippocampal astrocytes, we electroporated newborn mouse pups at postnatal age P0-P01 with a plasmid expressing the fluorescent protein mCherry fused to Channelrhodopsin-2 (ChR2). We show that ChR2-mCherry incorporates into the plasma membrane of single electroporated hippocampal astrocytes, and STORM imaging visualizes the intricate spongiform morphology of fine astrocytic processes well below the diffraction limit. Dual-color STORM imaging revealed that our approach has the sufficient resolution to localize astrocytic proteins inside processes and to discriminate them from neighboring synaptic structures. We present important controls to assess the channel crosstalk and chromatic aberration arising in dual-color super-resolution images, and provide analysis methods using tessellation and nearest neighbor distance measurements to validate the astrocytic presence of selected proteins. By combining STORM imaging with confocal microscopy, we also show how astrocytic processes contact the different hippocampal synapse types in non-dehydrated tissue

samples. Our data highlight the importance of studying the nanoscale arrangement of astrocytic proteins and fine processes in their native tissue context.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Program #/Poster #: P156.12

Topic: B.11. Glial Mechanisms

Support: Carleton University Discovery Grant
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Title: Translatomic database of cortical astroglia across mouse postnatal development reveals sex differences in developmental patterns

Authors: *G. RURAK[1], S. SIMARD[2], M. FREITAS-ANDRADE[5], B. LACOSTE[6], F. CHARIH[3], A. VAN GEEL[4], J. STEAD[4], B. WOODSIDE[7], J. R. GREEN[3], G. COPPOLA[8], N. SALMASO[2]; [2]Neurosci., [3]Systems and Computer Engin., [4]Dept. of Neurosci., [1]Carleton Univ., Ottawa, ON, Canada; [5]Cell. & Mol. Sci., Univ. of Ottawa, Ottawa, ON, Canada; [6]Neurosci. Program, The Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [7]Concordia Univ., Montreal, QC, Canada; [8]Child Study Ctr., Yale Univ., New Haven, CT

Abstract: Astroglial cells are emerging as key players in the development and homeostatic maintenance of neurons and neuronal networks. Astroglial cell functions are critical to neuronal migration and maturation, myelination, and synapse dynamics, however little is known about astroglial phenotypic changes over development. Furthermore, astroglial cells express steroid hormone receptors and show rapid responses to hormonal manipulations, however, despite important sex differences in telencephalic regions such as the cortex and hippocampus, few studies have examined sex differences in astroglial cells in telencephalic development. To phenotype cortical astroglial cells across postnatal development while considering potential sex differences, we used translating ribosome affinity purification together with RNA sequencing (TRAPseq) and immunohistochemistry to phenotype the entire astroglial translatome in males and females at key developmental time points: P1, P4, P7, P14, P35 and in adulthood. Overall, we found two distinct astroglial phenotypes between early (P1-P7) and late development (P14-Adult), independent of sex. The astroglial translatome also showed significant sex differences in gene expression patterns over development, with peak sex differences observed at P7. At least part of the sex differences observed at P7 appear to be due to males reaching a more mature astroglial phenotype earlier than females. Together, these data clearly delineate and phenotype astroglia across development and identify sex differences in astroglial developmental programs. Importantly, these developmental sex differences could have an impact on the construction and maintenance of neuronal networks and potential developmental windows of vulnerability to neurologic and psychiatric disease.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: NIH Grant F31 AG067632
NIH grant T32 GM007445

Title: Mechanism and function of microvesicle release by GDE3

Authors: *R. LEVY-MYERS, S. SOCKANATHAN;
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Abstract: Neuron-glia communication is critical for proper brain function. Specifically, astrocytes are known to regulate aspects of neuronal health, synaptic function, and disease progression. Extracellular vesicles (EVs) comprise one pathway that astrocytes communicate with neurons. EVs are small (100-500nm) vesicles that are released and received by all cells. EVs contain protein and nucleic acid cargo that can exert large effects on recipient cells. GDE3 (Glycerophosphodiester Phosphodiesterase 3 or GDPD2) is a 6-transmembrane protein expressed on the plasma membrane of astrocytes but not neurons. Mice lacking GDE3 (Gde3-KO) exhibit signs of neurodegeneration suggesting that GDE3 regulates a non-cell autonomous function of astrocytes. We found that GDE3 is necessary and sufficient to release a subclass of EVs called Microvesicles (MVs) from the plasma membrane of astrocytes. We hypothesize that GDE3 promotes the release of specialized MVs from astrocytes that are necessary for neuronal health and survival. To investigate this possibility, we have performed unbiased screens to define the mechanism of GDE3 MV release and to identify cargos of MVs released by GDE3 from astrocytes. Here we investigate the model that GDE3 reorganizes the actin cytoskeleton network via the WAVE Regulatory Complex (WRC) to release MVs and that these MVs are required for neuronal survival and function. This work has potential to identify a novel modifier of MV release from astrocytes and define new subtypes of MVs that play critical roles in regulating neuronal health and function.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: T32 NIH Neuroscience Training Grant

Title: The critical role of ARL13B in mechanisms of astrocyte development

Authors: *R. BEAR, T. CASPARY;
Human Genet., Emory Univ., Atlanta, GA

Abstract: Astrocytes are the most abundant glial cell in the brain and are essential for neuron function and neural circuit formation. Astrocytes have an indispensable role in the developing brain, yet our understanding of the mechanisms that allow astrocytes to develop remains behind our growing knowledge of astrocyte function. Several neurodevelopmental disorders that result in intellectual disability are attributed to astrocyte dysfunction during development, highlighting the importance to resolve mechanisms that regulate astrocyte development. Astrocytes contain a critical signaling appendage, the primary cilium, a crucial regulator of neuronal development but overlooked in astrocytes. ADP-ribosylation factor-like protein 13B (ARL13B) encodes a regulatory GTPase enriched in cilia that controls many neurodevelopmental processes, including neuron specification, migration, and axon guidance. Recessive mutations in *ARL13B* result in the ciliopathy, Joubert Syndrome, a disorder characterized by several neurological phenotypes including intellectual disability. Joubert Syndrome motivates studying the relationship between ciliary signaling and astrocytes because they converge in the pathogenesis of neurodevelopmental disorders. The goal of my research is to determine the role of ARL13B in regulating signaling pathways underlying astrocyte differentiation and proliferation. Here, I employ genetic mouse models to specifically and temporally manipulate ARL13B expression and function in developing astrocytes *in vivo*. I show that astrocytes lacking ARL13B have altered rates of proliferation and changed timing in astrocyte stage-specific gene expression. These results indicate a key role for ARL13B during astrocyte development. This work informs a novel relationship of ARL13B and cilia to mechanisms of astrocyte development and reveals previously enigmatic functions of astrocyte primary cilia.

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Poster

P156. Astrocytes: Cellular and Molecular Mechanisms

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Program #/Poster #: P156.15

Topic: B.11. Glial Mechanisms

Title: Dark neurons of the rat sensorimotor cortex and changes in neuroglyal relationships after short time occlusion of the common carotid arteries

Authors: A. GORBUNOVA, S. STEPANOV, D. AVDEEV, A. SHORONOVA, L. MAKARYEVA, M. KORZHUK, ***V. AKULININ**;
Omsk State Med. Univ., Omsk, Russian Federation

Abstract: To study the processes of the hydropic dystrophy and gliocytoarchitectonics reorganization during formation of "dark neurons" within the sensorimotor cortex (SMC) in rats after the occlusion of the common carotid arteries. Acute ischemia was modeled on mature Wistar rats via 20- and 40- min occlusion of the common carotid arteries (OCCA). Nissl, hematoxylin-eosin staining, immunohistochemical typing have been used to perform comparative morphometric evaluation of the cyto- and glyocyto- architectonics of the neocortex 1, 3, 7 days after OCCA. Relative area of the edema/swelling zones and numerical density of the normal and hyperchromic (dark) pyramidal neurons, oligodendrocytes (ODC) and microgliocytes (MGC) were determined. The chosen method of the brain fixation significantly affects observed amount of the artifact dark neurons (ADN), which are similar in morphology and tinctorial properties to the degeneratively altered dark neurons (DDN). The appearance of reversibly and irreversibly altered DTN after OCCA in the SMC was accompanied by an increase in the relative area of edema-swelling zones (from 5.4% in the control to 17.6%). The maximum content of DDN (53%) was detected in layer V on the 7 day after ischemia. According to immunohistochemical typing data of NSE, MAP-2, HSP-70, p38, and CASP3, majority of the proteins specific for the DDNs were preserved, ensuring neuron recovery. The total numerical density of SMC neurons in the layer III decreased by 26.4% after 7 days, and in layer V - by 18.5%. The revealed changes were diffuse-focal in nature. The content of astrocytes, MGC and ODC increased in the areas of DDN accumulation. The neuro-astroglial index increased to 2.72 on the 3 day after the OCCA, compared to the control - 1.62. The peak in the MGC density was observed one day, and in the ODC density - 7 days after the acute incomplete ischemia. When compared to 20 min OCCA, 40 min ischemia caused increase in number and density of the dark neurons in the SMC, and, as a consequence, signs of the hydropic dystrophy. On that background, we also observed increase in the number of ODC, astrocytes, and MGC. It is likely that edema/swelling, and active MGCs and astrocytes sanitize neural tissue during first 1-3 days after ischemia, thus, providing for the future (7 days after) structural and functional recovery with the participation of the ODC.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

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Program #/Poster #: P237.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG059195
AG057768
AG056901

Title: Perinatal choline supplementation ameliorates some of the cognitive defects in the APP^{NL-G-F} mouse model of Alzheimer’s disease

Authors: T. J. MELLOTT[1], J. Y. LAGUNA-TORRES[1], T. A. BELLIO[1], S. YEE[1], M. S. CAMPION[1], J. H. CHOU[2], A. GAONA[1], H. K. JAMIESON[1], *J. K. BLUSZTAJN[1];
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Abstract: Previous studies demonstrated that high intake of the essential nutrient, choline, during gestation, ameliorates hippocampal amyloidosis, reduces gliosis, prevents cholinergic defects and increases hippocampal neurogenesis in hemizygous APPswe/PS1dE9 (APP.PS1) Alzheimer's disease (AD) model mice. Here, we investigated the effects of a similar treatment on behavioral phenotypes in the APP^{NL-G-F} mouse model for AD. These mice express a humanized APP with three mutations that cause familial AD in humans [Swedish (NL), Arctic (G), and Beyreuther/Iberian (F)] under the control of the endogenous mouse APP promotor. The latter permits to overcome problems related to the overexpression of APP observed in the transgenic mouse models for AD (e.g. APP.PS1) and is therefore considered a more physiologically relevant model well suited for studies of the pathophysiology of this disease. We maintained the pregnant and lactating wild type C57BL/6J control mice and homozygous APP^{NL-G-F} mice on a control AIN76A diet containing 1.1 g/kg of choline or a choline-supplemented (5 g/kg) diet. After weaning all offspring consumed the control diet. Mice were examined in a cross-sectional fashion at 3, 6, 9 and 12 months of age using the open field, elevated plus maze, Barnes maze and contextual fear conditioning experimental paradigms. As compared to controls, the APP^{NL-G-F} mice exhibited abnormalities in anxiety-related behaviors at 3 and 6 months of age and learning and memory deficits at 9 and 12 months of age. Perinatal choline supplementation ameliorated some of the memory deficits in the 12-month old APP^{NL-G-F} mice observed in the contextual fear conditioning test. The data suggest that dietary supplementation with choline during fetal development and early postnatal life prevents some of the behavioral abnormalities in the APP^{NL-G-F} AD model mice.

Disclosures: T.J. Mellott: None. **J.Y. Laguna-Torres:** None. **T.A. Bellio:** None. **S. Yee:** None. **M.S. Campion:** None. **J.H. Chou:** None. **A. Gaona:** None. **H.K. Jamieson:** None. **J.K. Blusztajn:** None.

Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

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Program #/Poster #: P237.02

Topic:

Support: AG059195
AG057758
AG056901

Title: Deficiency of brain-derived insulin-like growth factor 2 (IGF2) promotes seizures and exacerbates cognitive defects in a mouse model of Alzheimer's disease (AD): effects of perinatal choline supplementation

Authors: T. A. BELLIO, S. C. YEE, T. JAYASINGHE, V. CHINTHAREDDY, M. CAMPION, H. JAMIESON, S. DEVARAJ, J. K. BLUSZTAJN, *T. J. MELLOTT;
Pathology & Labortory Med., Boston Univ. Sch. of Med., Boston, MA

Abstract: High intake of the essential nutrient, choline, during early life increases brain expression of the growth factor IGF2 and protects Alzheimer's disease model mice from several features of AD-like pathology. The goals of our study are to understand if IGF2 may mediate the beneficial effects of perinatal choline supplementation and to examine the effects of reducing brain-derived levels of IGF2 in AD model mice. We generated wild-type and APPswe/PS1dE9 (APP.PS1) mice with a forebrain-specific *Igf2*$^{fl/fl}$ genotype by crossing mice carrying a tamoxifen-inducible *Camk2a*-promoter-driven Cre recombinase (CAMK2a-ERT2) with transgenic mice with the floxed *Igf2* gene. The pregnant and nursing mothers of these progeny consumed a control- or a choline-supplemented diet, and all offspring consumed a control diet after weaning. The forebrain-specific deletion of the *Igf2* gene was induced on postnatal day 60 with 5 consecutive days of i.p. injections of tamoxifen. At 6 months of age, there was a noticeable reduction (approximately 58-67%) in the levels of IGF2 protein in the hippocampus and cortex in mice with CAMK2a-CreERT2. There were no changes in the IGF2 levels within the liver of these mice suggesting that induction with tamoxifen specifically reduced forebrain-derived IGF2. It is possible that the remaining 40% of IGF2 protein expression in the brain tissues is the result of circulating IGF2 or glial-derived IGF2 rather than neuronal-derived production. As these tamoxifen-induced mice aged, we observed an increased mortality rate within APP.PS1 mice with CAMK2a-CreERT2 in both sexes, which may indicate increased vulnerability to AD in IGF2-deficient mice. Animal subjects were behaviorally tested at 6, 9 and 12 months of age. At 12-months of age, all APP.PS1 mice exhibited a deficit during the acquisition training in the Barnes maze compared to all non-AD model mice, with APP.PS1/CAMK2a-CreERT2 mice being the most impaired during the training. Interestingly, 1-day probe testing in the Barnes maze revealed significantly impaired memory recall in APP.PS1/CAMK2a-CreERT2 mice compared to their IGF2-intact APP.PS1 counterparts. In addition, APP.PS1/ CAMK2a-CreERT2 mice were more prone to seizures during behavioral testing. These results show that long-term reduction of brain-derived IGF2 can be tolerated in non-AD mice but can further impair cognitive function in APP.PS1 mice. This suggests increased vulnerability to AD pathophysiology in these mice and supports the notion of beneficial role of brain-derived IGF2 in later stages of AD progression.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

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Program #/Poster #: P237.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Lisa Dean Moseley Foundation-2019

Title: Nanotechnology-driven non-viral neurogenic and vasculogenic reprogramming of fibroblast: potential applications in the treatment of Alzheimer's Disease

Authors: *D. ALZATE-CORREA[1], W. R. LAWRENCE[2], M. A. RINCON BENAVIDES[1], L. DIAZ-STAROKOZHEVA[1], J. FITZGERALD[3], J. STRANAN[1], A. TRAN[1], A. VALENTINE[1], O. KOKIKO-COCHRAN[3], N. HIGUITA-CASTRO[1,4], D. GALLEGO-PEREZ[1,4];
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Abstract: Alzheimer's Disease (AD) is characterized by a progressive cognitive decline, loss of synaptic connections and neurons, and the formation of amyloid plaques and neurofibrillary tangles lesions. In addition, numerous studies suggest a strong correlation between a reduced Cerebral Blood Flow (CBF) and Blood-Brain-Barrier (BBB) dysfunction with the development of AD. These cerebrovascular alterations precede the formation of amyloid plaques, tangles, and the onset of cognitive decline, suggesting that impaired cerebrovascular function plays a key role in the onset and/or progression of AD neuropathology. Pro-neuronal cell-based therapies have emerged as a promising alternative strategy for the repair or replacement of deteriorating neurons and neuronal networks in AD, whereas pro-vasculogenic cell-based therapies have also been used to address vascular deficiencies in the brain. However, cell-based therapies face numerous limitations. In many cases, progenitor or stem cell sources are insufficient, difficult to isolate, or pose major risks in terms of uncontrolled differentiation, tumorigenesis, genetic abnormalities, and immunogenicity. To implement safe and efficient cell therapies in AD, here we show a non-viral, nanotransfection-driven strategy to deliver pro-neurogenic and pro-vasculogenic factors to reprogram fibroblasts into therapeutic neurons and endothelial cells to treat females from the triple transgenic murine model of AD (3xTg-AD). In our experimental design, we performed a single intra-hippocampal injection of fibroblast pre-programmed to convert into neurons; or three intra-cerebroventricular injections of fibroblast pre-programmed to convert into endothelial cells. Fibroblasts with no pre-programming were used as control. Our preliminary results indicate that fibroblasts pre-programmed into neurons can survive and express markers of mature neurons inside the brain parenchyma after at least 6 weeks post-injection. Also, assessment of spatial learning and memory with the Barnes Maze significant improvement in long-term memory capacity and reduced aggregation of amyloid-beta peptides. On the other hand, fibroblasts pre-programmed into endothelial cells were detected 5 weeks after the last injection, and analysis of spatial memory with the Barnes Maze shows that the deficits presented by the 3xTg-AD mice were mitigated by the pre-programmed fibroblast. Together, our results indicate that the development of nanotransfection-based cell therapies by direct reprogramming is a promising therapy for AD that could overcome many of the limitations of current cell therapies.

Disclosures: D. Alzate-Correa: None. **W.R. Lawrence:** None. **M.A. Rincon Benavides:** None. **L. Diaz-Starokozheva:** None. **J. Fitzgerald:** None. **J. Stranan:** None. **A. Tran:** None. **A. Valentine:** None. **O. Kokiko-Cochran:** None. **N. Higuita-Castro:** None. **D. Gallego-Perez:** None.

Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P237.04

Topic:

Support: Usher 1F collaborative

Title: Role of PCDH15 in the neurosensory retina & retinal pigment epithelium along with exogenous retinoid delivery to rescue the dysfunctional photoreceptors activity in a novel preclinical mouse model.

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Abstract: Abstract Purpose Usher syndrome type I (USH1) is characterized by congenital deafness, vestibular areflexia, and progressive retinal degeneration with age. The protein-truncating p.Arg245* founder variant of *PCDH15* has ~2% carrier frequency among Ashkenazi Jews, accounting for nearly 60% of their USH1 cases. We have developed and characterized *Pcdh15*$^{R250X/R250X}$ mouse model (*Pcdh15*^{R250X}; equivalent to human p.Arg245*) to investigate the precise role of protocadherin-15 in the neurosensory retina and RPE including, light transduction and mechanism of visual deficits and rescue of the vision by exogenous retinoid delivery. **Approach***Pcdh15*^{R250X} mice were generated using CRISPR/Cas9 technology. Retinal function was assessed using electroretinography (ERG), while structure integrity was assessed via optical coherence tomography (OCT). Rescue strategies for visual deficits included exogenous retinoids delivery via intraperitoneal injections. **Results**Our results showed that deficiency of *Pcdh15* causes early visual deficits, as evaluated by ERG, similar to USHIF patients. The neurosensory retina is a light-sensitive tissue lining the inner surface of the eye. ERG showed attenuated a- and b-wave amplitudes suggesting dysfunctional photoreceptors, while histology and OCT showed no gross retinal degeneration at early ages. At the molecular level, we found light-dependent mislocalization of arrestin and transducin, key dark cycle proteins, in mutant mice. We also found reduced levels of RPE-specific visual retinoid cycle proteins, RPE65 and CRALBP, and reduced levels of retinoid chromophores. Next we assessed exogenous retinoid delivery to rescue the visual deficits. First, a single intraperitoneal injection of exogenous 9-*cis* retinal, an analog of the naturally occurring 11-*cis* retinal improved ERG amplitudes in mutant mice suggesting improvements in the photoreceptor functional activity which are important part of neural retina. Single injection of 9-*cis* retinal was effective for one week at younger (2-3 months) and older ages (6-7 months) of mice.**Conclusions**Our results showed *Pcdh15*^{KI} mutants recapitulates human p.Arg245* visual deficit phenotype. Functional evaluation revealed a dual role for protocadherin-15 in photoreceptors and RPE. Our current findings support a role for visual retinoid cycle dysfunction in *Pcdh15*^{R250X} mutant mice suggesting a basis for a clinical trial of exogenous FDA approved retinoids to preserve vision in USH1F patients.

Disclosures: S. Riaz: None. **S. Sethna:** None. **T. Duncan:** None. **M. Redmond:** None. **S. Riazuddin:** None. **Z. Ahmed:** None.

Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P237.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Key R&D Program of China (2018YFE0203600)
Guangdong Provincial Key S&T Program (2018B030336001)
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Hong Kong Research Grants Council Theme-based Research Scheme (T13-605/18-W)
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Innovation and Technology Commission (ITCPD/17-9), the Lee Hysan Foundation (LHF17SC01)
Shenzhen Knowledge Innovation Program (JCYJ20180507183642005, and JCYJ20200109115631248)

Title: Aav-mediated brain-wide genome editing alleviates amyloid-associated pathologies in familial alzheimer's disease mouse models

Authors: *Y. DUAN[1,2], T. YE[1,2,3,4], Z. QU[5], Y. CHEN[1,3,4], A. MIRANDA[1], X. ZHOU[1,2], K.-C. LOK[1,2], Y. CHEN[4,1,2,3], A. K. Y. FU[1,2,3], V. GRADINARU[5], N. Y. IP[1,2,3];
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Abstract: Familial Alzheimer's disease is caused by dominant mutations in the genes that encode amyloid precursor protein, presenilin 1, and presenilin 2, which affect multiple brain regions. Although targeting mutations using CRISPR/Cas9-mediated genome editing is a promising disease-modifying treatment strategy, brain-wide amelioration of Alzheimer's disease phenotypes using this approach has not been demonstrated. Here, we show that CRISPR/Cas9-mediated genome editing by intravenous administration of a modified adeno-associated virus (AAV) that can cross the blood-brain barrier efficiently disrupts mutated *APP* in various brain regions of the transgenic mouse models that carry the human *APP* Swedish mutation. Systemic delivery of the modified AAV-Cas9 virus decreases amyloid plaque deposition throughout the brain. In addition, this single-dose administration of the modified AAV-Cas9 virus globally alleviates AD-associated pathologies including microgliosis and neurite dystrophy. Moreover, systemic delivery of AAV-Cas9 virus ameliorates the cognitive impairment of the AD transgenic mice, resulting in improved habituation ability, working memory, and risk-taking behavior. Thus, our work on brain-wide gene editing provides a novel approach toward developing a noninvasive, single-administration, disease-modifying treatment for familial Alzheimer's disease and other monogenic diseases that affect multiple brain regions.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P237.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA/NIH 5R01AG06943302

Title: Nano-pulsed laser therapy-treated hippocampal neural stem cells differentiate into neurons resistant to amyloid beta oligomer toxicity

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Abstract: Objective Synaptic and mitochondrial dysfunction driven by toxic amyloid oligomers (Aβo and Tauo) are early events leading to cognitive decline in Alzheimer's disease (AD). Transcranial treatment of adult WT mice with near-infrared light (NIL) decreases synaptic vulnerability to Aβo and preserves mitochondrial function after Aβo treatment. Nano-pulsed laser therapy (NPLT) combines photobiomodulatory effects of NIL with optoacoustic ultrasound waves to deliver two therapeutic components with greater penetration than static NIL therapy. We have previously shown that preserved hippocampal neurogenesis correlates with synaptic and cognitive resilience in non-demented individuals with AD neuropathology. Here we sought to determine whether adult rat hippocampal stem cells (NSCs) treated with NPLT differentiate into neurons with decreased synaptic and mitochondrial vulnerability to Aβo toxicity. **Methods** Adult rat hippocampal NSCs were exposed for five minutes to NPLT or sham treatment and allowed five days to differentiate into mature neurons (MN). For analysis of Aβo binding, MNs were incubated with 2.5μM Fluor-647-labeled Aβo for 30 minutes at 37ºC and immunostained for βIII-tubulin (a neuronal marker). Aβo puncta on neurites were quantified using ImageJ. For analysis of mitochondrial membrane polarization, Aβo-treated MNs were incubated with the mitochondrial membrane potential-dependent dye, MitoTracker Deep Red (MTDR) and potential-independent MitoTracker Green (MTG). Flow cytometric analyses of MTDR and MTG was conducted 30 minutes post-Aβo treatment. Mitochondrial respiration was evaluated using Seahorse XF analyzer. **Results** NPLT induced a significant enhancement of major mitochondrial bioenergetic parameters in NSC (ATP production, maximal respiration, and spare capacity). MNs generated from NPLT-treated NSCs showed significantly fewer Aβo puncta per neurite compared to MNs from sham-treated NSCs ($p=0.0049$), and lower percentage of total neurites with bound Aβo ($p<0.0001$). We also found that Aβo treatment induced a significant reduction in total mitochondria and mitochondrial membrane potential in MNs from sham-treated NSCs but not in MNs from NPLT-treated NSCs. **Conclusions** Here we show that adult rat hippocampal NSCs treated with NPLT display enhanced mitochondrial function and generate neurons resistant to Aβo binding and to Aβ-induced mitochondrial dysfunction. These data suggest that NPLT, approved for use in humans for unrelated clinical applications, could be a valuable therapeutic tool for inducing cognitive resilience to AD neuropathology.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

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Program #/Poster #: P237.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA R01AG069433
R01AG060718
R56063405

Title: Near-infrared light reduces glia activation and modulates neuroinflammation in the brain of diet-induced obese mice

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Abstract: Obesity is one of the most prominent risk factors for Alzheimer's Disease (AD); obesity and AD share several pathological features, notably neuroinflammation. Hippocampal neuroinflammation, in rodents, correlates with poor memory performance, while in humans, growing evidence shows that obesity increases three times the risk of developing AD. The overall objective of this work is to reduce the impact of obesity on neuroinflammation, with the long-term goal of reducing the risk of later dementia. Recently, near-infrared (NIR) light has been proposed as potential treatment for cognitive deficits, showing improvement of learning and memory in both humans and animal models. Previous work demonstrated that a transcranial delivery of NIR light reduced Aβ and Tau pathology and improved memory function in mouse models of AD. Here, it was tested whether NIR light may prevent obesity-induced neuroinflammation, in a diet-induced obese mouse model. After 13 weeks of high-fat diet (HFD), the mice received the NIR light treatments for 4 weeks in single daily sessions of 90 seconds each. Using fluorescence immunostaining to evaluate glial activation we found that in both hippocampus and parietal/occipital cortex, HFD caused increased expression of CD68 (activated microglia) and GFAP (astrocytic marker), whereas NIR light reversed this increase. On the other hand, we found no change in frontal cortex either due to HFD or NIR light. Furthermore, using quantitative real-time PCR analyses we evaluated the effects of NIR light on cytokines mRNA levels in hippocampus and frontal cortex and found that in the hippocampus, HFD caused an increase of pro-inflammatory IL-1β and TNF-α, as well as of the anti-inflammatory IL-10, which were brought back to basal levels by NIR light treatment. Also, BDNF mRNA was upregulated in HFD mice treated with NIR light, compared to HFD not-treated mice, thus suggesting that the NIR light triggers neuroprotective mechanisms contributing to reduced neuroinflammation. Collectively, this data suggests that obesity-induced neuroinflammation may be reduced by NIR light and that this is a reversible process that may be targeted to prevent neurodegeneration. These results thus support the notion of NIR light as a potential preventative, non-invasive therapeutic approach against obesity-induced CNS deficits that are known to concur to AD neuropathological cascade.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

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Program #/Poster #: P237.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 MH 087463
NIH K99 AG 068306
Gary & LaDonna Wicklund Research Fund for Cognitive Memory Disorders
Roy J. Carver Charitable Trust

Title: Endoplasmic Reticulum Chaperone Genes Encode Effectors of Long-Term Memory

Authors: *S. CHATTERJEE[1], E. BAHL[1], U. MUKHERJEE[2], E. WALSH[3], M. S. SHETTY[4], A. YAN[1], Y. VANROBAEYS[1], J. LEDERMAN[1], K. P. GIESE[5], J. MICHAELSON[1], T. ABEL[4];
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Abstract: Hippocampus-dependent memory loss is a key symptom of neurodegenerative diseases such as Alzheimer’s disease and related dementias (ADRD). Because the mechanisms underlying memory loss associated with ADRD remain unclear, no effective treatments exist. Fundamental studies have shown that a set of transcriptional regulatory proteins of the nuclear receptor 4a (Nr4a) family serve as critical molecular switches for long-term memory in the hippocampus. Here, we show that Nr4a proteins regulate the transcription of a group of genes encoding chaperones that localize predominantly to the endoplasmic reticulum (ER). Nr4a-driven expression of these chaperones is critical for the trafficking of plasticity-related proteins to the cell surface, as well as for long-lasting forms of synaptic plasticity and long-term memory. Analysis of human ADRD data revealed that pathological progression correlates with downregulation of Nr4a transcription factors in the hippocampus. Further, in a tau-based mouse model of ADRD-associated neurodegeneration, hippocampal levels of both the Nr4a family members and the ER chaperone effector genes were shown to be reduced. Importantly, overexpressing Nr4a1 or ER chaperone Hspa5 ameliorated the long-term memory deficits in this mouse model. Thus, our findings identify ER chaperones and the protein folding pathways that they regulate as key effectors of memory consolidation. This essential molecular switch to long-term memory appears impaired in ADRD, pointing towards novel therapeutic approaches for treating memory loss in these neurodegenerative diseases.

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Poster

P237. Therapeutic Strategies: Preclinical Animal Models and Non-Pharmacological Therapeutic Approaches II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P237.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG068215
seed funds UK Department of Neuroscience

Title: Thermoneutral temperature exposure increases slow-wave sleep in the 3xTg-AD mouse model of Alzheimer's Disease

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Abstract: There is growing evidence that disordered sleep, which is known to be associated with Alzheimer's disease (AD), may accelerate neuropathology, thus promoting a vicious cycle. Strategies for improving sleep quality may slow disease progression. Here we investigate the feasibility of sleep enhancement through ambient temperature regulation and examine the effect on amyloid- pathology. Female 3xTg-AD mice (~12 m.o.) were instrumented for EEG/EMG monitoring. After a week-long baseline, one half of the mice (n=9, EXPT; one animal did not survive for analysis) were exposed to stepwise diurnal increases in ambient temperature (Ta) to reach 30ºC (thermoneutral for mice) during the light phase while the rest (n=8, CTRL) remained at room temperature (22ºC). Vigilance state - i.e., Wake, REM, NREM, and slow wave sleep (SWS) within NREM - was scored in 4-second epochs and sleep metrics computed. SWS and REM were significantly greater ($p<0.05$) in the light phase for EXPT mice. These effects suggest better sleep consolidation and greater sleep depth with thermoneutral warming. After four weeks of treatment, the animals were euthanized, and the brains removed to assay amyloid pathology by ELISA. We found that thermoneutral warming caused a significant reduction in both Aβ40 and Aβ42 in the hippocampus, but not in the cortex. These data imply that thermoneutral warming might have some regional specificity in its effects, the effects appear to be specific to some brain areas more than others, with implications for the cognitive and neuropathologic changes found in AD. Furthermore, since SWS and REM support memory, future studies should investigate the effects of thermoneutral enhancement of SWS and REM on cognition.

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Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P281.01

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Ataxia Foundation
Dixon translational grant

Title: Neurodevelopmental deficits as a therapeutic target for adult-onset Spinocerebellar Ataxia type 1

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Abstract: Spinocerebellar ataxia type1 (SCA1) is an adult-onset neurodegenerative movement disorder caused by a pathogenic polyglutamine expansion (CAG repeat) in the protein Ataxin-1 (ATXN1). SCA1 is a condition characterized by progressive problem with movement. People with this condition initially experience problems with coordination and balance (ataxia). Main pathological hallmark of the disease is Purkinje cell loss in cerebellum. Since ATXN1 is a transcriptional regulator it is not surprising that transcriptional misregulation appears as the initiating pathogenic event— indeed occurring as early as the first week of postnatal life. It is still unclear whether pathogenic changes occur only in Purkinje cells (PCs), the cells that are especially vulnerable in the disease, or whether other cell types contribute to pathogenesis. Given the importance of this postnatal period for cerebellar development, we asked whether this region might be developmentally altered by mutant ATXN1. We found that mutant ATXN1 — through transcriptionally upregulating the sonic hedgehog pathway—stimulates the proliferation of a relatively understudied cerebellar stem cell niche (defined by prominin-1; also, called CD133). Because these stem cells differentiate into GABAergic interneurons (basket cells and stellate cells) in molecular layer, there is an exaggerated inhibitory synapse formation with Purkinje cells. We have also confirmed the exaggerated GABAerigc interneuron connections in human SCA1 patients. This leads to significant increase in GABAergic interneuron inhibition of PCs, disrupting cerebellar Purkinje cell function in a non-cell autonomous manner. Mutant ATXN1 thus alters the neural circuitry of the developing cerebellum, setting the stage for the later vulnerability of Purkinje cells in SCA1. To interfere with the excessive GABAergic inhibition, we activated the endocannabinoid system (known to tamp down GABAergic inhibition in cerebellum by acting on presynaptic release of GABA) using endocannabinoid receptor agonist. We found that treated SCA1 mice performed significantly better on rotarod assay than untreated mice. This is the first drug that shows such a dramatic and prompt symptomatic improvement. Cannabinoid agonists are already FDA-approved for several disorders and we are optimistic that this might lead to a novel therapeutic treatment for SCA1.

Disclosures: C. Edamakanti: None. **P. Opal:** None.

Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P281.02

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Therapeutic drug search for multiple system atrophy-cerebellar type and primary progressive multiple sclerosis using novel mice model

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Abstract: Aim : Multiple system atrophy (MSA) is characterized by α-synuclein (α-syn)+ glial cytoplasmic inclusions in oligodendrocytes and demyelination. Primary progressive multiple sclerosis (PPMS) has focal lesions of demyelination due to oligodendrocyte degeneration. Both MSA and PPMS commonly show oligodendrogliopathy, demyelination and glial inflammation. We previously developed a novel mouse model of MSA-cerebellar type (MSA-C) and PPMS by overexpression of mutant α-syn in oligodendrocytes in a temporarily restrictive manner using Tet-off system. We aimed to identify novel drug targets for MSA-C/PPMS using our model. Methods: We generated and analyzed TetO-α-SynA53T Tg/+; PLP-tTA Tg/+ double transgenic mice (A53Tα-syn mice), which express mutant human A53Tα-syn in oligodendrocytes starting at 8 weeks of age when doxycycline was removed from the feed. Results: A53Tα-syn mice developed progressive mono-, hemi-, and paraparesis and ataxia around 22 weeks, culminating in death around 30 weeks. Phosphorylated α-syn (p-α-syn) aggregated mainly in oligodendrocytes showing loss of connexin (Cx)47 and Cx32 in the spinal cord and brainstem/cerebellar white matter. Focal demyelination and oligodendrocyte loss started from the p-α-syn-deposited areas, leading to widespread demyelination. In the lesions, reactive astroglia showed extensive loss of Cx43 and Cx30, and activated microglia had marked up-regulation of arginase-1, colony stimulation factor 1 receptor (CSF1R) and Toll-like receptor 2. Single-cell RNA sequencing reveled the characteristics of microglia involved in the disease. Re-inhibition of A53Tα-syn expression at 23 weeks improved neurological symptoms and glial inflammation, whereas re-inhibition at 27 weeks resulted in only partial improvement. A CSF1R inhibitor administration eliminated activated microglia, but did not improve p-α-syn accumulation, demyelination or symptoms. Conclusion : Our model showed α-syn aggregation in oligodendrocytes and rapid progression with remarkable glial inflammation and demyelination. Early removal of α-syn could be novel therapeutic measures for MSA-C/PPMS.

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Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

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Program #/Poster #: P281.03

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR PJT-153150
Healthy Brains for Healthy Lives PhD fellowship (A.A.C.)
NSERC USRA (J.S.)
CIHR MOP-130570

Title: Exercise acts via BDNF-TrkB signaling to rescue deficits in a mouse model of spinocerebellar ataxia type 6

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Abstract: Spinocerebellar ataxia type 6 (SCA6) is an inherited neurodegenerative disease, presenting with mid-life onset of motor coordination difficulties and eventual cerebellar degeneration. We used a knock-in mouse model ($SCA6^{84Q/84Q}$) that carries a CAG expansion mutation in the *CACNA1A* gene to characterise the pathophysiology of SCA6 and identify potential treatments. We have previously shown that at 7 months these mice display deficits in motor coordination, as well as abnormalities in the intrinsic firing patterns of the Purkinje cells in the cerebellum. A 1 month program of voluntary exercise was able to rescue both motor coordination deficits and the frequency of intrinsic Purkinje cell firing. In order to identify the mechanism by which exercise acts therapeutically in the $SCA6^{84Q/84Q}$ model, we investigated brain-derived neurotrophic factor (BDNF) since BDNF levels are reduced in post-mortem brain tissue from SCA6 patients[1] and BDNF administration has been implicated in the pathophysiology of other ataxias[2]. We found that $SCA6^{84Q/84Q}$ mice had reduced levels of cerebellar BDNF, but this could be reversed by exercise. To determine whether exercise acts therapeutically in this model via BDNF-TrkB signaling, we administered 7,8-dihydroxyflavone, a small molecule that mimics BDNF as an agonist of the TrkB receptor. Chronic oral administration of 7,8-DHF rescued both motor coordination and Purkinje cell firing frequency deficits in the $SCA6^{84Q/84Q}$ mouse. The rescue of motor coordination deficits was sustained over several months of administration, demonstrating the potential of 7,8-DHF as a long term treatment for SCA6. By identifying a pathway by which exercise exerts its positive effect on cerebellar function, we have identified novel therapeutic strategies for SCA6.

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Disclosures: A.A. Cook: None. **S. Jayabal:** None. **J. Sheng:** None. **T.C.S. Leung:** None. **A.J. Watt:** None.

Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P281.04

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Assessing and mitigating neuroinflammation in X-linked dystonia parkinsonism

Authors: *T. PETROZZIELLO, C. A. VAINE, S. E. KIM, E. B. PENNEY, R. F. SÎRBULESCU, M. C. POZNANSKY, D. C. BRAGG, R. E. TANZI, C. ZHANG, G. SADRI-VAKILI;
Massachusetts Gen. Hosp., Boston, MA

Abstract: X-linked Dystonia Parkinsonism (XDP) is a severe neurodegenerative disease endemic to the Philippines and characterized by generalized dystonia combined with or followed by parkinsonism. Although several genetic studies mapped the XDP locus to TATA Binding Protein (TBP)-Associated Factor-1 (TAF1), the exact molecular mechanisms leading to neuronal loss remain to be clarified. Recently, we have demonstrated an increase in astrogliosis and microgliosis in human post-mortem prefrontal cortex (PFC) from XDP patients indicating an increase in neuroinflammatory processes in XDP. Furthermore, we reported a concomitant increase in the levels of histone H3 citrullination as well as myeloperoxidase (MPO) in XDP PFC. Both histone H3 citrullination and MPO have been linked to inflammatory processes in several pathological conditions, including neurodegenerative diseases. Here, we sought to unravel the molecular mechanisms underlying neuroinflammation in XDP and we hypothesized that mitigating inflammation may provide a potential therapeutic strategy for XDP. Therefore, we set out to assess the levels of known cytokines and chemokines in post-mortem XDP PFC using Meso Scale Discovery (MSD) assay. Our results revealed that several pro- and anti-inflammatory cytokines had differential expression in XDP PFC compared to controls. Additionally, there was a significant increase in the pro-inflammatory chemokines CXCL13 and CXC3L1 in fibroblasts derived from XDP patients compared to unaffected family members as detected by reverse transcription followed by qPCR. Together, our findings provide the groundwork for us to further assess the role of inflammation in XDP pathogenesis and to begin targeting these pathways as a potential therapeutic strategy to mitigate neuroinflammation in XDP.

Disclosures: T. Petrozziello: None. **C.A. Vaine:** None. **S.E. Kim:** None. **E.B. Penney:** None. **R.F. Sîrbulescu:** None. **M.C. Poznansky:** None. **D.C. Bragg:** None. **R.E. Tanzi:** None. **C. Zhang:** None. **G. Sadri-Vakili:** None.

Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P281.05

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH R21NS104799
NIH R37NS033123
National Ataxia Foundation Junior Investigator Award

Title: Gene therapy in the Shaker rat model of Christianson syndrome.

Authors: *C. J. ANDERSON[1], K. P. FIGUEROA[1], S. PAUL[1], W. DANSITHONG[1], M. GANDELMAN[1], D. R. SCOLES[2], S. M. PULST[1];
[1]Neurol., Univ. of Utah, Salt Lake City, UT; [2]Neurol., Univ. of Utah, SALT LAKE CITY, UT

Abstract: Objective: The objective of this work is to optimize a gene therapeutic treatment strategy in the Wistar Furth *Shaker* rat, a spontaneous model of ataxia based on mutation of the Slc9a6 gene.
Background: Christianson syndrome (CS) is a complex developmental and neurodegenerative disorder characterized by a number of severe symptoms, including ataxia epilepsy, intellectual deficit, autistic features. In recent years, we have worked to characterize a naturally occurring rat model of Purkinje cell (PC) degeneration and ataxia, the Wistar Furth *shaker* rat, and in the process, we tied the shaker phenotype to a loss-of-function mutation in *Slc9a6*.
Design/Methods: We generated an AAV that uses an L7 promoter to target expression of the wildtype Slc9a6 rat gene to PCs along with a GFP tag to evaluate target engagement. We administered this AAV via intracerebroventricular injection prior to PC degeneration and evaluated therapeutic effect in the context of molecular, cellular, and motor phenotype. As NHE6, the gene product of SLC9A6 is widely expressed in brain, in our current work, we are evaluating the use of the ubiquitous CAG promoter for more widespread expression.
Results: Small doses of L7-Slc9a6-GFP AAV (as low as 2.26 x 10^11 vg copies) were well tolerated and sufficient to substantially reduce the ultimate motor phenotype. Interestingly, only a modest molecular improvement was required to generate substantial motor benefit. We will additionally present data evaluating safety and efficacy of the CAGpromoter-based construct.
Conclusions: AAVs are a promising candidate for treatment of the motor symptoms associated with *Slc9a6* mutation. Given the relative ease of targeting different cell types with AAVs through various promoters, we are currently in evaluation of AAVs to treat the developmental and epileptic components of the *shaker* phenotype.

Disclosures: C.J. Anderson: None. **K.P. Figueroa:** None. **S. Paul:** None. **W. Dansithong:** None. **M. Gandelman:** None. **D.R. Scoles:** None. **S.M. Pulst:** None.

Poster

P281. Ataxia and Dystonia: Preclinical Interventions

Location: Virtual Only

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Topic: C.04. Movement Disorders other than Parkinson's Disease

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The ABCD Charitable Trust

Title: Rna toxicity and perturbation of rrna processing in spinocerebellar ataxia type 2

Authors: *P. P. LI[1], R. MOULICK[1], H. FENG[1], X. SUN[1], N. ARBEZ[1], J. JIN[1], L. O. MARQUE[1], E. CHAN[2], C. A. ROSS[3], S. M. PULST[4], R. L. MARGOLIS[5], S. WOODSON[1], D. D. RUDNICKI[1]; [1]Johns Hopkins Univ., Baltimore, MD; [2]The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong;

[3]Johns Hopkins Med. Sch., Baltimore, MD; [4]Univ. of Utah Clin. Neurosciences Ctr., Salt Lake City, UT; [5]Johns Hopkins Univ. Sch. Med., Baltimore, MD

Abstract: Spinocerebellar ataxia type 2 (SCA2) is a neurodegenerative disease caused by expansion of a CAG repeat in *Ataxin-2* (*ATXN2*) gene. The mutant ATXN2 protein with a polyglutamine tract is known to be toxic and contributes to the SCA2 pathogenesis. Here we tested the hypothesis that the mutant *ATXN2* transcript with an expanded CAG repeat (*expATXN2*) is also toxic and contributes to SCA2 pathogenesis. The toxic effect of *expATXN2* transcripts on SK-N-MC neuroblastoma cells and primary mouse cortical neurons was evaluated by caspase 3/7 activity and nuclear condensation assay, respectively. RNA immunoprecipitation assay was performed to identify RNA binding proteins (RBPs) that bind to *expATXN2* RNA. Quantitative PCR was used to examine if rRNA processing is disrupted in SCA2 and Huntington disease (HD) human brain tissue. RESULTS: *expATXN2* RNA induces neuronal cell death, and aberrantly interacts with RBPs involved in RNA metabolism. One of the RBPs, transducin β-like protein 3 (TBL3), involved in rRNA processing, binds to both *expATXN2* and expanded *huntingtin* (*expHTT*) RNA *in vitro*. rRNA processing is disrupted in both SCA2 and HD human brain tissue. These findings provide the first evidence of a contributory role of *expATXN2* transcripts in SCA2 pathogenesis, and further support the role *expHTT* transcripts in HD pathogenesis. The disruption of rRNA processing, mediated by aberrant interaction of RBPs with *expATXN2* and *expHTT* transcripts, suggest a point of convergence in the pathogeneses of repeat expansion diseases with potential therapeutic implications.

Disclosures: P.P. Li: None. **R. Moulick:** None. **H. Feng:** None. **X. Sun:** None. **N. Arbez:** None. **J. Jin:** None. **L.O. Marque:** None. **E. Chan:** None. **C.A. Ross:** None. **S.M. Pulst:** None. **R.L. Margolis:** None. **S. Woodson:** None. **D.D. Rudnicki:** None.

Poster

P281. Ataxia and Dystonia: Preclinical Interventions

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Program #/Poster #: P281.07

Topic: C.04. Movement Disorders other than Parkinson's Disease

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UL1 TR001860
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Shriners Hospital for Children grant 87400-NCA-21
Shriners Hospital for Children grant 85113-NCA-18
Dana Foundation

Title: Examining the role of NAA transport in Canavan disease pathology

Authors: *V. L. HULL, Y. WANG, D. E. PLEASURE;
Neurol., UC Davis, Davis, CA

Abstract: Canavan disease (CD) is an incurable leukodystrophy which develops in infancy and childhood as the result of *ASPA* mutations which disrupt the functionality of aspartoacylase. Aspartoacylase is an oligodendroglial-enriched enzyme responsible for cleaving the abundant brain amino acid, N-acetyl-L-

aspartate (NAA). Infants and children with CD are therefore unable to metabolize NAA and have extremely elevated levels of brain NAA accompanied by spongiform white matter degeneration, motor and cognitive delays, ataxia, and progressive neuronal atrophy. Attempts at *ASPA* gene replacement have largely proven ineffective, resulting in an urgent need to define new therapeutic targets for this fatal disease. Our lab has previously published studies showing that knockout and viral mediated neonatal knockdown of the neuronal enzyme Nat8l, which is responsible for the synthesis of NAA, is preventative against development of white matter vacuolation and ataxia in the well characterized CD model mouse (*Aspa*$^{nur7/nur7}$, "CD mouse"). Our most recent publication shows that intracisternal administration of an antisense oligonucleotide targeting *Nat8l* is capable of lowering brain NAA concentration, repairing white matter vacuolation and improving motor deficits in adult CD mice. Our current study seeks to further understand what role brain NAA transporters play in the cell specific accumulation and maldistribution of NAA in Canavan disease.

Disclosures: V.L. Hull: None. **Y. Wang:** None. **D.E. Pleasure:** None.

Poster

P295. Other Neuromuscular Diseases

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P295.01

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant GM000708
Dept. of Neurology, U. Arizona
Dept. of Pathology, U. Arizona

Title: A sporadic case of severe peripheral neuropathy expands the phenotypic range of TUBB2A mutations

Authors: K. SCHERER[1], M. F. HAMMER[2], W. A. DAY[3], W. R. MONTFORT[4], J. H. MILLER[5,6], L. M. JOHNSTONE[2], D. R. ANDREW[1,7], ***L. L. RESTIFO**[1];
[1]Neurol., [2]Genet. Core, [3]Pathology, [4]Chem. & Biochem., Univ. of Arizona, Tucson, AZ; [5]Phoenix Children's Hosp., Phoenix, AZ; [6]Child Hlth., UAz, Col. of Med. - Phoenix, Phoenix, AZ; [7]Lycoming Col., Williamsport, PA

Abstract: An 8-year-old boy was evaluated for progressive loss of strength and sensation in his extremities and developmental delay. Birth history was unremarkable and family history was negative. Motor and language milestones were delayed; dysarthria and swallowing difficulties were noted. On exam, the patient had symmetric distal weakness, muscle wasting, and sensory deficits, consistent with sensorimotor peripheral neuropathy. Neurophysiological testing revealed markedly reduced nerve-conduction velocities, consistent with demyelination. Compound motor action potential amplitudes were only moderately reduced, but declined considerably over the next four years, indicating interim axonal loss. At age 11, he lost ambulation. He never had seizures, and EEG was normal. Brainstem auditory evoked responses were abnormal. Neuropsychological testing showed mild intellectual disability affecting many cognitive domains. Brain MRI demonstrated mildly reduced volume of gray matter and

corpus callosum white matter, but no cortical gyration defects or abnormal myelination. Sural nerve biopsy showed reduced axon-fiber density and myelination. Electron micrographs revealed abnormal Schwann-cell processes with onion-bulb formation, reflecting attempted remyelination. Some axons showed abnormal microtubule orientation. Clinical genetic testing (including high-resolution karyotype, copy-number variants, and sequencing of genes commonly altered in peripheral neuropathies) failed to identify a cause of the phenotype. Whole-exome sequencing, using Illumina's massively parallel sequencing-by-synthesis method, was performed on peripheral blood DNA from the patient, his parents, and his unaffected sister. Sequence analysis using custom variant-filtering software revealed the proband has three amino-acid-altering germline variants not shared with any family members; two variants were eliminated as potential candidates to explain his condition. In *TUBB2A*, encoding β-tubulin 2A, the proband has a heterozygous *de novo* mutation at a highly conserved amino acid position, Arg262Pro, which is predicted to be deleterious. Crystal structure of wild-type β-tubulin (Protein Data Bank 4HNA) shows Arg262 lying on the surface, along a contact zone with the kinesin motor domain. Arg262Pro would disrupt an intramolecular hydrogen-bond network through interaction with three other amino acid residues. In the closely related gene, *TUBB3*, mutations at Arg262 also cause neuropathology with PNS and brain components. However, the proband's phenotype is distinct from the cortical dysplasia and epilepsy caused by other dominant *TUBB2A* mutations.

Disclosures: K. Scherer: None. **M.F. Hammer:** None. **W.A. Day:** None. **W.R. Montfort:** None. **J.H. Miller:** None. **L.M. Johnstone:** None. **D.R. Andrew:** None. **L.L. Restifo:** None.

Poster

P295. Other Neuromuscular Diseases

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Program #/Poster #: P295.02

Topic: C.06. Neuromuscular Diseases

Support: NIH R01 NS038526
NIH P30 NS045758
Charcot-Marie-Tooth Association

Title: A comparative study of mouse models of dominant and recessive Charcot-Marie-Tooth disease type 2E

Authors: S. D. KING[1], P. C. MONSMA[1], E. J. STONE[1], A. UCHIDA[1], R. RODRIGO[2], G. OWENDOFF[3], W. D. ARNOLD[2], *A. BROWN[1];
[1]Neurosci., [2]Neurol., [3]Biomed. Sci. Honors Program, Ohio State Univ., Columbus, OH

Abstract: Charcot-Marie-Tooth disease type 2E (CMT2E) is a slowly progressing peripheral neuropathy caused by mutations in the gene for neurofilament protein L (NEFL), which is a component of neurofilaments. Neurofilaments are space-filling cytoskeletal polymers that accumulate in myelinated axons, contributing to the expansion of axon caliber and consequent increase in axonal conduction velocity during postnatal development. CMT2E-causing mutations can be dominant (mostly missense mutations) or recessive (null mutations). The *Nefl*$^{N98S/+}$ mouse, which is heterozygous for the N98S

mutation, is an established model of dominant CMT2E. The *Nefl*$^{-/-}$ "knockout" mouse, which is homozygous for a null mutation, is a potential model of recessive CMT2E. We are characterizing these mice in order to understand how both missense and null mutations in the same gene cause disease. Tail nerve conduction measurements at 4,8,12 and 16 weeks of age revealed that *Nefl*$^{-/-}$ and *Nefl*$^{N98S/+}$ mice had lower compound action potential velocities and amplitudes compared to *wt* mice. Tasked with traversing a horizontal ladder, the *Nefl*$^{N98S/+}$ mice had significantly more footfalls than *wt* mice, whereas the *Nefl*$^{-/-}$ mice appeared normal. Visual assessment of open field locomotion using the Basso Mouse Scale revealed mild locomotor impairment that increased with age in both *Nefl*$^{-/-}$ and *Nefl*$^{N98S/+}$ mice. Histologically, the sciatic nerves of *Nefl*$^{-/-}$ and *Nefl*$^{N98S/+}$ mice were indistinguishable, with a widespread reduction in myelinated axon caliber and g-ratio. Ultrastructurally, myelinated axons in the sciatic nerves of both *Nefl*$^{-/-}$ and *Nefl*$^{N98S/+}$ mice were largely devoid of neurofilaments, whereas unmyelinated axons appeared unaffected. As reported by others, *Nefl*$^{N98S/+}$ mice exhibited neurofilament accumulations in the soma and proximal axons of some neurons in the ventral horn and sensory ganglia. In contrast, no such accumulations are encountered in *Nefl*$^{-/-}$ mice, which lack neurofilaments. In conclusion, the phenotype of the *Nefl*$^{-/-}$ and *Nefl*$^{N98S/+}$ mice appears to converge on a lack of neurofilaments in peripheral myelinated axons, leading to a failure of these axons to expand during postnatal development, but diverge in the soma and proximal axons. The nerve conduction defects likely reflect the reduced axonal caliber, whereas the greater locomotor impairment in the *Nefl*$^{N98S/+}$ mice suggests an additional toxic gain of function. Thus, it is possible that there are multiple disease mechanisms at work in CMT2E that act at different locations in the neuron and/or nervous system.

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Poster

P295. Other Neuromuscular Diseases

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Program #/Poster #: P295.03

Topic: C.06. Neuromuscular Diseases

Support: MDA295271
NIH AG051470

Title: Aging at the Mouse Neuromuscular Junction and the Therapeutic Effect of a Novel Calcium Channel Modifier

Authors: *Y. LI[1], J. BAROUDI[1], M. PATEL[1], M. WU[1], S. GATTI[2], M. LIANG[3], G. VLADOMIR[3], Y. BADAWI[1], P. WIPF[3], S. MERINEY[1];

[1]Univ. of Pittsburgh Ctr. For Neurosci., Pittsburgh, PA; [2]Tufts Univ., Tufts University, MA; [3]Chem., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: There is still a gap in the literature regarding longitudinal changes of the neuromuscular junction (NMJ) in the process of aging, and such knowledge is vital to discoveries of novel therapeutic treatments and to the timing of prophylactic strategies. In this study, we used electrophysiology and immunohistochemistry to investigate structural and functional changes between 4 and 28 months of age at the mouse NMJ. We observed significant and dynamic changes in neurotransmitter release in the epitrochleoanconeous (ETA) nerve-muscle preparation from both male and female C57/BL6 mice. The changes are time-dependent, leading us to further separate the aging time course into epochs named ”Adult” (4-18 months), “Early Aging” (19-24 months), and “Later Aging” (25-28 months).We have applied these epochs to our morphological data on the motor axons (with antibody against neurofilament-M) and acetylcholine receptors (AChR, with α-Bungarotoxin) at the NMJ and characterized their changes during the aging process. Lastly, we have used forelimb grip strength as the behavioral measurement for muscle strength. Here, we report an increase in action potential-triggered transmitter release in the Early Aging epoch, and a decreased transmitter release in the Later Aging epoch - a biphasic change. During these same epochs miniature end plate amplitude continuously decreases. This suggests a compensatory homeostatic mechanism in the Early Aging epoch that is not maintained in Later Aging. In terms of morphology, we identified a significant decrease in AchR area and synaptic motor axon area. In addition, the ACHR area broke into islands. The average island numbers of AChRs increased from 5 in Adult Epoch to 10 in Later Aging epoch. The percentage of multi-innervated synapses significantly increased from 1% in Adult epoch to 12% in Early Aging epoch, and 30% in the Later Aging epoch. Additionally, grip strength/body weight significantly decreased from 1.75 in Adults to around 1.5 in both Early Aging and Later Aging epochs. Finally, we have treated the aged ex vivo nerve muscle preparation with the small molecule calcium channel gating modifier, GV-58, and found a 1.64-fold increase in quantal content. To summarize, we have studied aging at the NMJ in a longitudinal fashion, identifying important time epochs for development of prophylactic strategies, and shown that our small molecule acutely and successfully rescued loss of transmitter release in aged NMJs.

Disclosures: Y. Li: None. **J. Baroudi:** None. **M. Patel:** None. **M. Wu:** None. **S. Gatti:** None. **M. Liang:** None. **G. Vladomir:** None. **Y. Badawi:** None. **P. Wipf:** None. **S. Meriney:** None.

Poster

P295. Other Neuromuscular Diseases

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Program #/Poster #: P295.04

Topic: C.06. Neuromuscular Diseases

Title: Stabilization of an Iodinated Chimeric Acetylcholine Binding Protein Containing the Main Immunogenic Region of the α1 Subunit of Human Muscle Nicotinic Acetylcholine Receptor by Tyrosine Substitution

Authors: B. S. LAWSON[1], ***Y. PENG**[1], Q. XU[2], A. Q. PHAM[1], O. A. GARDEN[3], J. LUO[1];
[1]Dept. of Clin. Sci. and Advanced Med., Univ. of Pennsylvania Sch. of Vet. Med., Philadelphia, PA; [2]Fox Chase Cancer Ctr., Philadelphia, PA; [3]Louisiana State Univ. Sch. of Vet. Med., Baton Rouge, LA

Abstract: Myasthenia gravis (MG) is caused by antibody-mediated autoimmune responses to muscle acetylcholine receptors (AChRs) that induce complement-mediated destruction of the AChRs and impairment of neuromuscular transmission. Serological testing for the detection of AChR antibodies is currently used for MG diagnosis but does not correlate with disease severity. The main immunogenic region (MIR) at the extracellular end of the AChR α1 subunit contains a cluster of tightly-overlapping B cell epitopes that are targeted by more than half of autoantibodies in MG. Autoantibodies to the MIR passively transfer experimental autoimmune MG (EAMG) in healthy animals, exhibit all the major pathological activities of MG serum: causing focal complement-mediated lysis of the postsynaptic membrane and cross-linking-induced endocytosis of AChRs (antigenic modulation), and show better correlations with disease manifestations in MG. The acetylcholine binding protein (AChBP) from the snail *Aplysia californica* is a structural homologue of the extracellular domain of AChRs. A chimeric AChBP containing the conformational intact MIR exhibits high affinity for mAbs to the MIR and reacts with serum antibodies from cats, dogs, and humans with MG. We found that the iodinated MIR/AChBP chimera, which is used to develop a serological radioimmunoassay (RIA) to detect pathological anti-MIR autoantibodies in sera from MG patients, was destabilized and lost antibody-binding capacity more rapidly than the decay rate of iodine-125, limiting its potential clinical practicality. We hypothesized that the instability results from the steric strain caused by the proximity of the incorporated large iodine atoms and adjacent structural components. Computational analysis revealed that only six of the twelve tyrosine residues on each subunit of the MIR/AChBP chimera are accessible for iodination. We generated three mutants, in each of which two of the six identified tyrosine residues were mutated into phenylalanine. Only two of these mutants showed improved stability after iodination. Studies are currently underway to further pin down those tyrosine residues directly responsible for the instability and generate a stable mutant of the chimera, ideally for use in RIA, by replacing these residues with other amino acids.

Disclosures: B.S. Lawson: None. **Y. Peng:** None. **Q. Xu:** None. **A.Q. Pham:** None. **O.A. Garden:** None. **J. Luo:** None.

Poster

P295. Other Neuromuscular Diseases

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS110727

Title: Characterization of neuromuscular defects in a Drosophila model of muscular dystrophy

Authors: *J. SIDISKY, D. BABCOCK, R. CARATENUTO;
Lehigh Univ., BETHLEHEM, PA

Abstract: Muscular Dystrophies are a group of diseases characterized primarily by the progressive weakness in muscle and loss of muscle mass. Recent evidence has demonstrated that synaptic defects are among the earliest hallmarks of neurodegenerative diseases, including neuromuscular defects seen in Amyotrophic Lateral Sclerosis (ALS). However, much less is known about synaptic defects in diseases of the muscle, including Muscular Dystrophies. Our work here describes the neuromuscular defects that precede muscle cell loss in an adult Drosophila model of Duchenne Muscular Dystrophy, which is caused by a mutation in the *dystrophin* gene. Through characterization of locomotive behavior, analysis of *dystrophin* mutants, as well as tissue-specific knockdown of *dystrophin*, we demonstrate the progressive loss of functional and structural integrity at adult Neuromuscular Junctions (NMJs) that precede cell death. Additionally, we characterize defects in synaptic proteins in pre-synaptic motor neurons including Bruchpilot (BRP) and Synapsin (Syn). We also investigate changes in post-synaptic muscle cells through staining Glutamate Receptors (GluRs) and post synaptic density (PSD) marker Disc-large (DLG). Together, our results describe the early pre- and post-synaptic deficits present at NMJs in a Drosophila model of Duchenne Muscular Dystrophy and provide insight into the mechanisms underlying synaptic defects that ultimately lead to muscle cell death.

Disclosures: J. Sidisky: None. **D. Babcock:** None. **R. Caratenuto:** None.

Poster

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Topic: C.06. Neuromuscular Diseases

Support: NSF 2011648

Title: Passive transfer of Lambert-Eaton myasthenic syndrome to mice does not alter the presynaptic AP waveform or reduce BK channel contribution to the AP waveform or transmitter release

Authors: C. KAUFHOLD[1], S. GINEBAUGH[1], K. OJALA[1], M. DAVEY[1], E. MILLER[2], G. ORTIZ[2], ***Y. BADAWI**[1], S. MERINEY[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: The autoimmune neurological disease Lambert-Eaton myasthenic syndrome (LEMS) is known to attack and remove presynaptic voltage-gated calcium channels and disrupt the normally organized active zone structure at the neuromuscular junction. This leads to a significant reduction in presynaptic calcium entry and transmitter release. We wondered if these pathological alterations would also affect the activation of presynaptic calcium-activated potassium (BK) channels. At the adult neuromuscular junction, BK channels are known to be co-localized with voltage-gated calcium channels in the active zone. The BK channel tight spatial association with voltage-gated calcium channels leads to BK channel activation late in the action potential waveform, locally accelerating the falling phase of the action potential waveform, which decreases the duration of the presynaptic action potential, and subsequently reduces the probability of transmitter release at neuromuscular active zones. Because LEMS reduces calcium entry, we hypothesized that BK channel activation might decrease due to the reduction in the

calcium trigger for activation, broadening the presynaptic action potential waveform. We tested this hypothesis using passive transfer of LEMS to adult male and female mice using daily intraperitoneal injections of LEMS patient serum for 3-4 weeks. As expected, LEMS serum injections greatly reduced action potential triggered transmitter release as has been previously reported. However, using the voltage-sensitive dye BERST-1, we showed that LEMS serum injections did not change the presynaptic action potential waveform. Furthermore, the addition of IBTX (to block BK channels) was still able to broaden this waveform, indicating that BK channels were still present and contributing to action potential shape as observed in control un-injected animals. Furthermore, IBTX increased action potential-triggered transmitter release at neuromuscular synapses of LEMS injected mice, as is observed in controls. Therefore, using a previously validated mouse model of LEMS, we showed that the activation of calcium-activated potassium channels in the neuromuscular active zone and the presynaptic action potential waveform are not significantly affected by the pathological processes that underly LEMS.

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Poster

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Topic: C.06. Neuromuscular Diseases

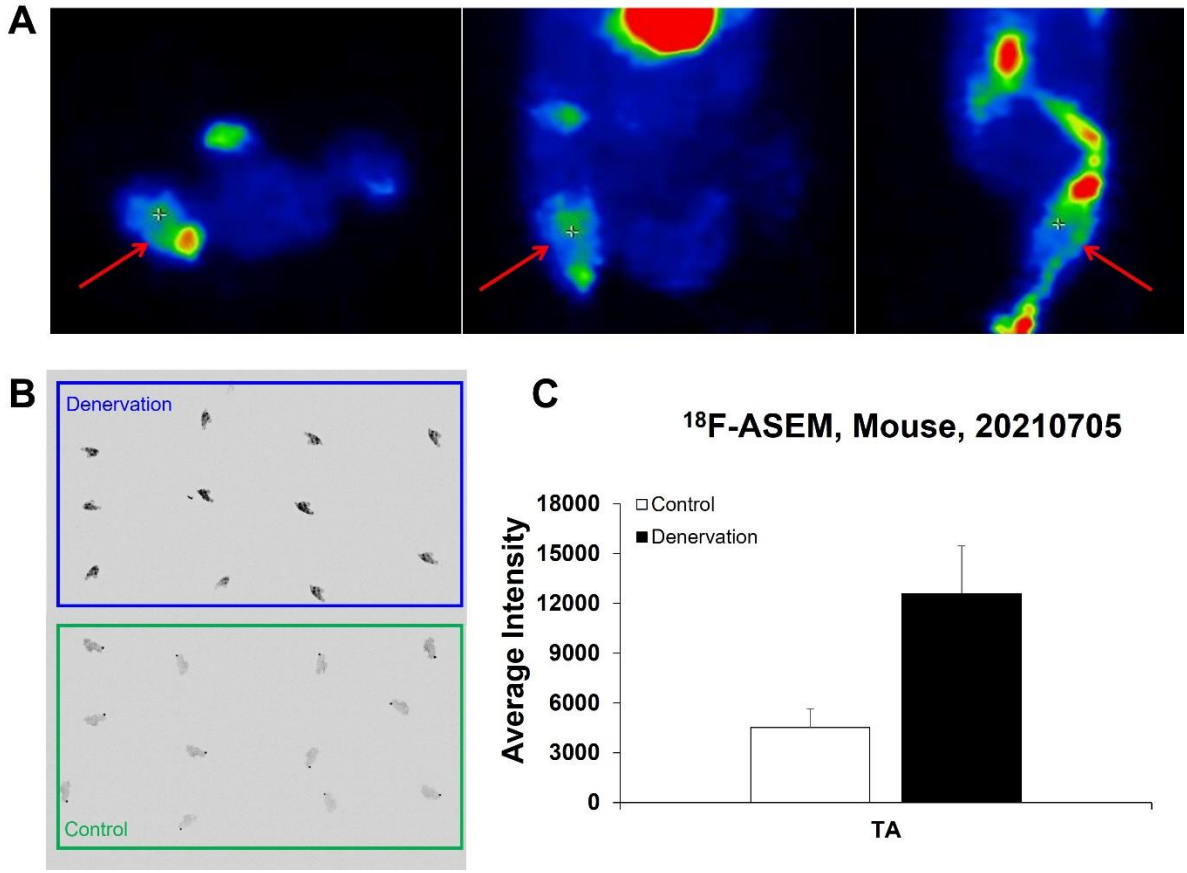
Support: National Research Foundation of Korea (NRF) grant (No. 2019R1A2C1088153).

Title: Nicotinic acetylcholine receptor PET-MR imaging for skeletal muscle denervation: a preliminary study

Authors: *S. LEE[1], Y.-I. KIM[2], J. CHUNG[2], S.-Y. KIM[3], S. LEE[2], S. OH[2], J.-S. RYU[2], W. KIM[4], D. KO[4], K. KIM[3];
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Abstract: Denervated muscle caused by peripheral nerve injury can be visualized by several imaging studies such as MRI and F-18-FDG PET scans. However, invasive needle electromyography is the current gold-standard diagnostic method for peripheral nervous system disorders. Increased expression of nicotinic acetylcholine receptors (nAChRs) of denervated skeletal muscle has been found in previous studies. This phenomenon is thought to be related to acetylcholine supersensitivity after muscle denervation. Therefore, nAChRs imaging study for skeletal muscle could be an imaging method for muscle denervation and used as a new diagnostic method for peripheral neuromuscular disorders. A 10 week old male c57bl/6 mouse was used for this study. The mouse was anesthetized and the left sciatic nerve was exposed by splitting the gluteal muscle. A nerve segment 5 mm long was resected in the proximal part of the nerve.The sham operation, exposing the sciatic nerve without resection, was done at the other side of the mouse. 1 week after the denervation, the mouse underwent micro PET/MR imaging. MR imaging was performed just after the mouse anesthesia for about 12-minutes. After MR imaging,

PET imaging was done after 0.485 mCi of F-18-ASEM intravenous injection for 60-minutes using dynamic mode. The mouse was sacrificed, and lower leg muscles were harvested for autoradiographic evaluation. F-18-ASEM PET showed increased uptake at denervated lower leg muscles, which were matched on signal change of MR. Maximum and mean standardized uptake value of these muscles was 15.07 and 4.77, respectively. In contrast, no significant uptake was observed at sham side muscles. Autoradiography results demonstrated that denervated tibialis anterior muscle has more than 2.79 times of average intensity than contralateral tibialis anterior muscle. In an animal model of sciatic nerve injury, F-18-ASEM PET/MR showed increased nAChRs expression in denervated muscles. Therefore, F18-ASEM PET/MR can be a potential imaging modality for the evaluation of denervation after nerve injury.



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Poster

P295. Other Neuromuscular Diseases

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P295.08

Topic: C.06. Neuromuscular Diseases

Title: Endogenous antigen presentation from damaged muscle cells initiates and sustains autoreactive antibody response in rats - a novel model for myasthenia gravis

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Abstract: Myasthenia gravis (MG) is a chronic autoimmune disease caused by antibodies that target muscle nicotinic acetylcholine receptors (AChRs) and impair neuromuscular transmission, thereby causing muscle weakness. What initiates and sustains MG is still largely unknown. Translation of therapeutic approaches developed in animal models of MG into positive results in humans faces difficulties, partially because of the lack of an ideal animal model. Experimental autoimmune MG (EAMG) is usually induced in mice or rats by immunizing with AChR purified from *Torpedo* electric organ. Immunized mice produce antibodies that cross-react with mouse muscle AChR, causing myasthenic symptoms, but do not induce a self-reactive CD4+ T cell response or a self-sustaining antibody response. EAMG rats develop a self-reactive CD4+ T cell response to rat muscle AChR, but it is difficult to investigate autoimmune responses due to the cross-reaction of anti-Torpedo AChR antibodies. We developed a chronic, self-perpetuated EAMG model in rats using a chimeric acetylcholine binding protein (AChBP) containing the main immunogenic region (MIR), a group of tightly-overlapping B cell epitopes that are targeted by more than half of autoantibodies in MG and EAMG, as an immunogen. Both the chimeras containing the human MIR and the syngeneic MIR were potent in inducing EAMG, though the latter was less potent. Immunizing with either chimera initially induced large amounts of antibodies to the immunogens, which cross-react with rat muscle AChR weakly. Trace amounts of cross-reactive antibodies induced by the chimeras caused focal lysis of the postsynaptic membrane, resulting in shedding of membrane fragments containing AChRs, which, in turn, initiated a secondary antibody response to rat muscle AChRs, as reflected by the development of autoantibodies to AChR cytoplasmic domains. This feedforward cycle of autoimmune stimulation sustained the autoimmune response. Fourteen months later, the mean value for total AChR extracted from these rats was less than 38% of the amount extracted from rats immunized only with adjuvants and more than 72% of the AChR extracted from these rats was complexed with antibody. This novel EAMG model enables us to investigate the autoimmune response to endogenous muscle AChR by measuring antibodies to the cytoplasmic domain of rat muscle AChR that the MIR/AChBP lacks, allowing rigorously assessing the effectiveness of immunosuppressive therapies in suppressing the autoimmune response rather than the immune response to an exogenous immunogen.

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Poster

P295. Other Neuromuscular Diseases

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Topic: C.06. Neuromuscular Diseases

Support: NIH grant NS054154
NIH grant NS098523
Charcot-Marie-Tooth Assoc.

Title: Two new mouse models of Charcot-Marie-Tooth Disease Type 1X (CMT1X) caused by mutations in the gap junction beta-1 gene (GJB1)

Authors: C. L. HATTON, A. L. D. TADENEV, R. SCHNEIDER, L. P. BOGDANIK, C. M. LUTZ, *R. BURGESS;
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Abstract: Charcot-Marie-Tooth Disease Type 1X (CMT1X) is caused by more than 400 X-linked mutations in the gap junction beta-1 gene (*GJB1*), which encodes gap junction protein connexin32 (Cx32). Loss of normal Cx32 function results in the failure of gap junction function, leading to clinical symptoms of demyelination and peripheral neuropathy. Loss of function results from many mechanisms, including severely truncated alleles (nulls), mutations affecting Cxn32 trafficking and localization, and mutations affecting gap junction channel function. These different mechanisms may require different therapeutic approaches, and therefore animal models reflecting the breadth of mutation types are necessary for rigorous preclinical studies. An existing knockout (KO) mouse model develops relevant demyelinating and neuropathy phenotypes, but only accurately models the subset of mutations that result in null alleles. As part of a larger effort to model additional human disease-associated *GJB1* mutations, we created a novel R15Q mouse model, as well as a new null allele, $Gjb1^{del2}$, resulting from an early frameshift caused by a deletion of 2 bases in codon 7.
Hemizygous male or homozygous female $Gjb1^{R15Q}$ mutant mice develop histological signs of demyelination and axonopathy by 6 months of age, which progresses and is more severe at 9 months. The phenotype is more severe in peripheral motor nerves than sensory nerves. The femoral motor branch shows demyelination and decreased axon areas, with increased space between axons, but no reduction in axon number. Nerve conduction velocities show a significant decrease of about 15% in the 9 month old mice compared to controls. The $Gjb1^{del2}$ mutant mice show similar phenotypes in the femoral motor nerves by 3-4 months, which also progress with age and closely resemble the previously reported KO mice. Behavioral testing for both genotypes is on-going, but so far has not shown significant differences in body weight, rotarod performance, or grip strength, for either allele.
Thus, we have successfully created two new models of CMT1X, $Gjb1^{R15Q}$ and $Gjb1^{del2}$. These mice have robust histological signs of disease that progress with age, but milder neurophysiological and behavioral defects. The full characterization of these mice will provide additional models for preclinical studies of CMT1X.

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Poster

P298. Mechanisms of Neurotoxicity II

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Program #/Poster #: P298.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: A1-S-21433

Title: Striatal administration of quinolinic acid induces impairment in autophagy flux and activation of necroptosis and apoptosis

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Abstract: Excitotoxicity is a common event in the pathophysiology of nerodegenerative disorders. Occurs due to the overactivation of NMDA receptor by agonist such as glutamate, NMDA and quinolinic acid (QUIN), promoting an intracellular overload of calcium and the subsequent impairment of cellular homeostasis, conducing to cell injury and the activation of different cell death pathways which contribute to brain tissue damage. There is evidence indicating that autophagy flux is impaired as a consequence of excitotoxicity, however the molecular mechanism of this impairment is not fully understood. Recent evidence suggests that oligomerization of p-MLKL the last event in necroptosis activation, as well as the increase in caspase 3 activity promotes autophagy disruption, nevertheless the participation of necroptosis and apoptosis in excitotoxic-induced autophagy flux impairment remains poorly explored. Intrastriatal administration of QUIN has been used as an excitotoxic/pro-oxidant model for the study of biochemical events impaired during excitototxicity. QUIN promotes tissue damage and increases neurodegeneration; nonetheless its effect on autophagy remains unexplored. In this work we explore the effect of QUIN on autophagy flux, as well as necroptosis and apoptosis activation. We administrated 1 µL of isotonic saline or QUIN at 120 or 240 nmol in the right striatum of male Wistar rats (260-300 g), and the brain tissue was extracted 7 days after injection. We evaluated ultrastructural change in the mitochondria, endoplasmic reticulum and axons of striatal neurons. Moreover, the autophagy flux, necroptosis and apoptosis were evaluated by western blot. QUIN administration produces mitochondrial crests swelling and fragmentation also decreases ribosomal density in the rough endoplasmic reticulum, as well as myelin sheaths discontinuity in axons. Furthermore, QUIN administration induces autophagy flux impairment observed as the increase in LC3-II and p62 levels, and decrease in mature cathepsin D and Beclin 1 levels. Additionally, QUIN administration increases TNFα and RIPK3 levels suggesting an activation of necroptosis as well as an increase in Bax levels and a decrease in Bcl-2 levels, suggesting an activation of apoptosis. These results indicate that QUIN causes subcellular compartments alteration, blocks autophagy flux and activates necroptosis and apoptosis at 7 days.

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Poster

P298. Mechanisms of Neurotoxicity II

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Research funding from Sumitomo Dainippon Pharma Co., Ltd., Japan
JSPS KAKENHI 20K07027
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Title: Zonisamide pre-treatment alleviates oxaliplatin-induced dorsal root ganglion neuron death in vitro

Authors: *K. SANGO, S. TAKAKU;
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Abstract: Oxaliplatin (OHP), a platinum-based agent commonly prescribed for patients with colorectal cancers, has been shown to evoke peripheral neuropathy; however, its pathogenesis remains obscure and no effective remedies for it have been developed. Previous *in vivo* and *in vitro* studies indicate that sensory neurons in spinal dorsal root ganglia (DRG) are the most common target of OHP. Zonisamide, an anti-epileptic and anti-Parkinson's disease agent, exerts neurotrophic activities toward DRG neurons, and therefore its potential efficacy for the OHP neurotoxicity defines the aim of this study. DRG neurons from 3-month-old female Wistar rats were seeded on poly-L-lysine-coated dishes and incubated for 24 h in a serum-free medium (SFM) in the presence or absence of 100 μM zonisamide, then maintained for 24 h in SFM in the presence or absence of 75 μM OHP. The average cell survival ratios (means±SD) determined by trypan blue exclusion were 60±13.5% in [control; n=16], 65.6±18.1% in [pre-zonisamide; n=10], 28.1±11.4% in [OHP; n=16], and 42.9±14.9% in [pre-zonisamide and OHP; n=16], respectively. Zonisamide pre-treatment significantly alleviated DRG neuron death under exposure to OHP, and its activity was attenuated by co-treatment with 25 μM phosphatidyl inositol-3'-phosphate-kinase (PI3K) inhibitor LY294002; the survival rations declined from 43.6±11% in [pre-zonisamide and OHP; n=9] to 35±11.4% in [pre-(zonisamide+LY294002) and OHP; n=10]. These findings suggest that zonisamide alleviates OHP-induced DRG neuronal cell injury and death via stimulating PI3K signaling pathway. Zonisamide pre-treatment may be efficacious against the neurotoxic adverse effects of OHP.

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Poster

P298. Mechanisms of Neurotoxicity II

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Program #/Poster #: P298.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01HL139712

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Foglia and Hills families

Title: Primary cilia loss renders pyramidal neurons susceptible to perinatal ketamine-induced dendritic degeneration and learning deficits

Authors: N. SARIC, F. SOMAA, *M. STRAUSS, C. FOSTER SADE, S. BEJUGAMA, G. N. RIVERO BALLON, L. WANG, K. HASHIMOTO-TORII, N. ISHIBASHI;
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Abstract: Recent clinical studies have demonstrated a strong link between anesthetic exposure and neurodevelopmental outcomes in children with CHD. Protein-damaging *de novo* gene mutations have been demonstrated to be strong predictors of neurodevelopmental anomalies in congenital heart disease (CHD), and at least 50% of these genes have been found to be associated with primary cilia structure and/or function. Therefore, studying the combined effect of anesthesia and primary cilia gene mutations may shed light on the neurodevelopmental abnormalities observed in CHD children. Using *Emx1cre; Ift88 f/f*, in which primary cilia are lost specifically in cortical excitatory neurons, we administered either PBS or Ketamine at postnatal day 7 (P7). We examined markers of cytoskeletal degeneration at P8 in the medial prefrontal cortex as well as behavioral testing at P30 using water T-maze to assess their spatial memory performance and cognitive flexibility. Separate cohorts were also tested for gross and fine motor deficits using the accelerated rotarod and pellet reach task, respectively. During the reversal learning paradigm, the *Ift88* knockout mice that were exposed to ketamine (cKO+Ket) showed a strongly reduced ability to learn compared to other groups, indicative of a cognitive flexibility deficit. This same group demonstrated significant motor deficits, with a reduced rate of motor learning in both gross and fine motor tasks. To assess pyramidal neuron morphology, we used two other inducible Cre/lox mice to specifically label layer II (*Nes-Cre/ERT2*) and layer V (*ER81-Cre/ERT2*) neurons. We found significant enhancement in immunoreactivity of cytoskeletal degeneration markers in the cKO+Ket mice compared to the other three groups (cHET+PBS, cHET+Ket, and cKO+PBS). The effects of ketamine on dendritic morphology were also specific to this group. To examine if the observed learning-related deficits were related to altered dendritic spine dynamics we then performed two-photon imaging on *Ift88* cHET+Ket and cKO+Ket *Thy1-GFPM* animals and compared spine density and turnover in the motor cortex. We also utilized human induced pluripotent stem cells (hiPSCs) to examine the impact of identified *de novo* CHD mutations (CHD7, WDR5, and KDM5B) on cilia length/expression and caspase-3 activation in response to ketamine in both neural progenitor cells (NPCs) and differentiated neurons. Our findings indicate that primary cilia deficiency, due to a common genetic predisposition with CHD, exacerbates the toxicity of neonatal anesthesia, suggesting a novel therapeutic treatment strategy for the prevention of neurobehavioral abnormalities in this population.

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Poster

P298. Mechanisms of Neurotoxicity II

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 5K12HD001399-20

Title: Immunometabolism in septic encephalopathy: a novel therapeutic target

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Abstract: Immunometabolism in septic encephalopathy: a novel therapeutic target
Introduction: Metabolic encephalopathy affects one in three intensive care unit (ICU) patients, with the most serious subtype occurring in the context of sepsis [septic encephalopathy (SE)], which is associated with up to 70% mortality. The cerebellum is particularly sensitive to injury early in the SE process. Here we utilized mesenchymal stem cell-derived extracellular vesicles (MSC EVs) to target immunometabolic dysfunction in metabolic encephalopathy using a murine model of SE.
Methods: We administered cecal contents by an intraperitoneal injection to 7-10-week-old, C57BL/6J mice to induce sepsis/SE. Encephalopathic and control mice received either MSC EVs or EV-depleted media intravenously 6 hours post-sepsis induction. Mice were scored every 2 hours until euthanasia (score ≥15) using a sepsis scoring system that also evaluates neurological status. We obtained cerebellar samples (n=8/group) for Hematoxylin-Eosin (H&E) staining. Total RNA was isolated from cerebellar samples (n=3/group) and was sequenced to identify differentially expressed genes (DEGs).
Results: Average scores at sacrifice were lower in the EV-treated group compared to non-treated mice with SE, indicating improved disease severity. H&E staining on septic cerebella revealed significant neuropathological alterations compared to controls, including shrunken Purkinje and granule cells with irregular nucleus and absent nucleolus, acidophilic (pink) cytoplasm, apoptotic profiles, and disrupted neuropil. Additionally, when comparing the DEGs in RNA seq, 103 downregulated and 119 upregulated genes were identified in the cerebella of EV-treated mice with SE, as compared to the non-treated group. Using the Ingenuity Pathway Analysis software, we showed that neuroinflammatory pathways remained activated in treated mice, while the IL-6 signaling pathway was inhibited. In addition to immune pathways, metabolic signaling pathways that promote ATP generation including PI3K/AKT, IGF-1, AMPK and PPARa were also activated, suggesting an SE-related decreased intracellular energy production.
Conclusions: We demonstrate that EVs alter cerebellar immune and metabolic pathways that may be responsible for the SE-induced neuropathological changes and poor outcomes. Targeting specific immunometabolic signaling pathways that promote energy generation and alleviating immune dysregulation present an opportunity to successfully treat septic and other metabolic encephalopathies.

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Poster

P298. Mechanisms of Neurotoxicity II

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R21 MH106441
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Title: Global analysis of RNA-protein interactions and RNA structure alterations in response to excitotoxicity in primary cortical neurons

Authors: *E. ALVAREZ-PERIEL[1], M. C. KRAMER[2], D. P. JACKSON[1], Ç. AKAY-ESPINOZA[1], J. TASCA[3], B. A. GARCIA[3], B. D. GREGORY[2], K. L. JORDAN-SCIUTTO[1];
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Abstract: A number of mechanisms have been implicated in neurodegeneration associated with Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and HIV-associated neurocognitive disorders (HAND) including protein aggregation, oxidative stress, inflammation, excitotoxicity, and disruption of RNA-binding protein function. For this reason, association between some of these processes has been examined and is partially understood. However, to our knowledge, the effect of excitotoxicity on RNA-protein binding alterations has not been thoroughly analyzed. To this end, we aimed to identify global changes in RNA-protein interactions and RNA secondary structure in an excitotoxicity *in vitro* model using rat primary cortical neurons. We have applied the novel protein interaction profile sequencing (PIP-seq) method to identify sites within an RNA molecule that are bound by an RNA-binding protein (RBP), termed protein protected sites (PPS). Our data show relevant shifts in RNA secondary structure between untreated- and NMDA-treated neurons near the start and stop codons of protein coding genes. Additionally, we identify sets of genes that have PPSs specifically in the control condition, after NMDA treatment or in both conditions but at different intragenic regions. Interestingly, GO analysis of these gene sets shows that transcripts that are protein-bound specifically in NMDA-treated samples are associated with several neurodegenerative disorders. Finally, we also detect sequence motifs enriched in NMDA-specific PPSs and use them to identify NMDA-dependent RBPs, which might shed light on RBPs post-transcriptional role in excitotoxic stress. In sum, we have globally examined RNA secondary structure and the RBP-ome of primary cortical neurons in a simple excitotoxic model, providing insights into the potential role RBPs and secondary structure changes in neurological diseases associated with excitotoxicity.

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Poster

P298. Mechanisms of Neurotoxicity II

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"Investissements d'Avenir" ANR-10-IAIHU-06, NeurATRIS

Title: Impact of endocrine disruptors on myelination and remyelination

Authors: *B. ZALC[1], P. JUBIN[2], E. M. MARTIN[3], M.-S. AIGROT[3], B. DEMENEIX[4], S. REMAUD[4]; [1]Sorbonne Université; Inserm, CNRS, AP-HP, ICM, Paris Cedex 13, France; [2]Sorbonne Université, Paris, France ; Inst. du Cerveau- Paris Brain Inst. – ICM, Paris, France ; Inserm, Paris, France ; CNRS, Paris, France ; AP-HP, Hôpital de la Pitié-Salpêtrière, Paris, France, paris, France; [3]Sorbonne University; Inst. du Cerveau- Paris Brain Inst. – ICM; Inserm; CNRS; AP-HP, Hôpital de la Pitié-Salpêtrière, Paris, France, Paris, France; [4]Muséum Natl. d'Histoire Naturelle (MNHN), Lab. PhyMa.2 CNRS UMR 7221, 75005 Paris, France, Paris, France

Abstract: Over the past 30 years an unexplained increased incidence in multiple sclerosis (MS) is observed in developed countries, suspected to be exacerbated by environmental factors. We questioned whether exposure to endocrine disrupting chemicals (EDC) may interfere with the process of myelin formation and remyelination after a demyelination insult. We analysed consequences of some EDC exposure notably flame retardant or fluorosurfactant such as Perfluorooctanoic acid and Perfluorooctane Sulfonate (PFOS) (at dose ranging between 10^{-5} to 10^{-11} M) on myelination and remyelination. To this end, we combined *ex vivo* and *in vivo* approaches to study cellular and behavioral effects of EDC using two models, mouse cerebellar explants and the optic nerve of *Xenopus laevis.* First, we exposed cerebellar slices derived from P4 *plp:GFP* transgenic mouse (before the onset of myelination) to PFOA and PFOS. At P8, we observed that exposure to PFOS (10^{-8} M) significantly delayed myelination. Second, we analyzed consequences of EDC exposure on remyelination using the transgenic *Xenopus laevis* model (*MBP-GFP-NTR*) of conditional demyelination that allow us to monitor behavioural effects. In this model, introduction of metronidazole (MTZ) leads to mature oligodendrocyte cell death and robust demyelination and withdrawal of MTZ leads to spontaneous remyelination. Extend of demyelination and remyelination was assayed by counting the number of GFP+ oligodendrocytes per optic nerve. We reasoned that demyelination should translate into loss of sensori-motor functions. To challenge this hypothesis, we measured speed and distance traveled before and after demyelination and during the ongoing spontaneous remyelination. In addition, to test the functional consequence of demyelination and repair of the optic tract of *MBP-GFP-NTR* transgenic *Xenopus* tadpole we adapted a visual avoidance paradigm, based on a virtual collision test. We evaluated how all these parameters are perturbated when tadpoles are exposed to EDC. Addition of PFOS in the swimming water during the recovery period was one of the strongest inhibitor of remyelination. The dose-response of PFOS toxicity to inhibit remyelination showed an inverted bell-shaped curve with a maximum effect at concentrations in the nanomolar range, typical of some EDC toxic effects reported in the literature. Our data illustrate the toxicity of some EDC on myelination and myelin regeneration evaluated histologically in two models of vertebrates and their behavioural consequences. Our finding questions a possible correlation between the dramatic increase in the number of EDC in our daily life, with the reported increase in the incidence of MS

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Poster

P298. Mechanisms of Neurotoxicity II

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS R01 079172
NINDS T32 041218
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Title: Cholinergic neurons of the basal forebrain are lost through a $p75^{NTR}$-mediated process in an animal model of HIV-associated neurocognitive disorder.

Authors: *A. SPEIDELL, I. MOCCHETTI;
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Abstract: Human immunodeficiency virus type 1 (HIV) positive individuals exhibit an array of neurological and neuropsychiatric symptoms, termed HIV-associated neurocognitive disorders (HAND). These symptoms continue to affect nearly one in two people living with HIV (PLH) even in the post-combined antiretroviral therapy era. HAND may be partially explained by the persistent neurotoxic effects of viral proteins on neural cells. Our lab previously demonstrated that the HIV-1 gp120 envelope protein alters neuronal proconvertase expression to increase proneurotrophin abundance in an age-dependent manner. This neurotoxic outcome is transduced through the pro-apoptotic proneurotrophin receptor $p75^{NTR}$. We hypothesized that basal forebrain cholinergic neurons (BFCNs), which highly express $p75^{NTR}$, are uniquely susceptible to gp120-driven neuronal apoptosis through this receptor. To examine the selective vulnerability of BFCNs to gp120 in vivo, we crossbred gp120 transgenic (tg) and $p75^{NTR-/-}$ mouse colonies to obtain wild type (wt), gp120tg, $p75^{NTR+/-}$ and $p75^{NTR+/-}$gp120tg mice. We then assessed behavioral and histological endpoints in separate 3- and 12-month old (mo) cohorts. Our data suggest that only 12mo gp120tg mice are impaired on a task of extinction of conditioned fear, a complex cognitive behavior subserved by BFCN innervation of the hippocampus and prefrontal cortex. Representative images of BFCNs from our experimental groups also indicate a reduction of neurite complexity and suggest a decrease in the population of choline acetyltransferase-positive cells in the forebrain of 12mo gp120tg. Our results show that loss of BFCNs in HAND individuals may underpin the observed collection of neurological impairments in PLH. Targeting $p75^{NTR}$ through emerging small molecule inhibitors may therefore serve as a viable strategy within adjunct therapies for HAND individuals.

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Poster

P328. Therapeutic Approaches for Ischemic Stroke I

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Brain Aneurysm Foundation
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Title: Surface modification of flow diverting stents for improved cerebral aneurysm repair

Authors: *J. W. THOMPSON, D. SHEINBERG, G. CORSALETTI, R. M. STARKE;
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Abstract: Cerebral aneurysm (CA) rupture produces a devastating form of stroke resulting in high rates of mortality and morbidity. As a result, a large number of CA patients are treated prior to rupturing by either open surgical or endovascular techniques. Detachable coils have been the mainstay of endovascular CA intervention. However, the use of flow diverting stents in endovascular CA treatment has become an increasing popular treatment modality since their introduction in the mid-2000s. Flow diverting stents (a braided cylindrical mesh) work by restoring the original, natural path of blood flow in the vessel, across the aneurysm neck, while providing permeant long-term occlusion of the aneurysm. However, this process requires stent endothelialization across the aneurysm neck, which can take months, resulting in increased risk of aneurysm rupture and treatment failure. The main objective of this study was to determine if a surface modification of flow diverting stents could increase endothelial cell (EC) attachment, proliferation, and stent coverage. In this study Pipeline Flex Embolization flow diverting stents were incubated overnight with either PBS or gelatin and then exposed to isolated human microvessel EC for three hours. EC attachment and proliferation were determined at various time points. Immediately following cell incubation, we found a significant increase ($p< 0.05$, fold increase) in EC attachment on gelatin (6.3 ± 2.1) surface modified stents compared to unmodified control stents. This increase in EC was maintained 5 days (gelatin 9.3 ± 2.5, fold of control) following cell incubation but gradually decreased becoming non-significant by day 17. We also observed a significant increase ($p < 0.05$, fold of control) in EC migration onto (1.8 ± 0.2) and from (1.5 ± 0.033) gelatin surface modified stents compared to unmodified controls. Since CA healing requires complete stent endothelization, we next determined the temporal rate of endothelial stent coverage. Following cell incubation, we found that 20% of surface modified stents were coated by EC at day 5 compared to just 2% in unmodified stents. This difference in cell coverage remained significant ($p<0.05$) with surface modified stents being completely covered by 2 weeks while unmodified stents were only 50% covered. There was no significant difference in cell death on modified versus unmodified stents in any of our studies. This study demonstrates that gelatin, a biocompatible and non-thrombogenic FDA approved product can enhance endothelialization of flow diverting stents which may lead to increased rates of aneurysm occlusion thereby reducing the risk of posttreatment rupture and treatment failure.

Disclosures: J.W. Thompson: None. **D. Sheinberg:** None. **G. Corsaletti:** None. **R.M. Starke:** None.

Poster

P328. Therapeutic Approaches for Ischemic Stroke I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P328.02

Topic: C.08. Ischemia

Support: NIH DSPAN Grant: 5K00NS105220-04
NIH: Medical University of South Carolina COBRE in Stroke Recovery Research Pilot Project Program

Title: The Impact of Intranasal Administration of BDNF on Functional Recovery in aNeonatal Mouse Model of Hypoxic Ischemia

Authors: *S.-K. SIMS[1], C. ROBINSON[1], T. LOWRY[1], L. MCGONEGAL[2], M. SADDOW[2];
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Abstract: A neonatal stroke is a medical condition that occurs when an infant's blood supply is disturbed within the first 28 days of life. One of the causes of neonatal stroke is hypoxia, an event when oxygen deprivation causes the brain to panic. While treatments for adult and aging ischemic strokes include anticoagulants, and motor and cognitive rehabilitation, neonatal ischemic treatment is limited to more supportive care such as hyperthermia and hyperbaric oxygen therapy. Previous studies in adult stroke have reported that administering brain derived neurotrophic factor (BDNF) in the acute post-ischemic period reduces cell death and infarct volume. Furthermore, pharmacologically enhancing downstream BDNF signaling pathways/targets such as cAMP response-element-binding protein facilitates cortical reorganization and functional recovery after focal ischemia in rats. Hence, while BDNF may be a useful therapeutic target for adult ischemic strokes, BDNF as a potential therapy following neonatal stroke has not been explored. Our overall hypothesis is that intranasal BDNF will improve functional recovery including overall brain health and development following neonatal stroke. We explored the benefit of intranasal BDNF treatment on functional recovery in a neonatal P7 hypoxic mouse model. For our model of hypoxic ischemic, a ligation of the right carotid artery was induced which is followed by a two-hour exposure to an 8% oxygen/ 92% nitrogen in an enclosed chamber. Pups were subjected to a 2 h hypothermia in a temperature-controlled chamber as a standard of care. Mice received BDNF intranasal infusions while awake. A solution of recombinant human BDNF (Harlan Laboratories .1uM in saline) was administered with a Gilson pipette, 3uL at the same time each day for 7 days into each nasal cavity. The objective of these studies is to address these gaps in knowledge and evaluate the role and therapeutic potential of BDNF in neonatal stroke recovery. Preliminary results suggest a differential impact of intranasal BDNF on pro and mature BDNF in cortical and hippocampal brain regions, which correlate with cognitive and motor outcomes. Our results suggest that higher levels of mature BDNF are predictive of better improvements at day 28 on cognitive and motor assessments.

Disclosures: S. Sims: None. **C. Robinson:** None. **T. Lowry:** None. **L. McGonegal:** None. **M. Saddow:** None.

Poster

P328. Therapeutic Approaches for Ischemic Stroke I

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Program #/Poster #: P328.03

Topic: C.08. Ischemia

Support: NIH, NINDS grant R01NS104117
NIH, NINDS grant R01109221
Brazilian CAPES (88881.311939/2018-01)

Title: Protecting against experimental ischemic stroke with pro-homeostatic docosanoids

Authors: *N. BAZAN[1], M. M. REID[1], A. OBENAUS[2], P. K. MUKHERJEE[1], L. KHOUTOROVA[1], C. R. ROQUE[3], N. N. DEASI[1], T. SIMONS[1], J. JI[1], N. PETASIS[4], R. B. ORIA[3], L. BELAYEV[1]; [1]Neurosci. Ctr. of Excellence, Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA; [2]Univ. of California Irvine, Irvine, CA; [3]Morphology, Federal Univ. of Ceara, Fortaleza, Brazil; [4]Chem., USC, Los Angeles, CA

Abstract: Ischemic stroke triggers lipid peroxidation, uncompensated oxidative stress, and neuronal injury. This study focuses on the neuroprotective bioactivity of docosanoid (DOC) mediators: Neuroprotectin D1 (NPD1), Resolvin D1 (RvD1), and their combination (NPD1+RvD1) against experimental ischemic stroke. These lipid mediators are biosynthesized "on-demand" in response to stroke onset to resolve neuroinflammation and restore homeostasis. This study investigated the dose-response and therapeutic window in a model of focal cerebral ischemia. Physiologically-controlled male Sprague-Dawley rats received 2h of middle cerebral artery occlusion (MCAo) by intraluminal suture. The behavior was evaluated on days 1, 2, 3, and 7, followed by an *ex vivo* MRI of the brains on day 7. In dose-response study, rats were treated with NPD1 (111, 222, and 333µg/kg), RvD1 (111, 222, and 333µg/kg), NPD1 + RvD1 or vehicle (n=4-5 per group). All treatments were administered IV at 3h after the onset of MCAo. In the therapeutic window study, vehicle, NPD1 (222 µg/kg), RvD1 (222 µg/kg), NPD1+RvD1 were administered IV at 3, 4, 5, and 6 h after onset of MCAo. Physiological variables were stable and showed no significant differences among groups. Treatments with NPD1 (111, 222, and 333µg/kg) alone greatly improved neurological scores (by 32, 28, 35%) and RvD1 (111, 222, and 333µg/kg) alone (by 35, 44, 31%) compared to the vehicle group. The neuroprotective effect was enhanced using the NPD1+ RvD1, which improved total neurological scores on days 1, 2, 3, and 7 by 25, 28, 28, 40% compared to the vehicle group. Ischemic core, penumbra, and total lesion volumes (computed from T2WI) were reduced with NPD1+RvD1 by 69, 70, and 67% compared to the vehicle. Therapeutic window: treatments with NPD1 and RvD1 alone when administered at 3h improved behavior on day 7 by 35%. Combinatory NPD1+RvD1 treatment improved behavior when administered at 3, 4, 5, and 6 h by 56%, 23%, 26%, and 28%, respectively, compared to vehicle. We have shown that treatment with NPD1, RvD1 alone provides high-grade neuroprotection in the MCAo model. Combination therapy with NPD1 and RvD1 is more effective than the single therapy, when administered up to 6 h focal cerebral ischemia in rats. These treatments might provide the basis for future therapeutics for patients suffering from ischemic stroke. This study was supported by NIH, NINDS grant R01NS104117, R01109221 (NGB and LB), and Brazilian CAPES (88881.311939/2018-01) (CRR)

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Poster

P328. Therapeutic Approaches for Ischemic Stroke I

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Program #/Poster #: P328.04

Topic: C.08. Ischemia

Title: Focal stimulation of movement related cortical potentials in mice using a novel TMS circuit design

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Abstract: Activity patterns exist at several levels in the brain and exhibit distinct temporal and spatial characteristics. Circuit level perturbations to rhythmic patterns are characteristics of altered arousal states and behaviors. Using pulsed electromagnetic fields, transcranial magnetic stimulation (TMS) alters states of cortical excitability and motor output. The changes in brain activity caused by TMS can be measured and quantified using electroencephalography (EEG). Developing a focally stimulating TMS model in mice is a multivariate problem requiring proper consideration of both circuit design and coil construction. A high voltage, fast switching, insulated-gate bipolar transistor (IGBT) pulse generator delivering large current pulses was developed for the generation of focal electromagnetic fields. To compare the validity of the presented design with current methods, stimulating pulses were delivered to mice using a butterfly coil attached to a standard TMS system compared to a compact coil attached to the novel circuit. Changes in cortical electrical potentials were recorded at two cortical surface electrode sites using electroencephalography (EEG). Butterfly coil stimulation resulted in movement related cortical potentials (MRCPs) at both EEG recording sites while stimulation with the compact coil elicited MRCPs at a single recording site. Furthermore, the compact coil evoked MRCPs similar in amplitude to MRCPs evoked by the butterfly coil. This novel circuit design enables exemplar stimulation of focal and robust MRCPs. The potential for focal stimulation in murine models will provide valuable insight into other neurological disorders including stroke.

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Poster

P328. Therapeutic Approaches for Ischemic Stroke I

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Program #/Poster #: P328.05

Topic: C.08. Ischemia

Support: NINDS Grant U01NS103882

Title: Systematic assessment of PAMAM dendrimer-conjugated N-acetyl cysteine (D-NAC) on long-term outcomes in both male and female mice after severe hypoxia-ischemic encephalopathy (HIE).

Authors: *V. TURNBILL[1], E. S. KHOURY[2], D. ASAFU-ADJAYE[1], B. SOLLINGER[1], T. TREINEN[1], N. RASTOGI[1], D. FLOCK[1], A. SHARMA[3], R. M. KANNAN[3], S. KANNAN[2], F. J. NORTHINGTON[1];

[1]Pediatrics, [2]Anesthesiol. and Critical Care Med., [3]Ctr. for Nanomedicine, Wilmer Eye Inst., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Neonatal hypoxia-ischemic encephalopathy (HIE) causes lifelong disability often in the form of cerebral palsy (CP); including motor, memory, and executive functioning deficits; and is difficult to treat even with therapeutic hypothermia. Challenges to effective treatment include (1) sex-related variations in disease mechanism and outcome and (2) a lack of antioxidants and anti-inflammatory drugs with adequate bioavailability and brain penetration. Previous studies in a rabbit model of CP have shown that dendrimer-conjugated n-acetyl cysteine (D-NAC), which uses PAMAM dendrimers as a drug delivery device, can penetrate the blood-brain barrier and selectively target the activated microglia and mitigate neuroinflammation and subsequently reduce neural injury and neurobehavioral deficits. Here we investigate the impact of D-NAC on a murine model of HIE with the goal of further elucidating long-term effects of D-NAC on phenotype and neuropathology in both sexes. At p10, HI was induced in C57BL6 mice in vehicle and D-NAC treatment groups using the Rice-Vannucci model adapted for mice; sham mice were given only anesthesia. D-NAC (10 mg/kg on a NAC basis) or vehicle was administered intraperitoneally on p10 after HI and then twice weekly from p14 to p46. Reflex testing occurred from p11 to p21; behavior tests began at p30 and included y-maze, open field, social interaction, and fear learning, memory, and extinction. Mice were perfused at p50 with 4% paraformaldehyde, postfixed overnight, and frozen. Striatal, hippocampal, and cortical regions were measured in 50μm, cresyl violet stained tissue sections. Our results demonstrate positive long-term effects of D-NAC treatment in this model of HI. Mortality was minimal; however, sex differences in mortality distribution were observed. D-NAC eliminated mortality only in female HI mice. Reflex testing revealed retention of cliff aversion and negative geotaxis reflexes in females after HI, which D-NAC remediated in the case of cliff aversion. Only D-NAC-treated males showed negative geotaxis reflex retention. Open field testing indicated no profound deficits in locomotion or exploratory behavior as a consequence of HI at p31. Y-maze testing revealed short-term memory deficits in both male and female HI mice that is remediated with D-NAC. In long-term memory testing after fear conditioning, female HI mice showed decreased memory of the cue which is rescued with D-NAC treatment. Taken together, these data indicate that, in addition to sex differences in pathology, response to treatment may vary by sex. Future work will continue to understand and optimize treatment strategies for HIE in both males and females.

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Poster

P328. Therapeutic Approaches for Ischemic Stroke I

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Program #/Poster #: P328.06

Topic: C.08. Ischemia

Support: NIH, NINDS grant R01NS104117
NIH, NINDS grant R01109221

Title: Intranasal delivery of novel lipid mediator precursors provides neuroprotection after experimental ischemic stroke

Authors: *M. M. REID[1], L. KHOUTOROVA[1], B. K. PARK[1], N. N. DESAI[1], P. K. MUKHERJEE[1], K. SHELVIN[1], B. JUN[1], A. OBENAUS[2], L. BELAYEV[1], N. G. BAZAN[1];
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Abstract: Stroke is the sixth leading cause of death and permanent disability in the United States. Following ischemic stroke, disruptions in neuroinflammatory signaling, the neurovascular unit, synaptic activity, and subsequent cell death and tissue damage occur. Current therapeutic options are limited and do not address the associated immune response and acute inflammation that occur at the site of cerebral ischemia. ELOVL4 (elongation of very long-chain fatty acids-4), an enzyme selectively located in neurons, catalyzes the biosynthesis of VLC-PUFAs (≥C28) from 26:6 fatty acids derived from docosahexaenoic acid (DHA,22:6,n-3) or eicosapentaenoic acid (EPA,20:5,n-3). We have previously shown that lipoxygenation of these VLC-PUFAs leads to the synthesis of a class of novel lipid mediators, termed elovanoids (ELVs). ELVs, when administered IV, reduce infarct volume and promote cell survival after 2h of MCAo in rats. This study aimed to investigate the neuroprotective efficacy of VLC-PUFA ELV precursors when administered intranasally. Male Sprague-Dawley rats received 2h of the middle cerebral artery occlusion (MCAo). Treatment with C-32:6, C-34:6 (1µg/µl, 20 µg per rat) or vehicle (saline + ethanol) was administered at 1, 24, and 48h after onset of MCAo. Behavior was evaluated using a composite neurological battery; a grading scale of 0-12 was employed (normal score=0, maximal deficit=12). Behavior testing was performed on days 1, 2, 3, and 7 followed by *ex vivo* MRI for lesion volumes and edema (T2WI). Immunohistochemistry was performed on day 7. No adverse physiologic effects were observed in any treatment groups. C-32:6 and C-34:6 improved behavioral function on days 3 by (41% and 20%) and 7 (45% and 24%), respectively. Total, cortical and subcortical infarct areas and volumes were dramatically reduced by treatments with C-32:6 (by 73% and 74%, 84%) and C-34:6 (by 85%, 58%, and 61%) compared to vehicle. Total lesion volumes computed from T2WI were reduced with C-32:6, C-34:6 (by 87% and 61%), respectively, compared to the vehicle group on day 7. We conclude that intranasal administration of VLC-PUFA precursors offers superior neuroprotection improving behavior and histopathological outcomes and reducing infarct areas and volumes. This provides a rationale to explore further ELVs and their precursors as a potential therapeutic for experimental ischemic stroke.
This study was supported by NIH, NINDS grant R01NS104117 and R01109221 (NGB and LB).

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Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P336.01

Topic: C.09.Stroke

Title: Novel protein inhibitors of nuclear factor kappa B as therapeutics for neuroinflammation following ischemic stroke

Authors: *J. A. HOWELL[1], E. PERKINS[2], G. L. BIDWELL, III[3];
[1]Program in Neurosci., [2]Neurosurg., [3]Neurol., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Strokes are the 5th leading cause of death in the U.S., and ~87% of strokes are ischemic, meaning that they are caused by occlusion of a cerebral artery or its branches. This results in tissue infarction at regions supplied by the occluded vessel, and it also activates inflammatory cascades that worsen damage by affecting infarct size and behavioral outcome. Therefore, drugs targeting the inflammatory response following ischemic stroke may be highly beneficial in reducing infarct size and improving neurological outcomes. We have designed a novel inhibitor of the nuclear factor kappa B cascade, a central pathway of inflammation that is activated by many cytokines and signals that are elevated following ischemic stroke. Our inhibitor is bound to protein drug carrier elastin like polypeptide (ELP), which is based on a sequence from human elastin and can increase plasma half-life. We hypothesize that ELPs can be used to deliver our inhibitory peptide SynB1-ELP-p50i to the damaged region after ischemic stroke, reduce inflammation, and spare brain tissue. To begin, BV2 microglia were treated with 10 μM of rhodamine labeled SynB1-ELP-p50i for 24 hours and imaged with confocal microscopy to determine if the protein was able to enter the cells. We found that SynB1-ELP-p50i enters the cells and is primarily localized to the cytoplasm. To assess efficacy of SynB1-ELP-p50i *in vitro*, we treated BV2 microglia and cortical organotypic slices from Brainbow mouse pups with 50 μM of SynB1-ELP-p50i before exposing them to oxygen and glucose deprivation (OGD). After OGD, media was collected and run on a cytokine array to assess any reduction in production of inflammatory signals during OGD. Preliminary data shows that treatment with SynB1-ELP-p50i resulted in a reduction of inflammatory signals following OGD exposure, with specific reductions in TNF-α, IL-1α, IL-1β, among others. Next, biodistribution of SynB1-ELP-p50i within the brain was assessed using the middle cerebral artery occlusion (MCAO) model of ischemic stroke in Wistar rats. Two routes of administration (intravenous (IV, femoral vein) and intraarterial (IA, carotid catheter)) were compared using a dose of 50 mg/kg rhodamine labeled SynB1-ELP-p50i. SynB1-ELP-p50i accumulated in the ischemic hemisphere at levels 3 fold higher than in the contralateral hemisphere following MCAO (two-way ANOVA $F(1,12) = 15.58$; Sidak's $p < 0.05$). However, there was no difference in intrabrain deposition between IV and IA routes. Future studies will assess effects of SynB1-ELP-p50i treatment on infarct size, inflammatory cytokine production *in vivo*, and neurological deficits following MCAO in Wistar and spontaneously hypertensive rats.

Disclosures: J.A. Howell: None. **E. Perkins:** None. **G.L. Bidwell:** None.

Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

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Topic: C.09.Stroke

Support: NIH Grant R01 NS109459

Title: Ascorbate Mediates Epigenetic Reprogramming of Neuroprotective Genes and Prevents Brain Damage After Stroke

Authors: *K. C. MORRIS-BLANCO[1], A. CHOKKALLA[2], T. KIM[3], S. BHATULA[4], M. J. BERTOGLIAT[4], A. B. GAILLARD[4], R. VEMUGANTI[5];
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Abstract: Vitamin C is an antioxidant that has recently been identified as an epigenetic regulator by activating ten eleven translocases (TETs), enzymes that produce the DNA hydroxymethylcytosine (5hmC) mark associated with increased gene expression. In the current study we investigated 1) whether Vitamin C may be involved in promoting neuroprotection through epigenetic modulation of 5hmC, 2) sex-specific differences in outcome following ascorbate treatment and 3) the therapeutic potential of Vitamin C treatment in stroke-related comorbidities in adult mice. Post-stroke treatment with ascorbate (reduced form of Vitamin C), but not dehydroascorbate (oxidized form of Vitamin C), increased TET3 activity, 5hmC levels and reduced infarct following focal ischemia. Hydroxymethylation DNA immunoprecipitation sequencing (hMeDIP-seq) showed that ascorbate increased 5hmC across the genome and in several stroke pathophysiology-related genes. Further analysis showed that ascorbate enhanced the expression of protective genes and prevented oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation up to 3 days of reperfusion in neurons of the peri-infarct cortex. Ascorbate further promoted motor function recovery up to 7 days of reperfusion, and enhanced cognitive function up to 25 days of reperfusion in a TET3-dependent manner. Post-stroke ascorbate treatment also reduced infarct and improved motor function recovery in aged, hypertensive and diabetic male and female mice. Delayed ascorbate treatment at 6h of reperfusion was less effective, but still reduced secondary brain damage and motor impairments up to 7 days of reperfusion. Collectively, this study shows that post-stroke treatment of Vitamin C protects the brain through epigenetic reprogramming and may function as a robust therapeutic against stroke injury.

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Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

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Topic: C.09.Stroke

Support: JSPS KAKENHI Grant JP17H02117
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Title: Treadmill exercise concurrent with pharmacological inhibition of alpha5-$GABA_A$ receptor improves motor function and enhances spinal cord plasticity after intracerebral hemorrhage in rats

Authors: *T. INOUE[1,3], Y. TAKAMATSU[2], T. NISHIO[1], K. SOMA[1], M. OKAMURA[1], H. TOHYAMA[2], H. MAEJIMA[2];
[1]Grad. Sch. of Hlth. Sci., [2]Dept. of Rehabil. Science, Fac. of Hlth. Sci., Hokkaido Univ., Sapporo, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Intracerebral hemorrhage (ICH) is a subtype of stroke that causes severe motor deficits. Rehabilitation, including therapeutic exercise, is an effective approach for improving motor deficits after stroke. Accumulating evidence indicates that excessive GABA-mediated tonic inhibition, which is primarily induced by extrasynaptic α5 subunit-containing $GABA_A$ receptors (α5$GABA_A$R), is an obstruction in post-stroke recovery. Although it has been shown that α5$GABA_A$R inhibitor promotes motor function recovery after ischemic stroke, no study has tested it in an ICH model. Interestingly, recent findings show that rehabilitation combined with pharmacotherapy enhances post-stroke recovery more effectively than individual treatments. Therefore, we examined the synergistic effect of treadmill exercise and pharmacotherapy to specifically inhibit α5$GABA_A$R on motor function recovery after ICH. Nine-week-old male Wistar rats were divided into five groups (n = 8 per group): 1) a sham group, 2) an ICH group, 3) an ICH treated with exercise group, 4) an ICH treated with α5$GABA_A$R inhibitor group, and 5) an ICH co-treated with exercise and α5$GABA_A$R inhibitor group. ICH was induced by the injection of collagenase in the left striatum near the internal capsule (AP: -2.0 mm, ML: 3.7 mm, DV: -6.0 mm). Intraperitoneal administration of α5$GABA_A$R inhibitor (0.5 mg/kg, L-655,708) and treadmill exercise (11 m/min for 30 min/day) were initiated 1 week after the ICH surgery and were performed for 3 weeks. Forelimb motor function was evaluated by the tape removal task. All study procedures were approved by the ethics committee for animal research of Hokkaido University in Japan and conducted according to the guidelines. While partial recovery was induced by each individual treatment of treadmill exercise or L-655,708 administration, combined treatment of these significantly promoted motor function recovery after ICH. L-655,708 administration increased brain-derived neurotrophic factor expression in the cortex and GAP-43 expression as an axonal growth marker in the spinal cord. Furthermore, combined treatment enhanced following expressions in the spinal cord: synaptophysin as a synaptic marker and Nogo-A as an axonal growth inhibitor. The present study is the first to provide a rationale that combined treatment of therapeutic exercise and α5$GABA_A$R inhibitor promotes motor recovery after ICH more effectively than individual treatments. This underlying mechanism could involve both growth and inhibitory modification in remote areas from lesion sites.

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Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

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Program #/Poster #: P336.04

Topic: C.09.Stroke

Support: NIH Grant NS074895
Discovery Foundation

Title: Intraperitoneal IGF1 treatment modulates the impact of ischemic stroke in reproductively senescent female rats by repairing the gut

Authors: *Y. EL-HAKIM[1], K. MANI[1], S. PANDEY[2], A. ELDOUH[1], F. SOHRABJI[3];
[1]Texas A&M Hlth. Sci. Ctr., Bryan, TX; [2]Texas A&M, Bryan, TX; [3]Neurosci. and Exp Therapeut., Texas A and M Univ. Syst., Bryan, TX

Abstract: Our previous studies have shown that reproductively senescent (RS) female rats, who have lower circulating levels of the peptide hormone Insulin-like Growth Factor (IGF-1), display worse outcomes after a stroke event than young adult female rats. ICV administration of IGF-1, decreases infarct volume, improves sensory motor performance, and reduces cytokine levels in the ischemic hemisphere of RS females as compared to vehicle-treated controls. Yet, icv IGF1 administration failed to attenuate cognitive decline and depressive behaviors in long-term stroke outcomes. In view of the evidence that stroke induces gut dysbiosis, and that gut dysfunction is implicated in depressive and cognitive behaviors, we hypothesize that unlike icv administration of IGF-1, which is restricted to the brain, systemic i.p. administration of IGF1 would repair the gut, attenuate peripheral cytokine levels and improve long-term behavior outcomes. To test this, acyclic middle-aged Sprague Dawley female rats (9-11 mos) were subjected to endothelin-1 induced middle cerebral artery occlusion (MCAo) or sham operation. Animals received IGF1 via i.p. injections 4h post MCAo and 24 h post MCAo, or icv infusions, while controls received vehicle. Sensory motor tests, blood and gut samples were acquired pre and post MCAo. Animals were terminated either in the acute phase (2d) or chronic phase (20d). The latter group was also subject to tests of cognition and depressive-like behavior.In contrast to icv treatment, i.p.-IGF-1 did not reduce infarct volume or acute sensory motor impairment but significantly attenuated circulating levels of TNFα and IL12p70. IP-IGF-1 significantly attenuated post stroke gut dysmorphology, by preserving villus:crypt ratio and expression of tight junction proteins ZO1 and claudin-2. In addition, i.p. IGF1 treatment attenuated the reduction of social interaction and novel object preference post MCAo. Since long term disability after stroke is correlated with elevated levels of peripheral cytokines, our data suggest that systemic IGF1 may be a better therapeutic option for long term cognitive and depressive behaviors after stroke.

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Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P336.05

Topic: C.09.Stroke

Support: Department of Neurological Surgery, Univ. of Wisconsin-Madison

Title: Tenascin-c inhibition prevents post-stroke neuroinflammation

Authors: *B. CHELLUBOINA, A. CHOKKALLA, S. L. MEHTA, S. BATHULA, J. PARK, R. VEMUGANTI;
Univ. of Wisconsin, Madison, WI

Abstract: The role of tenascin-C (TNC) in post-ischemic inflammation is not known despite its pathological role in CNS diseases. TNC upregulated as early as 3h of reperfusion after 1h of transient middle cerebral artery occlusion (MCAO). We presently investigated the effect of TNC knockdown on post-stroke brain damage and its putative mechanism of action in adult mice of both sexes. Male and female C57BL/6 mice were subjected to transient MCAO and injected (i.v.) with either TNC siRNA or a negative (non-targeting) siRNA at 5 min after reperfusion. Motor function (beam walk and rotarod tests) was assessed between days 1 and 14 of reperfusion. Infarct volume (T2-MRI), BBB damage (T1-MRI with contrast), and inflammatory markers were measured at 3 days of reperfusion. The TNC siRNA treated cohort showed significantly curtailed post-stroke TNC protein expression, motor dysfunction, infarction, BBB damage, and inflammation compared to the sex-matched negative siRNA treated cohort. TNC inhibition significantly curtailed neutrophil infiltration, post-stroke neuroinflammation and reduced the post-stroke mRNA expression of the inflammatory molecules such as IL-1β, IL-6, MCP-1, TNF-α, and TNF-related apoptosis-inducing ligand. These results demonstrate that the induction of TNC during the acute period after stroke mediates post-ischemic inflammation and secondary brain damage independent of sex.

Disclosures: B. Chelluboina: None. **A. Chokkalla:** None. **S.L. Mehta:** None. **S. Bathula:** None. **J. Park:** None. **R. Vemuganti:** None.

Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P336.06

Topic: C.09.Stroke

Support: American Heart Association Career Development Award 20CDA35310828

Title: The effects of NLY01, a GLP1R agonist, on neuroinflammation, infarct size, and functional recovery in mouse models of ischemic stroke

Authors: *K. PRESCOTT, J. T. HOLSTEN, R. L. BRIMBERRY, T. C. PETERSON;
Univ. of North Carolina Wilmington, Wilmington, NC

Abstract: In the United States, 2.7% of all adults have had a stroke. Using recombinant tissue plasminogen activator to break up the blood clot is the most common treatment for ischemic stroke, but it can only be used within 4 hours of stroke onset, so it is only effective in less than 3% of the population. Recent research into stroke outcomes has examined the beneficial effects of reducing neuroinflammation, which could potentially be accomplished by reducing maladaptive astrocyte reactivity. One way to reduce neurotoxic reactive astrocytes is by reducing the pro-inflammatory cytokines TNF, IL-1α, and C1q released by microglia after stroke. NLY01 is a glycogen-like peptide-1 receptor (GLP1R) agonist that has been shown to cross the blood-brain barrier and is capable of inhibiting microglia from releasing these

cytokines which reduces neurotoxic astrocytes. We hypothesize that NLY01 will reduce microglial activation, astrocyte activation, and infarct volume, as well as decrease behavioral deficits after an ischemic stroke. To examine how NLY01 would affect the neuroinflammatory response and reduce neurotoxic astrocytes following ischemic stroke, a distal medial cerebral artery occlusion (dMCAO) was performed on female C57BL/6J mice. NLY01 was administered 4 hours after surgery using retro orbital (RO) injection and every 48 hours for 7 days using an intraparietal (IP) injection. They were administered with either 0 mg/kg (n=12), 1 mg/kg (n=11), 3 mg/kg (n=11), or 15 mg/kg (n=7) of NLY01 following stroke, and the brain was perfused/extracted 7 days after injury. To examine behavioral deficits after NLY01, a photothrombotic stroke was induced over the motor cortex in female C57BL/6J mice and they were administered with either 0 mg/kg (n=11), 1 mg/kg (n=11), 3 mg/kg (n=11), or 15 mg/kg (n=12) of NLY01. Behavior tasks included grid walk, cylinder task, rotating beam, tapered beam, and grip strength. Brain extraction occurred 30 days after stroke. Infarct size, astrogliosis, and microgliosis are assessed for 7 days and 30 days after stroke. Immunohistochemistry was performed to examine microgliosis (CD68), astrogliosis (GFAP), and infarct size (NeuN). A one-way ANOVA was used for statistical analysis of astrogliosis (p=0.23) and infarct size (p=0.16), with no statistical differences found 7 days after dMCAO surgery. Macrophage differences are still being examined, as are the behavioral tasks. Although the preliminary results indicate that NLY01 does not reduce secondary neuroinflammation, data is still being collected and analyzed to measure its beneficial impact following stroke.

Disclosures: K. Prescott: None. **J.T. Holsten:** None. **R.L. Brimberry:** None. **T.C. Peterson:** None.

Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

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Program #/Poster #: P336.07

Topic: C.09.Stroke

Support: NIH Grant AG042189
AHA postdoc Award ID-831331
NIH F31 F31NS118970-01 A1

Title: Intestinal organoids transplantation: Potential Therapy To Improve Stroke Outcomes

Authors: *K. MANI;
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Abstract: Stroke is ranked as the second leading cause of death worldwide, with about 50% of all stroke patients experiencing a leaky gut, gut hemorrhage and gut epithelium damage. Gut leakiness may increase circulating inflammatory cytokines and other gut products such as endotoxins, which can impair stroke recovery. Here we tested the hypothesis that repairing gut function may improve stroke outcomes. Specifically, we tested whether transplantation of intestinal epithelial stem cells (IESC) after stroke may stimulate repair of gut structures and improve recovery after stroke. Acyclic (reproductive senescent) middle-aged Sprague-Dawley female rats were used for this study and assigned to the following groups: Control (sham), stroke with sham transplant (vehicle), or stroke with IESC transplantation. Rats were

subjected to stereotaxic middle cerebral artery occlusion (MCAo) using Endothelin-1, a chemical vasoconstrictor. Primary IESCs were isolated from young female rats to prepare organoid cultures. Dispersed organoid cells were labeled with PKH67 and injected iv at 4h/24h/48h after stroke. In animals that received PKH67-labelled IESC transplants, transplanted cells were seen in the basal part of the crypt. Behavioral assays and saphenous blood draws were performed pre-stroke and at 2d and 4d after stroke. Trunk blood, brain tissue, and a segment of the small intestine were collected at termination. TTC staining was used to quantify infarct volume. Intestine samples were processed for the histomorphometric analyses and immunohistochemistry to analyze specific markers of gut function (Lgr5+, Wnt3a, ZO-1, Ki67, and Villin). The blood-gut barrier was assessed by measuring serum levels of iFABP, LPS, and Muc-2, which are commonly used surrogate markers of gut permeability. MCAo-induced mortality and infarct volume were significantly reduced in reproductively senescent female rats that received young female IESCs compared to the vehicle group. Sensory-motor performance was similar in sham and transplanted groups but was significantly worse at 2d and 4d after stroke in the vehicle-treated group. Significant deterioration of the gut architecture (blunted or absent villi and irregular crypts) were observed in the non-transplantation group, while transplanted animals displayed improved gut architecture and gut repair, and a reduction of intestinal permeability compared to the vehicle group. Overall, these data show that a novel stem cell population derived from the gut can significantly improve stroke outcomes.

Disclosures: K. Mani: None.

Poster

P336. Pharmacological Approaches to Stroke Therapy in Animal Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P336.08

Topic: C.09.Stroke

Title: Neuropeptide role of α-Melanocyte-stimulating hormone against cerebral ischemia/reperfusion injury in type 1 diabetes

Authors: *R. GOIT[1], A. TAYLOR[2], A. LO[1];
[1]The Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Boston Univ. Sch. of Med., Boston, MA

Abstract: Type 1 diabetic patients have higher risk of stroke than the general population. α-Melanocyte stimulating hormone (α-MSH) is a peptide derived from a precursor polypeptide, proopiomelanocortin. Several studies showed that α-MSH has protective effects against ischemia/reperfusion (I/R) induced organ damages. Therefore, we aimed to find the neuroprotective role of this peptide on I/R induced cerebral damage after experimental stroke associated with hyperglycemia using C57BL/6J $Ins2^{Akita/+}$ mice. I/R injury was induced by blocking the right middle cerebral artery for 2 hours with reperfusion for 2 hours and 22 hours, respectively using the intraluminal method. Animals were treated intraperitoneally with either vehicle or α-MSH at 1 hour after ischemia and 1 hour after reperfusion. α-MSH treated animals has significantly higher survival rate with lower neurological scores. α-MSH significantly decreased relative infarct area, hemorrhage, glial cells activation as well as oxidative and nitrosative stress. Relative intensities of matrix metallopeptidases 9, cyclooxygenase 2 and nuclear factor-κB were

significantly decreased while intensities of protein kinase b (also known as Akt), heme oxygenase (HO) 1, HO-2 and B-cell lymphoma 2 were significantly increased after α-MSH treatment. In addition, gene expressions of monocarboxylate transporter (MCT) 1, MCT-2 and activity-regulated cytoskeleton-associated protein were significantly higher in brain samples treated with α-MSH. Finally, % TUNEL was significantly lower in α-MSH treated brain slices. In conclusion, α-MSH is neuroprotective under hyperglycemic condition against I/R induced brain damage by its anti-inflammatory, anti-oxidative and anti-apoptotic properties. The α-MSH analogues may be potential therapeutic agents against stroke under hyperglycemic condition.

Disclosures: R. Goit: None. **A. Taylor:** None. **A. Lo:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P338.01

Topic: C.09.Stroke

Support: FFG recoveriX-Leg

Title: Lower-limb stroke rehab for chronic patients utilizing brain-computer interface

Authors: W. CHO[1], M. SEBASTIAN-ROMAGOSA[2], F. CAO[3], K. MAYR[1], *C. GUGER[1,2,3]; [1]g.tec medical engineering GmbH, Schiedlberg, Austria; [2]g.tec medical engineering Spain S.L., Barcelona, Spain; [3]g.tec neurotechnology USA, Inc., Albany, NY

Abstract: Conventional rehabilitation regimes have proven to have limited success for chronic stroke patients with severe hemiparesis, however, studies have shown positive rehabilitation effects when neurorehabilitation based on Brain-Computer Interfaces (BCIs) has been applied.
Ten chronic stroke patients with lower-limb hemiparesis were recruited to complete a total of 25 BCI sessions over the course of 2 months (about 3 sessions per week). The patient had to perform a Motor Imagery (MI) task with either the paretic ankle dorsiflexion or the healthy wrist dorsiflexion to receive feedback in the form of an avatar as well as Functional Electrical Stimulation (FES). In order to objectively observe changes in the motor functions, various assessments were conducted before, after and during the 2-month period of BCI training. The main tests were the Timed Up and Go (TUG), the 10-meters walking test (10MWT) and the Range of Motion (ROM) of the ankle dorsiflexion.
The test results show a significant increase in the speed of the TUG by 0.06 m/s, P = 0.002. One out of ten patients could only perform the TUG after all 25 BCI sessions were completed and needed 92.2 seconds to do so. Also, the gait speed of the 10MWT fast velocity was increased by 0.16 m/s (SD = 0.14), which is above the minimally clinically important difference (MCID). Both active and passive ROM assessments increased after rehabilitation training, P =.008 by 8.61° (SD = 6.54), P = 0.002 respectively 8.50° (SD = 7.23).
These results support the proposal to use MI and FES-based non-invasive BCIs as a rehabilitation technique for severely impaired patients with limited mobility to improve their gait even in the chronic

stage after stroke. In order to develop this kind of therapy approach into a new rehab paradigm for stroke patients, the outcomes should be confirmed and validated by bigger studies including more patients.

Disclosures: W. Cho: None. **M. Sebastian-Romagosa:** None. **F. Cao:** None. **K. Mayr:** None. **C. Guger:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

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Program #/Poster #: P338.02

Topic: C.09.Stroke

Support: NFS Award # 1532239
NIH-R01HD062744
NIH-P41EB018783

Title: Visualization of multivariate behavioral data in stroke subjects during robotic rehabilitation therapy for fingers.

Authors: *S. RUEDA[1], J. C. PERRY[2], E. T. WOLBRECHT[2], D. GUPTA[3,4];
[1]Electrical Engin., [2]Mechanical Engin., Univ. of Idaho, Moscow, ID; [3]Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr., Albany, NY; [4]Electrical and Computed Engin., Univ. of Albany, State Univ. of NY, Albany, NY

Abstract: Interpreting multivariate data from impaired subjects presents a challenge in clinical evaluation. In this work, we seek to find common patterns in subjects for stratifying groups with respect to: a) overall impairment and b) response to therapy, in an effort to understand baseline features that can be related to greater gains in specific domains as a result of therapeutic protocols. Multidomain behavioral data from 27 patients with chronic stroke who underwent a month of therapy with the FINGER robot was obtained before and after rehabilitation. With up to 30 descriptors for each subject, the high dimensionality and low number of samples makes trends challenging to see. Observed values were normalized and scale-inverted when necessary, with values near 0 for poor outcomes and near 1 for good outcomes. We propose a data-driven approach that projects the distance structure of the multidimensional points representing each of the patients to a 2D plane, using: a) t-distributed stochastic neighbor embedding (t-SNE) with principal component analysis (PCA), followed by b) clustering with the affinity propagation algorithm which defines the number of clusters from the similarity matrix of the input data. Group averages on metrics are presented as a radar chart. Tests were performed by running the algorithm several times for baseline and inter-session difference (delta) sets with the same parameters and reducing the dimensionality of the input sets by selecting subgroups of similar metrics. Results reveal groups in datasets that share similar behavioral features. The groups found are robust to changes in parameters related to t-SNE and PCA, with the exception of a few subjects that get assigned to nearby clusters for different runs. In single-domain analyses where similar metrics are given to the model, groups are formed based on domain-specific metrics in ascending order. For multidomain analyses, the algorithm shows high sensitivity to groups with meaningful differences for different domains even though there are

important similarities in other domains. The algorithm described here aids the process of visualizing multidomain data from behavioral tests in stroke patients. Baseline data shows groups with shared features in sensorimotor domains that can be related to motor impairment; it also shows that some of the subjects in these groups are more affected by spasticity or depression (which can harm the gains from therapy). When applied to the delta set, groups of subjects emerge with specific gains in domains such as force, finger dexterity, or coordination, and may allow new insights on subject stratification for therapeutic approaches.

Disclosures: S. Rueda: None. **J.C. Perry:** None. **E.T. Wolbrecht:** None. **D. Gupta:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

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Program #/Poster #: P338.03

Topic: C.09.Stroke

Support: NIH Grant R01NS099210
NIH Grant R01NS112942

Title: Wearable myoelectric interface for neurorehabilitation training in chronic stroke

Authors: V. PAUL[1], N.-T. HUNG[1], P. PRAKASH[1], T. KOVACH[1], ***M. SLUTZKY**[2];
[2]Neurol., [1]Northwestern Univ., Chicago, IL

Abstract: Abnormal co-activation (also called abnormal synergies) is a significant cause of impaired arm movement after stroke. However, few stroke therapies aim to reduce this co-activation. We designed a myoelectric computer interface (MyoCI) to provide feedback to stroke survivors to reduce abnormal co-activation and associated arm impairment. Here, we describe a novel, wearable version of the MyoCI to control custom-designed computer games as a home-based therapy for chronic stroke survivors. This therapy, called the myoelectric interface for neurorehabilitation training (MINT), enables high-intensity, high-dose training using an inexpensive device at home. The MINT device records surface EMGs from 2-3 arm muscles and wirelessly controls games on a laptop or tablet. By mapping the muscle activities to orthogonal directions of cursor movements, the games operantly condition the participants to learn to reduce abnormal co-activation between the muscles. We are currently investigating home-based MINT therapy in a randomized controlled trial of severely impaired stroke survivors (Fugl-Meyer score <30). Participants were asked to train 90 min per day, 6 days a week, for a total of 6 weeks, with different variants of the paradigm (2 or 3 muscles at a time) vs. a sham control group that trained on one muscle. We surveyed participants about their engagement with the game using a modified Intrinsic Motivation Inventory. Thirty participants have completed the 6-week training to date. They averaged 85±18 min of daily training out of the 90 that were asked. Overall, 89% of participants surveyed found the training enjoyable and motivating. A few participants had significant difficulty with the laptops due to inexperience with computers. Participants' performance on the game, measured by weighted time-to-target, improved steadily overall in the experimental group, while the sham control group stayed at high performance throughout. Functional outcomes were measured using the Wolf Motor Function Test

(WMFT, timed portion). At 6 weeks, WMFT showed a trend of greater improvement relative to baseline in experimental groups than in sham controls (combined mean -3.6 vs -1.5 s, p=0.26, t-test). The group training 3 muscles at a time improved significantly more than sham (-7.3 s, p=0.03) at 6 weeks. Improvement continued 4 weeks after the training ended (-16.9 s in 3-muscle group, p=0.03; -9.4 s overall groups compared to -2.6 s for sham, p=0.14). MINT is a motivating way to provide home-based, high-intensity therapy to stroke survivors with a new mechanism of action. Early results suggest that it improves arm function and is not just overcoming learned non-use.

Disclosures: V. Paul: None. **N. Hung:** None. **P. Prakash:** None. **T. Kovach:** None. **M. Slutzky:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

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Program #/Poster #: P338.04

Topic: C.09.Stroke

Support: NIH Grant W81XWH2010863

Title: Retrieve: an automated stereognosis system for brain injury patients with chronic tactile deficits

Authors: *R. HUDSON, J. EPPERSON, J. WRIGHT, Y. DUONG, D. PRUITT, S. HAYS, M. KILGARD;
Univ. of Texas At Dallas, Richardson, TX

Abstract: We have endeavored to test the usability of a novel stereognosis-based system for automated somatosensory training designed for use in clinic or at home. Fourteen participants with chronic brain injury were recruited for this study. Three were excluded as they could not retrieve one object 3 times in 2 minutes. A total of 9 participants (5 male, 4 female, age 55+/-15, years since injury 8+/-8) completed 1 hour of system use in clinic. A total of 3 participants (1 male, 2 female, age 45+/-22, years since injury 4+/-1) completed 5 days of system use at home for 1 hour per day. When using the ReTrieve system, participants are asked to differentiate textures, shapes, weights, or lengths of objects. Harder versions of tasks use more similar objects. The system instructs the participant on the task, and records performance data. Participants averaged 175+/-135 retrievals per hour in clinic. Participants averaged 397+/-102 retrievals per day at home. Participants' percent correct was significantly better than chance ($p < .001$). When participants were presented with "hard" tasks rather than "easy" tasks, retrieval rate decreased for weight and length objects ($p < .05$) and percent correct decreased for weight objects ($p < .05$). Participants distinguish objects at rates above chance and perform worse on more similar objects, indicating that this task could be modified to serve a range of ability levels. The expected decrease in task performance with increase in difficulty for two of our four object types indicates a successful difficulty scaling paradigm for these objects. Repetitions per hour are more than ten times the average of 13 somatosensory repetitions in clinic and could significantly assist in recovery if used at home for an extended period. An ongoing randomized study is investigating whether this fully automated stereognosis improves sensory function as measured with the Erasmus modified Nottingham Sensory Assessment when used at home for 6 weeks.

Disclosures: R. Hudson: None. **J. Epperson:** None. **J. Wright:** None. **Y. Duong:** None. **D. Pruitt:** None. **S. Hays:** None. **M. Kilgard:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

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Program #/Poster #: P338.05

Topic: C.09.Stroke

Support: NM4R

Title: Operant conditioning of RF H-reflex for treatment of spasticity

Authors: *K. KIM[1], K. MANELLA[2], R. LEE[3], J. S. SULZER[1];
[1]Mechanical Engin., Univ. of Texas at Austin, Austin, TX; [2]Col. of Rehabilitative Sci., Univ. of St. Augustine, Austin, TX; [3]St. David's Med. Ctr., Austin, TX

Abstract: Spasticity, or more specifically hyperreflexia, is a common impairment following neurological injury such as stroke. Clinical interventions aimed at reducing RF hyperreflexia have shown modest results but with side effects and limited clinical evidence. Our previous research has shown that hyperreflexia of the rectus femoris (RF) during pre-swing is closely associated with reduced knee flexion in post-stroke with Stiff-Knee gait (SKG). Thus, reduction of RF hyperreflexia should improve walking function following SKG after stroke. Our recently developed procedure can non-pharmacologically target hyperreflexia using operant conditioning. Operant H-reflex conditioning allows the patient to self-modulate one's own monosynaptic spinal reflex activity, elicited via electrical stimulation on peripheral nerve. At present, operant H-reflex conditioning has shown that individuals with spinal cord injury can learn to self-modulate soleus reflex excitability with improvements in clinical function. Our study is a proof-of-concept study to examine the feasibility of this procedure on the RF muscle. Total of 7 subjects (5 healthy 2 stroke) participated in this study, where we measured surface EMG of RF and provided surface stimulation on femoral nerve. Subjects were asked to regulate visual feedback of their RF H-reflex activity. The protocol consisted of 6 Baseline/24 Training sessions over a 12-week (2-3 time/wk). Sessions consisted of three runs of 75 trials in a standing posture, where no feedback of RF H-reflex was provided during Baseline sessions. Training began with an additional 20 Baseline trials to establish a within-session baseline. Participants were asked to reduce the height of the RF H-reflex bar while maintaining background RF EMG within inactive zone. A successful trial (i.e. below threshold) resulted in a color change of the bar on the screen and an increased success rate. We compared averaged RF H-reflex amplitude of the six Baseline sessions and last six training sessions. We assessed gait speed, spasticity, reflex modulation, and joint kinematics during gait pre-/post- training in stroke. In five healthy individuals, we found an overall decrease in average RF H-reflex magnitude (33% drop, $p<0.001$, paired t-test), and stronger decrease in post-stroke individuals (49% drop, $p<0.001$). Post-stroke individuals also exhibited improvements in peak knee-flexion velocity, reflex excitability during 4 gait-phases, and in spasticity (32° to 43° in 1st swing excursion on the quadriceps pendulum test). These outcome provide promising initial results that operant RF H-reflex conditioning is feasible both in healthy and post-stroke individuals.

Disclosures: K. Kim: None. **K. Manella:** None. **R. Lee:** None. **J.S. Sulzer:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

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Program #/Poster #: P338.06

Topic: C.09.Stroke

Title: Comparison between the effect of unihemispheric and bihemispheric transcranial direct current stimulation on spasticity, and motor outcome in subacute ischemic stroke patients

Authors: *H. YOUSSEF[1,2], M. ZEINELDIN[3], N. ABDELHAMED[4], M. HAMDY[5];
[1]Neurosci. & Biotech., Alexandria Univ., Alexandria, Egypt; [2]Physical Therapy & Rehabil., Marmara Univ., Istanbul, Turkey; [3]Clin. Pharmacol., Fac. of Pharmacy, Alexandria Univ., Alexandria, Egypt; [4]Dept. of Zoology, Fac. of Science, Alexandria Univ., Alexandria, Egypt; [5]Dept. of Neuropsychiatry, Fac. of Medicine, Alexandria Univ., Alexandria, Egypt

Abstract: Background Despite the central origin of stroke affecting the primary motor cortex M1, most of the rehabilitative approaches rely on peripheral techniques to regain motor capabilities. The goal of this study was to compare the effects of unihemispheric and bihemispheric transcranial direct current stimulation tDCS on motor outcomes, and spasticity in patients with subacute ischemic stroke. The trial registration in the clinical trial ID is NCT04770363. **Methods** Thirty-six sub-acute ischemic stroke survivors participated in the study, randomly assigned to one of three groups receiving (tDCS), bihemispheric (Anodal over affected M1, and cathodal over healthy M1) or unihemispheric (Anodal over affected M1, and cathodal stimulation over the supraorbital bone of the healthy side) or sham group (electrode placement as Unihemispheric but no current delivered). ActivaDose tDCS (USA) used, to deliver noninvasive brain stimulation, consisted of 20 minutes of 2 mA anodal and cathodal applications according to different groups in each session for 12 sessions three sessions per week. All participants received physiotherapy directly following the tDCS session for 45 minutes/day. Participants assessed by Fugl-Meyer assessment (FMA), and Modified Ashworth scale (MAS) for muscle tone, all measured at baseline, and after four weeks of the treatment. Both of the participants, and the external examiner, was blinded for which interventional groups they had joined. **Sample size calculation** Assuming that the effect size of tDCS on "Subacute ischemic stroke patients" was 0.30, the number of groups= 3, and repetition = 2. The minimum required sample size is 24 patients' alpha error = 5% and study power of 80%. Calculated using G. Power software. **Results** A repeated measures ANOVA yielded a significant effect of tDCS regarding UE (F = 9.857, P = .001), and LE (F = 3.861, P = .034). Post-hoc analyses revealed that unihemispheric stimulation improved performance significantly more than sham stimulation (P = .001) for UE and (P = .029) for LE, and bihemispheric stimulation improved performance significantly more than sham stimulation (P = .008) for UE and (P = .023) for LE. Revealing no additives effects of bihemispheric over unihemispheric cerebral stimulation. (P = .939). Data analysis revealed a significant effect between groups tested by the Kruskal Wallis test for muscle spasticity of biceps (P = .036), and wrist flexors (P = .025). **Conclusion** Adding tDCS to the neuro-rehabilitation plan would promote the advantageous effect of neurorehabilitation of motor measures, and normalizing muscle tone of the stroke survivors.

Disclosures: H. Youssef: None. **M. Zeineldin:** None. **N. Abdelhamed:** None. **M. Hamdy:** None.

Poster

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Topic: C.09.Stroke

Support: AHA Grant 18TPA34230052

Title: Effects of repetitive transcranial magnetic stimulation of contralesional dorsal premotor cortex on interhemispheric functional connectivity in severe chronic stroke

Authors: *X. LI[1], D. A. CUNNINGHAM[2], K. SAKAIE[3], M. LOWE[3], Y.-L. LIN[4], S. L. WOLF[5], A. CONFORTO[6], A. G. MACHADO[7], A. MOHAN[1], K. O'LAUGHLIN[1], X. WANG[8], M. WIDINA[1], E. B. PLOW[1];
[1]Biomed. Engin., Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [2]Physical Med. and Rehabil., Case Western Reserve Univ., Cleveland, OH; [3]Imaging Sci., Cleveland Clin. Imaging Inst., Cleveland, OH; [4]Physical Therapy and Assistive Technol., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [5]Emory Univ. Sch. Med., Atlanta, GA; [6]Hosp. Das Clínicas/São Paulo Univ. and Inst. Israelita De Ensino E P, Sao Paulo, Brazil; [7]Ctr. Neurolog. Restoration, [8]Quantitative Hlth. Sci., Cleveland Clin., Cleveland, OH

Abstract: Introduction: Up to 50% of stroke survivors experience persistent, severe upper limb paresis despite intensive rehabilitation. Treatment options for severely impaired survivors are often limited and ineffective. Brain stimulation has received widespread attention for its potential to augment effects of rehabilitation through neuroplasticity. Repetitive transcranial magnetic stimulation (rTMS) is a well-known technique used to promote motor improvement through facilitating excitability of ipsilesional primary motor cortex (iM1). Despite promising early evidence, this approach has failed to produce motor gains in severely impaired survivors. Recent evidence indicates the dorsal premotor cortex in the undamaged, contralesional hemisphere (cPMd) may be a more suitable target due to alternate, viable, bi-hemispheric and ipsilateral contributions. A single session of rTMS delivered to facilitate cPMd increased paretic limb reaching speed in association with heightened interhemispheric connectivity in more severely impaired survivors who otherwise showed little gain with conventional iM1 rTMS. Multiple sessions of cPMd rTMS coupled with rehabilitation may generate longer lasting, clinically meaningful gains. Thus, this ongoing study seeks to investigate whether multiple sessions of cPMd rTMS coupled with rehabilitation produce greater motor improvement than conventional iM1 rTMS coupled with rehabilitation based on recruitment of available neural substrates in severely impaired survivors. We hypothesize that cPMd rTMS coupled with rehabilitation will produce greater motor functional gains along with enhanced interhemispheric functional connectivity quantified using resting state functional magnetic resonance imaging (rs-fMRI). **Methods**: In this pilot randomized, blinded clinical trial, 12 participants with severe chronic stroke have been randomized to receive cPMd or iM1 rTMS both in conjunction with upper limb rehabilitation (2x/wk, 6 wks). Assessments of motor function, neurophysiology, and rs-fMRI are made at baseline and at end of treatment. Interhemispheric connectivity between bilateral motor areas is evaluated as correlation in low frequency blood oxygen level dependent

activity. **Results**: Case series analysis suggests severely impaired survivors who receive cPMd rTMS show gains in functional connectivity between cPMd and iM1 with functional improvement compared to counterparts who receive iM1 rTMS. **Discussion**: Addition of the remaining 12 participants is expected to give insight on mechanisms of a novel brain stimulation approach developed for severely impaired stroke survivors.

Disclosures: X. Li: None. **D.A. Cunningham:** None. **K. Sakaie:** None. **M. Lowe:** None. **Y. Lin:** None. **S.L. Wolf:** None. **A. Conforto:** None. **A.G. Machado:** None. **A. Mohan:** None. **K. O'Laughlin:** None. **X. Wang:** None. **M. Widina:** None. **E.B. Plow:** None.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P338.08

Topic: C.09.Stroke

Support: Battelle Memorial Institute

Title: An interactive activity assistant to facilitate motor and cognitive rehabilitation following acquired brain injury

Authors: *C. DUNLAP, I. BAUMGART, D. MORALES, L. WENGERD, S. COLACHIS, IV; Battelle Mem. Inst., Columbus, OH

Abstract: Acquired brain injuries (ABI), including traumatic brain injury (TBI) and stroke, affect over a million Americans a year and can cause long-term motor and cognitive disability. The current state of the art for ABI rehabilitation is occupational therapist (OT)-guided exercises. Constraints such as time limitations and insurance reimbursement restrict the number of therapy sessions a patient receives, potentially hindering recovery potential. Furthermore, it is challenging for therapists to track quantitative performance metrics while simultaneously leading therapy sessions. We have developed the Battelle Activity Assistant™, a portable computer-vision based assistive device, to aid both cognitive and motor function, as well as quantify longitudinal functional gains during rehabilitation. Using a video camera, machine learning algorithms, and an optional functional electrical stimulation device to enhance grasp function, the Activity Assistant guides the user through a broad range of tasks including activities of daily living and clinical assessments. The Activity Assistant leverages artificial intelligence methods to understand the kinematics, task performance, and cognitive function of the patient and provides real time biofeedback and task performance information. In an IRB-approved feasibility study, we tested the Activity Assistant with participants with both cognitive and motor impairments due to ABI. We demonstrate feasibility of the Activity Assistant to enhance rehabilitation, autonomously supplement motor function with context-aware functional electrical stimulation, and to quantify performance in the nine-hole peg clinical assessment. We present our successes and challenges in using artificial intelligence to aid occupational therapy for ABI. Lastly, we discuss future opportunities for machine learning interventions to facilitate motor and cognitive rehabilitation. Disclaimer: This is an investigational device,

it is not commercially available, and it has not been cleared or approved by the FDA. Results discussed are from research studies performed.© 2021 Battelle Memorial Institute. All rights reserved.

Disclosures: C. Dunlap: A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **I. Baumgart:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **D. Morales:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **L. Wengerd:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **S. Colachis:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute.

Poster

P338. Wearable Devices and Other Approaches for Stroke Treatment

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P338.09

Topic: C.09.Stroke

Title: Upper extremity flexion synergy torque patterns are not exacerbated following ischemic conditioning post stroke.

Authors: E. KLEVENOW[1], P. BALASUBRAMANIAN[2], T. RUOPP[2], B. SCHMIT[2], *A. HYNGSTROM[1];
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Abstract: Ischemic conditioning (IC) is an emerging intervention that may improve motor function in individuals with chronic stroke. IC is a vascular stimulus that induces transient tissue ischemia through five-minute intervals of blood flow occlusion and reperfusion by inflation and deflation of a blood pressure cuff around a limb. The mechanisms of IC's motor benefits are not completely known but likely involve excitation of afferents sensitive to ischemia which then engage the autonomic nervous system resulting in a release of neuromodulators such as norepinephrine. As these neuromodulators may also be involved in the expression of upper limb synergy patterns post stroke, we aimed to determine if IC affects the expression of the upper extremity flexion synergy torque patterns which could potentially hamper motor performance. Eleven participants >6 months post stroke (4 Male, 50.8 ± 14.5 yrs) completed two study sessions of IC (cuff inflation 225 mmHg) or IC sham (10 mmHg). Isometric shoulder abduction maximal voluntary contraction (SABD MVC) and secondary elbow flexion torques were measured before and after a single session of either IC or IC sham in a randomized order. On average, after IC, SABD MVC increased (mean +8.79% ± 23) versus a smaller +0.64% ± 13.95 change after IC sham. While SABD MVC values increased, involuntary secondary elbow flexion torque measured during SABD MVC did not consistently increase or decrease with torque at the shoulder after IC (+3.63% ± 46.55) or IC sham (+19.84% ± 54.73). These data suggest that IC does not exacerbate secondary elbow flexion torques associated with upper extremity flexion synergy presentation.

Disclosures: E. Klevenow: None. **P. Balasubramanian:** None. **T. Ruopp:** None. **B. Schmit:** None. **A. Hyngstrom:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NS106325

Title: Spinal cord injury induced neuropathic pain associates with plasticity in peripheral cutaneous sensory encoding and increased spinal sensory circuit excitability

Authors: *M. BRYSON, H. KLOEFKORN-ADAMS, S. GARRAWAY, S. HOCHMAN;
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Abstract: Spinal cord injury (SCI) commonly leads to neuropathic pain, which manifests largely as tactile allodynia (pain from non-painful stimuli). Spontaneous firing in nociceptor dorsal root ganglia (DRG) due to changes in ion channel expression has been implicated in the emergence of neuropathic pain. Similar changes are seen in 2nd and 3rd order CNS neurons, at least in part due to alterations in Na^+ channel expression. Here, in the thoracic contusion SCI neuropathic pain mouse model, we used *ex vivo* isolated truncal skin-nerve and isolated whole spinal cord preparations to assess the changes in excitability of primary afferents and dorsal horn circuitry, independent of DRG. We performed electrophysiology experiments in parallel in naïve (n = 1), sham (n = 1), and T12 contusion SCI (n = 5) adult mice several months after surgery. Initial analysis of skin-nerve data identified the following possible changes after SCI; (a) reduced frequency of spontaneous events with emergent activity in high-amplitude, fast-rising spiking units. (b) Temperature reduction from 32ºC to 22º recruited unique spontaneous bursting in 2/4 SCI mice. (c) Mechanical activation of truncal hairy skin with air pressure pulses at various forces led to unique amplification of recruited units at lower temperature. In spinal cord, recordings were made at the dorsal root (DR) entry zone of multiple roots bilaterally above and below the lesion and DRs were stimulated at Aβ, Aδ and C fiber intensities to characterize evoked changes in afferent fiber excitability, measured as dorsal root potentials (DRPs) or dorsal root reflexes (DRRs). Compared to sham (n=2) and naïve (n=1) mice, initial analyses suggest that SCI mice (n=4) have increased circuit excitability. (a) Spontaneous afferent activity was increased and synchronized events were able to cross nearby ipsilateral roots, indicating interneuron involvement. (2) High threshold afferent stimulation evoked stronger multi-segmental responses. (3) 4-AP, thought to preferentially recruit superficial dorsal horn pain circuits, induced paroxysmal bursting that included synchronous bilateral activity. A role for recruitment of commissural interneurons was further supported by the fact that DR stimulation evoked contralateral DRRs in SCI mice. More generally, as 4-AP induced bursting was strongly depressed with bicuculline, while CNQX/APV had much less effect, the observed plasticity appears to be primarily driven by GABAergic inhibitory interneurons that may become functionally excitatory. Together, these data support the hypothesis that somatosensory circuits change at multiple levels after SCI, leading to injury-induced neuropathic pain.

Disclosures: M. Bryson: None. **H. Kloefkorn-Adams:** None. **S. Garraway:** None. **S. Hochman:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: AMED JP20bm0204001, JP19bm0204001, and JP18bk0104017

Title: High-resolution 3D visualization of neural fibers in spinal cord with BDA tracing and tissue-clearing

Authors: *M. SHINOZAKI, K. NAKANISHI, N. NAGOSHI, M. NAKAMURA, H. OKANO; Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: [Background] Neural circuits constitute a complicated three-dimensional network, and histological aspects such as direction, branching, and branching angle of neural fibers cannot be sufficiently evaluated in sliced sections. In this decade, various techniques to make neural tissue transparent have emerged, and the targeted neural circuit can be visualized in three dimensional ways with fluorescent materials. On the other hand, many clearing-methods are complicated, and various conditions of the protocols are needed to be tested in order to obtain an image that can withstand the evaluation of each neural fiber. Therefore, we developed a method of clearing a spinal cord transparent and of observing it three-dimensionally by using BDA tracer, which was traditional but enabled high-resolution visualization of neural fibers. [Methods] Thoracic spinal cord injury model-mouse was used. A total of 1.2 ul of 10% BDA was injected into four sensorimotor sites of lower limb-area to trace corticospinal tracts. Ten days later, the harvested spinal cord was first immersed in 4% PFA, and then immersed in alexa-conjugated streptavidin solution for one week. After that, clearing method PACT was modified as follows. The tissue was immersed in an acrylamide hydrogel solution at 4 °C for 3 days. Then the gelation was performed at 37 ° C for 3 hours in a water bath. After removing the gel from the tissue surface, the tissue was moved to thermostat chamber at 47 °C in a clearing solution. When the tissue got semitransparent (3 days for spinal cords of mice), it was immersed in observation-solution in room temperature to be completely transparent in half a day. Observation was performed using a Zeiss lightsheet microscope. The obtained sequential images were reconstructed with ImageJ software. [Results] During the staining process, the labeled area expanded from the surface to the center of the tissue block over time, and the whole staining was completely performed in seven days. In the clearing process, transparency was gradually increased. After the tissue was transferred to the observation solution, a completely transparent tissue was obtained. Sequential images were captured with Lightsheet microscope, and the stitching was made in ZEN software, and 3D reconstruction was made with ImageJ. We output 2D images from the reconstructed 3D data, and confirmed that the resolution of images was comparable with that of usual slice sections. It was possible to demonstrate the corticospinal tract fibers and varicosity sprouted in the gray matter. [Conclusion] We have established a tissue clearing method for high-resolution and three-dimensional evaluation of anterograde tracing.

Disclosures: M. Shinozaki: F. Consulting Fees (e.g., advisory boards); advisory boards of K pharma inc.. **K. Nakanishi:** None. **N. Nagoshi:** None. **M. Nakamura:** F. Consulting Fees (e.g., advisory boards); advisory boards of K pharma inc. **H. Okano:** F. Consulting Fees (e.g., advisory boards); advisory boards of K pharma inc..

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.03

Topic: C.11. Spinal Cord Injury and Plasticity

Title: The role of TLR4 in the secondary pathogenesis of spinal cord injury

Authors: *R. D. FESSLER[1], N. BOLES[1], Q. SHEN[1], Y. LOPEZ-RAMIREZ[1], D. TUCKER[1], B. T. DAVID[1], R. G. FESSLER[1], K. DHANDIAPANI[2];
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Abstract: Introduction: Spinal cord injury (SCI) is a leading cause of paralysis worldwide, however no treatments have been developed partly due to poor understanding of SCI pathophysiology. Toll-like receptor 4 (TLR4), a pro-inflammatory receptor, has been implicated in initiating the sterile inflammatory response to neurologic injury, and presents a potential therapeutic target. VGX-1027, a TLR4 inhibitor, has shown promise as a neuroprotective agent after injury. Objectives: This study established a model of compression SCI in mice for investigation of the role of TLR4 in the secondary pathogenesis of SCI, and evaluation of TLR4 inhibition as a potential therapeutic target. Methods: TLR4 expression was quantified by western blot and cell-type specific expression was evaluated using both immunohistochemistry and flow cytometry. Functional analysis (BMS and mTarlov) was performed comparing wild type vs TLR4 mutants, and in mice treated with the TLR4 inhibitor VGX-1027. Results: TLR4 expression was biphasically upregulated on western blot analysis at 6 and 48hrs after SCI. Immunohistochemistry showed TLR4 colocalization with neurons, but not with astrocytes or macrophages. Flow cytometry showed significant up regulation of TLR4 in neurons, astrocytes, and macrophages, with the greatest upregulation in neurons. TLR4 mutants showed diminished functional deficits compared to the wild type, as well as diminished lesion size and number of Fluoro-Jade B positive cells. Pretreatment with VGX-1027 also showed diminished functional deficit, however delayed treatment showed no significant difference. Conclusion: TLR4 shows biphasic upregulation primarily in neurons following SCI. Both genetic and pharmacologic inhibition of TLR4 appear to diminish injury severity. However, when VGX-1027 treatment is delayed until after the 6hr peak of TLR4 expression, the effect is lost, suggesting that the initial upregulation is associated with increased functional deficit. These data suggest that TLR4 signaling plays a significant role in the pathogenesis of SCI and further investigation of TLR4 inhibition as a potential therapy for acute SCI is warranted.

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Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS081112
Lisa Dean Moseley Foundation

Title: Tailoring Neural Transplants for Repair of the Injured Cervical Spinal Cord

Authors: *T. A. FORTINO[1], L. V. ZHOLUDEVA[3], M. L. RANDELMAN[1], A. K. PONNA[1], S. SINGH[1], J. PARDIECK[4], M. A. CUSIMANO[1], N. WHITE[4], A. NICEFORO[1], K. J. DOUGHERTY[1], S. E. SAKIYAMA-ELBERT[4], M. A. LANE[2];
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Abstract: The phrenic motor network is directly compromised by cervical SCI, resulting in diaphragm paralysis and impaired breathing. Despite these consequences, some limited plasticity typically occurs weeks post-injury resulting in increased interneuronal integration with the damaged phrenic network and modest improvement of diaphragm recovery. In an effort to harness and enhance this plasticity, we have engineered stem-cell derived spinal interneurons that can be transplanted directly into the injured spinal cord. We recently found that transplanting neural precursor cells (NPCs) rich with phrenic spinal interneuron precursors promotes phrenic recovery post-SCI. Building on these initial results, the present work tests the hypothesis that enriching neuronal and glial lineage restricted progenitor cells, with stem cell derived V2a and V0 spinal interneuronal (SpIN) precursors, will further enhance diaphragm recovery. Sub-acutely (1week) following a lateralized, mid-cervical contusion injury in the adult female rat (Sprague Dawley), SpIN-enriched NPCs were transplanted into the lesion epicenter. Donor SpINs also express the hM4Di receptor, allowing inhibition of these donor cells during subsequent functional assessments. Clozapine application during diaphragm electromyography is used to assess the functional contribution of donor SpINs. Initial patch-clamp and multi-electrode array recordings are used to confirm silencing *in vitro*. Pseudorabies virus tracing of the injured phrenic network has shown synaptic integration of donor NPC and V2a cells with host neurons. Ongoing analysis of functional data will provide insight into the relative contribution of these integrated cells with phrenic motor recovery. This research provides the first in depth assessment of how these donor spinal interneuron populations contribute to phrenic recovery.

Disclosures: T.A. Fortino: None. **L.V. Zholudeva:** None. **M.L. Randelman:** None. **A.K. Ponna:** None. **S. Singh:** None. **J. Pardieck:** None. **M.A. Cusimano:** None. **N. White:** None. **A. Niceforo:** None. **K.J. Dougherty:** None. **S.E. Sakiyama-Elbert:** None. **M.A. Lane:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

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Program #/Poster #: P361.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS: 2R01NS064004
Craig H. Neilsen Foundation (NZ:385743)

Title: Motor cortex and spinal cord electrical neuromodulation remodel corticospinal axons after injury by deactivating endogenous PTEN

Authors: *N. ZAREEN[1], *E. MAZALKOVA[3], L. CHEN[4], H. ALEXANDER[3], H. YUNG[2], J. H. MARTIN[5];
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Abstract: Repairing the damaged corticospinal tract (CST) after spinal cord injury (SCI) is a challenge. Neuron-intrinsic and -extrinsic barriers prevent CST neurons from mounting an effective regenerative repair process. Spared CST axons also fail to achieve substantial collateral branching on their own. Augmenting neuronal activity has been shown to coax CST axons into extensive sprouting, to reestablish connectivity and restore function in pyramidotomy (PTx) and SCI models. We previously described that chronic electrical stimulation of the motor cortex (MCX) in intact rats activated mTOR and Jak/Stat signaling (Zareen et al 2018). mTOR and Jak/Stat are necessary for promoting activity-dependent axonal outgrowth and synapse formation, respectively. Importantly, we found that neuromodulation does not alter the expression levels of PTEN protein, a negative regulator of mTOR and a major target for genetic manipulation to promote axon regeneration. Instead, stimulation increases the expression levels of phosphorylated PTEN (pPTEN). This post-translational modification of endogenous PTEN at Ser380 residue suppress PTEN activity in tumor studies (Vazquez et. al 2000; Das et. al 2003). CST sprouting after neuromodulation is remarkably similar to that following PTEN gene deletion. Our laboratory has identified that after PTx and SCI, CST sprouting is promoted following electrical stimulation protocols: high frequency multipulse stimulation (MPS), intermittent theta burst stimulation (iTBS) and cathodal trans-spinal direct current stimulation (c-tsDCS). In this study we ask if pPTEN protein, the deactivated form of PTEN, and mTOR activation are common to these three neuromodulation protocols. Additionally, to understand when this growth-promoting program switches on, we examined their expression levels and extent of CST sprouting at various time points. We find that short-term MPS activates mTOR, does not deactivate PTEN, and does not result in CST sprouting. This indicates a dissociation between PTEN and mTOR and that insufficient pPTEN levels do not lead to sprouting. In contrast, long-term MPS and c-tsDCS activate mTOR signaling, deactivate PTEN, and produce concurrent CST sprouting. Both short- and long-term iTBS result in mTOR activation, PTEN deactivation and CST sprouting. Finally, there is long-term persistence of PTEN deactivation following MPS and iTBS. Thus, PTEN deactivation via phosphorylation is a key mechanism for activity-dependent CST sprouting, can potentially serve as its biomarker and its persistence can help define the length of therapeutic neuromodulation a patient needs to undergo in clinical settings.

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Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: VA Merit Award (I01RX002969)
Taylor Foundation for Chronic Diseases
PVA Research Foundation

Title: Astrocytic Rac1 Contributes toFibroticScarFormation after SCI: ALongitudinal IntravitalImaging Study

Authors: M. L. REIMER[1], C. BENSON[2], S. G. WAXMAN[3], ***A. TAN**[4];
[1]Neurol., Yale University/Dept of VA, West Haven, CT; [2]Neurol., Yale Univ., New Haven, CT; [3]Neurol., Yale University, Neurosci. and Regeneration Res. Ctr., West Haven, CT; [4]Yale University/VA Connecticut Healthcare Syst., West Haven, CT

Abstract: A major challenge in SCI research is identifying biological factors that underlie dysfunction and developing mechanism-based treatments to restore function. Our prior work has shown that astrocytes contribute to fibrotic scar formation at the spinal injury site. However, these published studies were performed in vitro or in a post-mortem setting, only, which prevented a direct physiological analysis of astrocytic scar development. Here, we leveraged our whole-animal, spinal intravital imaging platform to measure the impact of Rac1 activity in astrocytic scar formation within live spinal cord tissue with a spinal injury.

We hypothesized that Rac1 activity is required for rapid fibrotic scar development after SCI and may contribute to inhibiting axonal regrowth. This work is an opportunity for advancing our effort in the search for novel interventions and more effective clinical treatment strategies for SCI and its related complications.

In transgenic mice with astrocytes expressing a fluorescent reporter, and a normal Rac1 or conditional Rac1 knockout (Rac1 KO) phenotype, we implanted a “glass window” over a spinal cord stab injury. Image series over a two week period were analyzed for the proliferation and migration of astrocytes into the injury site. These in-depth longitudinal analyses of the fibrotic scar in vivo revealed both linear and volumetric changes of the scar tissue. Behavioral studies were also performed to assess functional recovery after SCI.

Our in vivo morphological observations demonstrate that the lack of Rac1 in astrocytes reduced the speed of fibrotic scar formation; suggesting that astrocytes decrease migration or proliferation into the injured region, as compared with controls.

Taken together, our study provides a specific and physiologically relevant understanding of the temporal dynamics of astrocyte behavior in fibrotic scar formation after SCI. This work complements and extends our preclinical SCI research space, which seeks to identify and validate novel treatments for SCI/D.

Disclosures: M.L. Reimer: None. **C. Benson:** None. **S.G. Waxman:** None. **A. Tan:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life - Spinal Cord Research Foundation
Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Characterizing chromatin accessibility changes identifies CTCF as transcriptional repressor of CNS regeneration

Authors: *Y. CHENG[1], F. TIAN[2], Z. HE[2], D. H. GESCHWIND[1];
[1]UCLA, Los Angeles, CA; [2]Children's Hosp Boston, Boston, MA

Abstract: The inability of adult neurons to regenerate long axons within the CNS is a major impediment to improving outcome after spinal cord injury, stroke, and other CNS insults. How CNS neurons can acquire a growth-permissive state after being damaged is a central question in the field of neural repair. A specific cell state ultimately represents the readout of a specific gene expression program, driven by epigenetic regulatory events including transcription factor (TF) binding and chromatin remodeling. We hypothesize that chromatin regulations of growth-associated gene programs play a major role in setting the permissive or non-permissive growth state between the regenerating and non-regenerating neurons. Here, we leveraged chromatin accessibility and transcriptomic analysis of CNS-injured neurons, predicting CTCF as negative regulator of chromatin state associated with growth-associated gene transcription. Coupling with *in vivo* CRISPR/Cas9 perturbations, we experimentally validated the bio-informatic predictions, showing that mature mice bearing cell type-specific deletions of CTCF displayed improved optic nerve regeneration. As part of the insulator protein complex that organizes chromatin into sub-domains to control enhancer-promoter interactions, CTCF could act on growth-associated transcription through modeling the chromatin structure. This prediction is supported by chromatin accessibility measurement of CNS-injured neurons with or without CTCF deletion, where we observed a number of peaks differentially accessibility when CTCF is ablated. The core chromatin regulatory mechanisms of CTCF on regenerative gene programs will be further investigated via integrating chromatin structure and transcriptomic analysis.

Disclosures: Y. Cheng: None. **F. Tian:** None. **Z. He:** None. **D.H. Geschwind:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Program #/Poster #: P361.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS. 2R01NS064004
NIH Diversity Supplement. 2R01NS064004

Title: The role of GABA presynaptic inhibition in hyperreflexia in forelimb and hindlimb muscles after acute and chronic unilateral corticospinal injury in rats

Authors: *T. BETHEA[1,2], J. MARTIN[1,2];
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Abstract: Hyperreflexia is a consequence of spinal cord injury (SCI). A better understanding of the mechanisms driving hyperreflexia is essential for the optimization of rehabilitative therapies that can restore quality of life to SCI patients. Excitatory proprioceptive afferent (PA) sprouting is one of several mechanisms underlying hyperreflexia. We previously demonstrated activity-dependent competition between PAs and the corticospinal tract(CST), whereby muscle electrical stimulation produced PA sprouting, increased PA connections, and reduced CST connections. Following a pyramidal tract lesion (PTX), and the associated loss of CST projections, we observed PA sprouting and an increase in excitatory PA terminals on motoneurons. Another potential mechanism for hyperreflexia is reduced GABAergic presynaptic inhibition (GABApre) of PA terminals on motoneurons. GABApre are involved in the normal regulation of PA afferent terminal excitability. There is evidence of changes in presynaptic inhibition after ischemic stroke in mice, as well as following bilateral pyramidal lesion in rats.In this study we examine these two mechanisms to understand whether a reduction in GABApre regulation further augments excitability in addition to PA sprouting, or if GABApre appropriately regulates newly sprouted afferent terminals after CST injury. Further, we expect persistent hyperreflexia to accompany reduced GABApre regulation in chronically injured animals. We compared naïve, and PTX animals. Injury was followed by weekly H-reflex assessments of rate dependent depression (RDD). At the end of the experiment, animals were injected with cholera toxin subunit b (CTB) to trace PA fibers and identify motoneurons. PA terminals were labeled with Vglut1, and GABApre with GAD65. Motoneurons were individually imaged, reconstructed, and analyzed using Imaris 3D Software. Morphological results acquired 10 days post-PTX show similar and significant increases in excitatory PA terminals on motoneurons in both the cervical and lumbar spinal cord of PTX compared to naïve animals. This indicates PA sprouting after loss of CST. Comparison of the ratio of GAD65 to Vglut1, which indicates the proportion of PA terminals receiving GABApre, revealed a significant reduction in GABApre in the cervical, but not lumbar cord. This suggests impaired GABApre regulation of PA terminals in the cervical, but maintained regulation in the lumbar spinal cord, despite PA sprouting at both levels. H-reflex experiments are ongoing to test the hypothesis that hyperreflexia will be stronger in the cervical than the lumbar cord.

Disclosures: T. Bethea: None. **J. Martin:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

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Program #/Poster #: P361.09

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shriners Grant SHC-85101
Shriners Grant SHC85400
Shriners Grant SHC-85220
NIH grant NS097846
NIH grant NS092876

Title: Single-cell RNA-seq analysis of axoplasm transcriptomes from growing, static and retracting axon tips in the lamprey spinal cord

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Abstract: Local protein synthesis in axon tips plays an important role in axon regeneration. Microarray or next-generation technologies studies in mammals have shown that axon growth cones contain hundreds to thousands of mRNAs. Most of these studies were performed on cultured embryonic or early postnatal peripheral neurons. To confirm that local protein synthesis is involved in CNS axon regeneration after spinal cord injury *in situ*, and to identify key proteins responsible for axon growth or retraction, we micro-aspirated axoplasm from 10 growing, 9 static and 5 retracting tips belonging to large reticulospinal neurons of lamprey larvae approximately 4 years old, and performed 2x100 bp paired end read sequencing on Illumina Novaseq 6000 System. Three lists of genes that were differentially expressed between growing tips and retracting tips (group A=1488 genes), growing tips and static tips (group B = 151), and static tips and retracting tips (group C = 1067) were identified (FC >= 1.5, FDR <= 20). Gene ontology enrichment analysis using DAVID (v. 6.8) for Group A genes revealed that they are involved in ribosome biogenesis, mitochondrion function, endocytosis, RNA degradation or splicing, axon guidance, and multiple pathways such as the PI3K-Akt, mTOR, MAPK, AMPK signaling pathways. Analysis of the Group B genes revealed that they are involved in ribosome biogenesis, RNA transport, amino acid metabolism, nucleotide metabolism and multiple signaling pathways including the PI3K-Akt, MAPK, ErbB, Ras, Wnt pathways. Analysis for the Group C genes indicated that they have very similar functions to Group A genes in participating ribosome biogenesis, amino acid metabolism, nucleotide metabolism, endocytosis, axon guidance, RNA degradation and splicing, and multiple signaling pathways. These results indicate: A) more genes are expressed in growing tips or static tips than in retracting tips, except genes for c-terminus binding proteins, which are more highly expressed in retracting tips than in growing tips. The significance of this is unknown. B) Genes found in growing tips are functionally similar to those found in static tips. C) Multiple signaling pathways that are known to be involved in axon regeneration are present in the axoplasm of growing and static tips, but are missing or incomplete in retracting tips.

Disclosures: L. Jin: None. **Y. Zhou:** None. **Y. Li:** None. **G. Zhang:** None. **J. Hu:** None. **M.E. Selzer:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P361.10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: TIRR Foundation
Craig H. Neilsen Foundation #648714

Title: Clearing through the lesion site after spinal cord injury using iDISCO+

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Abstract: Spinal cord injury (SCI) triggers a diverse array of processes including cell death, inflammation, and scarring. In contusion injuries in mice, the SCI site typically forms into a dense lesion filled with fibroblasts, macrophages, and extracellular matrix (ECM) components that is surrounded by layers of reactive astrocytes and other cell types, which are collectively referred to as the glial scar. While the glial scar limits expansion of the spinal cord lesion and prevents further damage to the cord by the lesion, it may also inhibit axon regeneration and functional recovery. Optical tissue clearing techniques can allow for the close study of whole tissues and the use of 3D imaging for analysis can enable the up-close study of glial scarring and lesion formation after SCI. Optical tissue clearing works by removing lipids and proteins that scatter light, either through the use of detergents such as sodium dodecyl sulfate or organic solvents such as dichloromethane, and then equilibrating the refractive indices of the tissue to match with the imaging medium thus rendering the sample optically transparent. These cleared samples can then be imaged using a lightsheet microscope and the resulting images can be rendered in 3D through computer software such as Imaris. One issue that arises with using optical tissue clearing techniques is that efficient clearing of the sub-acute and chronically injured spinal cord using aqueous-based clearing protocols, such as CLARITY and the passive CLARITY technique (PACT), has proven to be problematic due to the dense ECM deposition within the lesion site by 10-14 days post-SCI. Organic-based clearing methods such as iDISCO+ have been previously shown to clear ECM-rich tissues and may be suitable for clearing the sub-acute and chronic SCI lesion. In this study, the organic optical clearing technique iDISCO+ was tested for its ability to clear the sub-acute lesion site following a contusion SCI. Injured spinal cord tissue was collected 14 days post-SCI and cleared with a modified iDISCO+ protocol, utilizing ethyl cinnamate (ECI) instead of dibenzyl ether (DBE) for the final refractive index matching step. The modified iDISCO+ protocol successfully cleared the spinal cord lesion site and enabled 3D lightsheet imaging of immunofluorescent labeling for the entire spinal cord tissue and specifically the site of injury. Further optimization of the iDISCO+ protocol will enable the robust interrogation of the glial scar and lesion formation after SCI using 3D lightsheet imaging.

Disclosures: F.L. Jalufka: None. **S.W. Min:** None. **M.E. Platt:** None. **D.A. McCreedy:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Program #/Poster #: P361.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 5R01NS094527-05

Title: Interaction between autophagy initiator ULK1 and SARM1 in axonal degeneration

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Abstract: Autophagy is a cellular catabolic pathway involving the formation of double-membrane vesicles called autophagosomes which sequester cell contents including proteins and organelles and deliver these cargoes to lysosomes for degradation. Autophagy is generally thought to be neuroprotective. However, previous studies found that inhibition of autophagy can delay axonal degeneration in primary dorsal root ganglion neurons and optic nerve injury models. The underlying molecular mechanisms remain unclear. We thereby examined the role of autophagy in axonal degeneration using mouse traumatic spinal cord injury (SCI) model. Consistent with the potential involvement of autophagy in axonal degeneration after SCI, we observed accumulation of the autophagosome marker LC3 and the autophagy initiator ULK1 in the axonal bulbs and injured axons after contusive SCI in mice. Phospho-ATG13, a marker of ULK1 kinase activity, also increased in the $LC3^{+}$ axonal bulbs, indicating that ULK1 is activated. This suggests activation of autophagy in the injured axons and potential relationships between autophagy pathway, ULK1 activity and axonal degeneration after SCI. Interestingly, SARM1, a TIR domain protein with pivotal role in axonal degeneration, was also found to colocalize with ULK1 in axonal bulbs and axons, suggesting potential interaction between autophagy and SARM1-mediated axonal degeneration. Consistent with this notion, in our *in vitro* experiments, ULK1 inhibitor SBI0206965 attenuated neurite fragmentation and reduced SARM1 puncta formation in neurites of primary cortical neurons upon glutamate excitotoxicity. Furthermore, our immunoprecipitation data demonstrated that ULK1 can physically interact with SARM1 in HEK293T cells. These findings suggest a crosstalk between autophagy and axonal degeneration pathways by ULK1-SARM1 interaction. Supporting the hypothesis of autophagy regulating SARM1 in axonal degeneration, we found that axonal accumulation of SARM1 was decreased after SCI in *Becn1*$^{+/-}$ autophagy hypomorph mice as compared to WT controls. Further study will be required to directly manipulate ULK1 *in vivo* to examine the effects on ULK1-SARM1 interaction and axonal degeneration after SCI.

Disclosures: H.M.C. Choi: None. **Y. Li:** None. **J. Wu:** None. **M.M. Lipinski:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Program #/Poster #: P361.12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: IBRO Early Career Awards 2020
FAPEMIG - Universal grant (APQ-00218-17)
CNPq - Universal grant (425669/2018-1)

Title: Aav-mediated overexpression of mir-26a stimulates regeneration in the central nervous system in vitro

Authors: *C. R. O. CYRINO[1], C. G. FERREIRA[2], R. A. A. COSTA[2], V. U. S. MATOS[2], L. CALDI-GOMES[4], U. MICHEL[5], V. T. RIBAS[3];
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Abstract: The central nervous system (CNS) neurons have low capacity for functional axon regeneration in part due to an imbalance in gene expression. Thus, investigating the role of molecules that control gene expression, such as microRNAs, may lead to the identification of novel targets to treat neurodegenerative disorders. MicroRNAs are small non-coding RNA molecules involved in the post-transcriptional regulation of gene expression. Recent studies highlighted the importance of microRNAs, such as miR-26a, in axonal regeneration control. The miR-26a promotes neurite outgrowth and axonal regeneration in the peripheral nervous system, by targeting mRNAs that encode proteins directly related to regeneration pathways, such as PTEN and GSK3β. However, the role of miR-26a in axon regeneration in the CNS is still not completely known. In the present study, we tested whether the overexpression of miR-26a promotes regeneration of CNS neurons in vitro. We produced recombinant adeno-associated viral (rAAV) vectors expressing miR-26a (rAAV.miR-26a) or EGFP (rAAV.EGFP), as control. Both vectors express EGFP fluorescent protein for identification of transduced neurons. All animal experiments were approved by the ethics committee for animal experiments of the Federal University of Minas Gerais. We used primary cortical neuron culture of Wistar rats at embryonic age 18 days to evaluate AAV transduction efficiency, neurite regeneration after scratch lesion and using a microfluidic device. Quantifications were done in a blinded fashion. We also did an in silico analysis to evaluate the mRNA targets of miR-26a. Both viral vectors showed proper and efficient transduction of primary cortical neurons, showed by positive expression of the reporter gene EGFP. In the neurite regeneration analysis, we found a significant increase in neurite length in the group transduced with rAAV.miR-26a compared to the control rAAV.EGFP. We also found that rAAV.miR-26a significantly increased the number of neurites at a distance of 200μm from the lesion border. Finally, in the in silico evaluation, we found 164 predicted and 33 validated mRNA targets of the miR-26a. Gene ontology analysis showed that some of these targets are involved in biological process and molecular function related to axon growth. These results suggest that miR-26a might control the regeneration of CNS neurons in vitro, however, further experiments are required to confirm this pro-regenerative effect in vivo. Therefore, this study points to the miR-26a as an interesting therapeutic target to promote regeneration in the CNS.

Disclosures: C.R.O. Cyrino: None. **C.G. Ferreira:** None. **R.A.A. Costa:** None. **V.U.S. Matos:** None. **L. Caldi-Gomes:** None. **U. Michel:** None. **V.T. Ribas:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Topic: C.11. Spinal Cord Injury and Plasticity

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Shriners Hospital Grant 86700-NCA
Shriners Hospital Grant 85111-NCA

Title: Role of Hedgehog signaling in the differentiation of motor and sensory neurons during spinal cord regeneration

Authors: M. R. KRUEGER, A. M. HAMILTON, *L. BORODINSKY;
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Abstract: Spinal cord injuries often result in loss of spinal cord neurons and atrophy of denervated muscle, causing devastating consequences to sensorimotor function and quality of life. Functional recovery depends on successful regeneration of the injured spinal cord and muscle. However, the signaling mechanisms that promote regeneration are unclear. Our previous studies have shown that Hedgehog (Hh) signaling is necessary for spinal cord and muscle regeneration in the tail of amputated larvae by enabling replenishment of neural stem cells and overall spinal cord outgrowth. Whether replenishing of motor and sensory neurons in the regenerating spinal cord is dependent on Hh signaling remains unknown. Here we investigate the signaling pathways that regulate the regeneration of motor and sensory neurons in *Xenopus laevis* larvae. Two-day old larvae were tail-amputated, allowed to regenerate for 2-4 days in the presence or absence of modulators of Hh signaling and processed for immunostaining for Sox2 (neural stem cell nuclei), HNK1 (sensory neuron axons), 3A10 (motor neuron axons), and HB9 (motor neuron transcription factor). The samples were then imaged and analyzed for sensory and motor neuron axonal density, and motor neuron number and localization. Preliminary data show that there is a decrease in the density of HNK1-labeled processes in the tail between 2 and 3/4 days post amputation (dpa), suggesting an initial overgrowth followed by pruning of sensory axons innervating the regenerated tail. Inhibiting Hh signaling by incubating larvae for 3 dpa with 10 μM cyclopamine, antagonist of Hh signaling effector Smoothened, increases sensory neuron axonal density by nearly 2-fold compared to larvae with enhanced Hh signaling by incubation with 1 μM SAG, Smoothened agonist. Motor neuron axon staining reveals that they are present in the regenerating tail as early as 3 dpa and run along the longitudinal axis of the larvae, but do not align with the dorsoventral axis of muscle chevrons, as observed in the stump, which may correlate with the lack of muscle chevrons in the regenerate. Motor neuron somas were detected in the regenerated spinal cord up to 300 μm from the amputation plane at a similar density as in the spinal cord of the stump. Current efforts are investigating the dependence of motor neuron regeneration on Hh signaling. These results suggest that sensory innervation of the regenerating skin remodels with the progression of regeneration in a Hh signaling-dependent manner. The presence and organization of motor neurons and their axons in the regenerating spinal cord alludes that by 3 days post injury, the spinal cord is resuming motor function in the regenerating tail.

Disclosures: M.R. Krueger: None. **A.M. Hamilton:** None. **L. Borodinsky:** None.

Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Program #/Poster #: P361.14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Alberta Innovates Health Solution

Title: The role of Sympathetic Preganglionic Neurons (SPNs) as spinal cord pressure sensors.

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Abstract: Rationale: Impairment of baroreflex is linked with numerous diseases including autonomic dysreflexia (AD), a condition that emerges after spinal cord injury (SCI) at or above the T6 spinal segment involving dysregulation of the autonomic control. Specifically, the absence of autonomic regulation in response to somatic or visceral stimulation below the SCI results in unmodulated reflexive sympathetic activation leading to episodic hypertensive peaks that may lead to life-threatening medical emergencies such as stroke, cardiac arrest, seizure, and even death. Although approximately >50% of patients with SCI experience AD, there is no effective permanent treatment for this disorder. The impaired reflexive sympathetic activation observed below the SCI suggests independent cardiovascular responsiveness originating from the spinal cord itself, which may be contributing to the hypertensive peaks. Previous data from the Wilson lab demonstrated that thoracic sympathetic preganglionic neurons (SPNs) located at the intermediolateral column (IML) are oxygen sensitive. As vasomotor control is tightly associated with the partial pressure of gases, it is likely that the SPNs may also have a pressure sensoring capability. **Aim:** To investigate the potential sensitivity and cellular mechanisms of SPNs acting as pressure sensors in the spinal cord, independent of regulation from peripheral baroreceptors and brainstem sites. **Methods:** Male Sprague Dawley rats were used in this study (50-150 g, n=6/ group). An *in-situ* artificially-perfused thoracic spinal cord preparation combined with electrophysiology recordings from the splanchnic nerve was performed to determine if sympathetic activity could be modulated by hypotensive events (40 mmHg) independent of descending baroreceptor inputs. Further, we investigated if ENaC and TRPM4/5 receptors might play a role in mediating pressure sensitivity in the IML. **Results:** Our results showed that hypotension stimulates the SPNs and increases sympathetic nerve activity in the absence of known baroreflexes. This response was significantly inhibited by selective ENaC and TRPM4/5 antagonists. Additionally, expression of TRPM4/5 in SPNs was confirmed using immunohistochemistry and RNAscope. **Conclusions:** These results demonstrate the potential role of thoracic SPNs as independent spinal pressure sensors, likely being regulated by the activation of TRPM4/5 and ENaC receptors present in the spinal cord. Further investigations on the pressure sensing mechanisms using *in vivo* models may reveal more effective treatment strategies to improve blood pressure control in spinal cord injured patients suffering from AD.

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Poster

P361. Spinal Cord Injury: Cellular and Molecular Mechanisms I

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Program #/Poster #: P361.15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FAPEMIG Universal Grant APQ-00218-17
CNPq Universal Grant 425669/2018-1
IBRO Early Career Awards 2020

Title: Microrna-22 promotes neurite regeneration of central nervous system neurons in vitro

Authors: *C. G. FERREIRA[1], C. R. O. CYRINO[1], R. A. DE ALMEIDA[1], V. U. S. MATOS[1], U. MICHEL[2], L. CALDI-GOMES[3], V. T. RIBAS[1];
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Abstract: The neurons that compose the central nervous system (CNS) of adult mammals have reduced axonal regeneration capacity due to intrinsic and extrinsic neuronal properties. Thus, damage to this system, including neurodegenerative diseases and traumatic injuries, can lead to permanent neurological deficits. In this sense, the search for a strategy that provides both neuroprotection and axon regeneration is crucial. The regulation of gene expression by gene transfer mediated by viral vector using microRNAs appears as a promising technique to promote the repair of CNS. The microRNAs are important in the regulatory pathways of gene expression. However, the available knowledge about their role in regeneration is still scarce. The aim of this work is to verify the role of microRNA-22 (miR-22), which has been shown to be an important regulator of neuronal survival, in neurite regeneration in the CNS in vitro. Experiments involving animals were performed with the approval of Ethics Committee for Animal Experiments of UFMG. First, we produced recombinant adeno-associated virus vectors (rAAV) expressing miR-22 (rAAV.miR-22). This rAAV vector also express mCherry fluorescent protein, allowing the identification of transduced neurons. As control, we produced a rAAV vector expressing only mCherry (rAAV.mCherry). We tested the transduction efficiency of rAAV.miR-22 and rAAV.mCherry *in vitro* using primary cortical neurons and *in vivo*, by intravitreal injection in Wistar rats to transduce retinal ganglion cells (RGCs). Then, we verified if rAAV-mediated overexpression of miR-22 promotes neurite regeneration in an *in vitro* model of scratch lesion of primary cortical neurons. Finally, we performed an *in silico* analysis to identify predicted and validated mRNA targets of miR-22 and also functional analysis for those targets. We observed that rAAV.miR-22 and rAAV.mCherry were, both, able to efficiently transduce primary cortical neurons *in vitro* and RGCs *in vivo*. *In vitro* neurite regeneration assay showed that rAAV.miR-22 increases neurite length and also the number of long distance regenerative neurites. According to the bioinformatics analysis, the miR-22 presents 178 predicted and 28 already validated mRNA targets. Functional analysis showed that these targets are related, for instance, to gene expression control, signaling pathways, anabolism and cell morphogenesis, important processes for axon regeneration. In conclusion, we showed a pro-regenerative effect of miR-22 in the CNS in vitro. Thus, this work provides a better understanding of the role of miR-22 in regeneration following CNS damage and points to miR-22 as an attractive target to promote CNS repair.

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Poster

P402. Pain Imaging and Perception I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P402.01

Topic: D.03. Somatosensation – Pain

Support: NIH R01AG059809
NIH R01AG067757

Title: Sex differences in cortical thickness and subcortical volume in knee osteoarthritis pain

Authors: *S. MONTESINO-GOICOLEA, P. A. VALDES-HERNANDEZ, A. JOHNSON, C. LAFFITTE NODARSE, J. A. PERAZA, R. B. FILLINGIM, Y. CRUZ-ALMEIDA;
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Abstract: Osteoarthritis (OA) affects 32.5+ million adults in the US (62% women). The neurobiology underlying sex differences in OA prevalence, as well as in experimental pain sensitivity, are poorly understood. In particular, studies on sex differences in brain structure in OA are virtually inexistent. This study aimed to compare brain morphological measures (BMM) among sexes. Our sample included 145 individuals 45-85 years with knee OA from the *Understanding Pain and Limitations in Osteoarthritic Disease-2* (*UPLOAD-2*) study at the University of Florida and the University of Alabama, Birmingham. Participants completed demographic, psychological, and self-reported and experimental pain assessments. T1-weighted anatomical images were acquired with a Phillips 3T scanner. Using FreeSurfer (v.7.1.0), cortical volume and thickness (CT) and subcortical volumes were calculated in selected areas of the Destrieux atlas known to be related to pain processing (subcentral, frontal, occipitotemporal, postcentral, insulae, cingulate, hippocampi and basal ganglia). Using SPSS v26, we tested BMM differences among sexes controlling for age, race, BMI, study site, and estimated total intracranial volume. In addition, for each sex, we calculated partial correlations (Pcorr), adjusted for same covariates, between BMM and each of several clinical and experimental pain, and psycological measures. Z tests were used to compare Pcorrs between sexes. Two tailed significance was set at alpha=0.05, corrected with False Discovery Rate. CT was significantly higher in females (Fs) than in males (Ms) in the: 1) left superior segment of the circular sulcus of the insula (CSI); 2) left anterior part of the cingulate gyrus and sulcus; and, 3) right middle-anterior part of the cingulate gyrus and sulcus. The Multidimensional Scale of Perceived Social Support (MSPSS) was negatively correlated with CT of left inferior segment of CSI in Fs. Pcorr between pain duration and 1) CT of left central operculum and middle frontal gyrus, and 2) volume of left hippocampus and amygdalae were lower in Ms than Fs. Pcorr between endogenous pain modulation and 1) CT of right middle frontal gyrus, and 2) volume of hippocampi were also lower in Ms than in Fs. Pcorr between CSQ-Passive coping and 1) CT of right parahippocampal gyrus, and 2) CT of right anterior segment of CSI were also lower in Ms than in Fs. Pcorr between endogenous pain modulation and volume of right amygdala, and between MSPSS and CT of left inferior segment of CIS were higher in Fs than in Ms. We provide initial evidence for a mediating role of brain structure in sex differences in clinical and experimental pain, and associated psychological factors.

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Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.02

Topic: D.03. Somatosensation – Pain

Support: NIH R35 NS097306
F32 DE029384
HHMI Hanna H. Gray Fellowship
Open Philanthropy

Title: Long-term imaging of spinal cord neural activity in awake, behaving mice

Authors: B. AHANONU[1], A. CROWTHER[1], M. ROSA CASILLAS[2], A. BASBAUM[1];
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Abstract: Pain and itch are complex, multidimensional percepts that require integration of incoming sensory information from the spinal cord with ongoing brain states to produce appropriate protective behaviors. It follows that studying this sensorimotor integration requires experiments in behaving animals. To date, however, unlike widely adopted techniques for imaging neuronal activity in the brain, the dorsal horn of the spinal cord presents major technical limitations for activity monitoring in awake animals. Thus, with very few exceptions, spinal imaging studies have been performed in anesthetized animals. That limitation precludes faithful study of stimulus-evoked activity in the awake preparation and cannot correlate activity changes over time in the same, genetically-defined neurons with behavioral endpoints of chronic pain or itch nor assess novel pain or itch treatments. A breakthrough, therefore, could result from the development of a durable spinal imaging method that permits longitudinal analysis of single neurons in awake, behaving animals. Building upon earlier methods to image the spinal cord *in vivo* (1,2,3), we have devised a microsurgical protocol to implant a custom-made metal chamber adjacent to vertebrae that, following laminectomy and glass window placement, provides stable optical access to superficial lamina of the lumbosacral spinal cord. Additional material components provided a critical feature, namely, long-term fibrosis inhibition. Our preparation achieved long-term optical clarity, for over three months postoperatively, and proved conducive to daily imaging via widefield and multiphoton time-lapse microscopy in awake, behaving mice. We demonstrate that this method allows long-term tracking of fine axonal structure in Thy1-GFP mice and repeated GCaMP-based calcium imaging of single-cell neural activity. Further, we observed neural responses to different somatic stimuli (noxious mechanical and thermal) that are somatotopically organized over the millimeter field-of-view. Importantly, using physiological measures, sensory and locomotor behavioral assays, and post-mortem histology, we verified spinal cord and animal health post-surgery. Our cost-effective method can empower future studies that aim to address outstanding questions about the processing of pain and itch messages, the longstanding labeled line vs. patterning controversy, referred pain and visceral organ cross-sensitization mechanisms, and spinal action of traditional and novel analgesics. 1. Herrero, J. et al 1993 J Neurosci Methods, 46: 225-232; 2. Sekiguchi, KJ et al 2016 Nat Comm, 7(11450);3. Farrar, MJ et al 2012 Nat. Methods 9: 297-302.

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Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.03

Topic: D.03. Somatosensation – Pain

Support: NIH-NIDDK F99-DK-126121
NIH-NCCIH R01-AT-007550

Title: Large scale momentary brain network behavior mediates action of insular excitatory-inhibitory neurotransmitter imbalance on chronic pain hypersensitivity

Authors: I. MAWLA[1], Z. HUANG[1], S. E. HARTE[1], D. J. CLAUW[1], G. A. MASHOUR[1], V. NAPADOW[2], R. E. HARRIS[1];
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Abstract: Background: Chronic nociplastic pain conditions such as Fibromyalgia (FM) are characterized by focal insular neurotransmitter imbalances (excitatory - inhibitory imbalance; E-I) as well as global brain network dysfunction. It is unknown if regional E-I imbalances impact large scale brain networks resulting in pain hypersensitivity.

Methods: Brain imaging was done on 64 females with Fibromyalgia (FM) and 19 healthy controls (HC). Proton magnetic resonance spectroscopy was collected in the right anterior insula (aINS) to calculate E-I balance using ratios of Glutamate+Glutamine to gamma-aminobutyric acid. Functional MRI was collected at task-free (REST) and tonic cuff pressure pain (PAIN) over the left lower leg. Temporal *k*-means clustering was conducted on REST across subjects to capture whole-brain momentary coactivation patterns (CAPs) at single timepoints. A supervised learning approach using REST CAPs was then applied to PAIN. Occurrence rates were computed as the presence of any particular CAP relative to total timepoints per subject. In addition, conventional whole-brain functional connectivity of the aINS was computed.

Results: FM patients required lower cuff pressure (p=0.0002) to evoke comparable painful experience to HC. Lower cuff pressures were associated with greater aINS E-I imbalance (r=-0.34) and pain interference (r=-0.32) in FM. Clustering produced eight distinct CAPs; support vector classification on pain-induced CAP occurrence rate changes (PAIN-REST: ΔP) distinguished FM from HC with 76% accuracy. In FM, ΔP decreased (p<0.0001) in a CAP with positive Salience/negative Default Mode (SLN+/DMN-), and ΔP increased (p=0.0004) in a CAP with positive sensorimotor/negative limbic (SMN+/Limbic-). Larger ΔP decrease in SLN+/DMN- was associated with greater pain interference (r=-0.29) and larger aINS E-I imbalance (r=-0.35). Larger ΔP increase in SMN+/Limbic- was related to greater pain interference (r=0.36) and lower cuff pressure (r=-0.36). The effect of cuff pressure on pain interference in FM was mediated by SMN+/Limbic- ΔP (indirect effect, BootCI=[-.0090,-.0007]). Whole-brain regression showed lower SLN+/DMN- ΔP was related to greater aINS-posterior cingulate (r=-0.51) and aINS-medial prefrontal (r=-0.50) connectivity. The effect of aINS E-I imbalance on aINS-posterior

cingulate connectivity in FM was mediated by SLN+/DMN- ΔP (indirect effect, BootCI=[.032,1.093]).

Conclusions: Hypersensitivity in chronic pain is mediated by a disruption of large scale dynamic brain patterns. In part this is initiated by increased excitability of the aINS leading to increased communication between SLN and DMN networks.

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Poster

P402. Pain Imaging and Perception I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P402.04

Topic: D.03. Somatosensation – Pain

Support: NIH Grant P01 AT009965-01
CIHR Fellowship MFE176554

Title: Association between trigeminal nerve microstructure and clinical characteristics in migraine: an ultra-high field 7 Tesla DTI study

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Abstract: Background & Aims: Migraine, a highly prevalent chronic pain disorder, involves sensitization of the trigeminal nerve system. Neuroimaging technologies offer a non-invasive, in-vivo approach to study the trigeminal nerve properties in humans. Notably, diffusion tensor imaging (DTI) studies have demonstrated microstructural alterations at the trigeminal nerve root in chronic pain conditions such as trigeminal neuralgia and temporomandibular disorder. However, the trigeminal nerve microstructure in migraine has not yet been adequately explored. We used ultra-high field (7 Tesla) DTI, allowing for improved spatial resolution, to evaluate the association between trigeminal nerve microstructural properties and clinical characteristics in episodic migraine. Methods: We enrolled 16 patients with episodic migraine in an ongoing treatment study (15F, mean age +/- SD: 38.1 +/- 13.5 yrs). All patients underwent a 7 Tesla DTI scan (64 directions, b=1,000, 1mm isotropic voxels) and self-reported clinical characteristics of their condition, including migraine disease duration (yrs), number of headache days/month, average headache duration (hrs), average headache pain intensity (0-10), and interictal phase (0-100; timing of DTI assessment relative to preceding (0) versus subsequent (100) attacks). DTI metrics of fractional anisotropy, axial, radial, and mean diffusivity were manually extracted from the root entry

zone of both trigeminal nerves. Spearman's rank-order correlations were performed to determine the association between each DTI metric and clinical measure. Results: High spatial resolution imaging successfully delineated the small-scale structure of the trigeminal nerve roots. There was a significant, negative correlation between axial diffusivity (AD) and disease duration (r=-0.55, p=0.029), and interictal phase (r=-0.53, p=0.043), such that AD was reduced with greater time since diagnosis and as patients approached their next attack. There was also a significant, positive correlation between AD and the number of headache days/month (r=0.57, p=0.022), such that AD was greater with more headaches experienced. No other significant correlations were observed. Conclusions: Trigeminal nerve root AD, a metric of axonal integrity, was correlated with disease duration, interictal phase, and the number of headache days per month. These preliminary results suggest both trait-like (i.e., disease duration, severity) and state-like (i.e., interictal phase) links to trigeminal nerve microstructure. Trigeminal nerve root remodeling may be an important aspect of the dynamics underlying migraine pathophysiology.

Disclosures: S. Tohyama: None. **M. Datko:** None. **L. Brusaferri:** None. **M. Hyman:** None. **K. Round:** None. **H. Housman:** None. **V. Le:** None. **R.G. Garcia:** None. **R.L. Gollub:** None. **R.R. Edwards:** None. **B.R. Rosen:** None. **N. Hadjikhani:** None. **H.T. Cheng:** None. **Z. Schuman-Olivier:** None. **M.L. Loggia:** None. **V. Napadow:** None.

Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.05

Topic: D.03. Somatosensation – Pain

Title: Dynamics of theta oscillations in the mouse primary somatosensory cortex represent the ongoing status of pain sensation

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Abstract: Pain, one of the most unpleasant sensations, is caused by tissue injury, inflammatory disease, pathogen invasion, and neuropathy. While several features of brain activity can represent the painful perception, predicting pain variability within a given individual and across individuals is difficult. Here, we examined oscillation dynamics of local field potentials to assess neuronal activity in the mouse primary somatosensory cortex, which is responsible for processing bodily pain, pressure, heat, cold, and vibration sensations. We found that the peak of theta-range oscillations (4-12 Hz) was shifted toward a slower frequency in response to a pain-induced stimulus following a peripheral formalin injection, which usually shows a bimodal behavioral response interposed between pain free periods. Importantly, the instantaneous theta-peak frequency inversely correlated with ongoing pain sensation. Instantaneous oscillatory analysis also revealed that the probability of slow theta oscillations increased during nociceptive phases associated with augmented slow theta power. Finally, phase-power cross-frequency coupling between theta and gamma oscillations demonstrated that the coupling peak frequency of theta oscillations was also shifted toward slower oscillations without affecting coupling strength or gamma

power. Together, these findings indicate that the dynamic changes in theta oscillations in the primary somatosensory cortex represent the ongoing status of pain sensation.

Disclosures: M. Tamura: A. Employment/Salary (full or part-time):; Mistubishi Tanabe Pharma Holdings America. **S. Iwamoto:** A. Employment/Salary (full or part-time):; Mitsubishi Tanabe Pharma Corporation. **A. Sasaki:** A. Employment/Salary (full or part-time):; Mitsubishi Tanabe Pharma Corporation.

Poster

P402. Pain Imaging and Perception I

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Topic: D.03. Somatosensation – Pain

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Title: Mapping neuronal activity provoked by general anesthesia-induced analgesia

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Abstract: Nitrous oxide (N_2O) is a fast-acting, weak general anesthetic that produces analgesia without loss of consciousness. Previous studies suggest that N_2O induces analgesia by engaging periaqueductal gray (PAG)-mediated descending inhibitory controls. Importantly, as N_2O is increasingly used for treatment-resistant major depressive disorder, N_2O anesthesia presents a unique opportunity to concurrently study the sensory-discriminative and the affective components of the pain experience. Based on its analgesic properties and on previous literature, we predicted that N_2O would decrease neuronal activity in the anterior cingulate cortex (ACC), which is implicated in pain's affective component. Surprisingly, however, N_2O exposure results in rapid, robust activation of ACC neurons (see Weinrich et al. poster). As the ACC provides excitatory input to the PAG, we hypothesized that N_2O-mediated analgesia involves cortically-mediated activation of PAG-derived descending controls. In adult male and female double transgenic TRAP2-Ai14 mice, we captured and compared brain-wide activity patterns in response to subanesthetic doses of N_2O and isoflurane, a sedating general anesthetic that induces unconsciousness. To permanently label neurons that were transiently activated during anesthesia, mice were injected with 4-hydroxytamoxifen and exposed to one hour of N_2O or isoflurane. Two weeks later, mice were exposed to one hour of a different gas and perfused one hour later for Fos immunostaining. We collected confocal images and used Imaris for cell counting and quantification. In both anesthesia experiences, we observed robust Fos+ labeling throughout the brain compared to control conditions, including in the ACC. This dose-dependent effect of anesthesia-induced activity is consistent with our calcium imaging data. We also observed Fos+ labeling in several pain-associated areas downstream of the ACC (e.g. PAG), but not in others (e.g. mediodorsal nucleus of the thalamus (MD)). Downstream regions

with higher N_2O-Fos+ labeling included the somatosensory cortex; regions with higher isoflurane-Fos+ labeling included the bed nucleus of the stria terminalis. Our findings suggest that the canonical understanding of ACC encoding of pain aversion ignores a differential contribution of cell type, layer specificity, and most importantly, projection target of the ACC neurons (e.g. PAG but not MD). Ongoing work includes identifying the cell types and projection targets of Fos+ neurons in the ACC and characterizing the extent to which N_2O and isoflurane activate distinct, non-overlapping, populations of neurons in the same regions.

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Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.07

Topic: D.03. Somatosensation – Pain

Support: ERC grant

Title: The multisensory integration between nociception and vision in the rubber hand illusion

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Abstract: Body ownership refers to the subjective perception of the body as one's own. The classic way to study body ownership in healthy individuals is to use a perceptual bodily illusion known as the rubber hand illusion (RHI). In the RHI, a rubber hand in the participant's view is synchronously stroked with the real hand hidden behind a screen. After ~20s of such stimulation, most participants start to experience the touches as originating directly from the rubber hand and that they own the rubber hand. Previous studies have demonstrated that this illusory percept arises from the integration of vision, tactile and proprioceptive signals. However, little is known about the role of nociceptive input to body ownership and the rubber hand illusion. Here we investigate the contribution of nociceptive signaling to body ownership by a "visuo-nociceptive RHI". To selectively activate nociceptors in the skin, we used Nd:YAP laser stimulator (Stimul 1340, Deka, 1.34 μm wavelength, 7 ms pulse) that specifically targets C and Aδ fibers. We recruited 90 naïve healthy participants over three separate experiments. In Experiment 1 we investigated the subjective experience of the visuo-nociceptive RHI with an 8 items questionnaire. We compared a condition with synchronous visual (a brief red light shining on the fake hand) and nociceptive stimulation on the rubber hand with a control asynchronous condition (the nociceptive input had 1000 ms delay compared to the red light). Experiment 2 used the same two conditions but quantified the illusion objectively with a proprioceptive drift task that registers the changes in hand position sense towards the rubber hand that occurs during the illusion and that is probed by asking the participants to close their eyes and point towards the location of their index finger. Finally, in experiment 3 we manipulated the spatial congruence of the orientations of the rubber and real hands. In the illusion condition, the rubber hand was placed in the same position as the real hand (0°) whereas in the control

condition the rubber hand was rotated 180°; we used the proprioceptive drift task. The results of Experiment 1 showed that people rated illusion-related items significantly higher in the synchronous condition than in the asynchronous condition ($p < .01$). In Experiment 2, the proprioceptive drift was significantly higher in the synchronous compared to the asynchronous condition ($p = .01$). Finally, in Experiment 3, the proprioceptive drift was significantly larger in the 0° condition compared to the 180° ($p = .001$). In conclusion, our results suggest that the RHI can be triggered by congruent nociceptive and visual signals and have a bearing on models of body ownership.

Disclosures: S. Coppi: None. **H. Ehrsson:** None.

Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.08

Topic: D.03. Somatosensation – Pain

Support: IBS-R015-D1

Title: The role of anterior cingulate cortex for active defensive response in pain processing

Authors: *J.-Y. LEE, T. YOU, G. IM, H. SEO, C.-H. LEE, S.-G. KIM;
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Abstract: Pain is an unpleasant experience that triggers defensive avoidance responses. The anterior cingulate cortex (ACC) is a critical brain region for signaling the unpleasantness of pain. However, the role of ACC in defense circuits is not well understood. Here, we use optogenetic fMRI (ofMRI) which is a combination of optogenetic modulation and fMRI to explore downstream neural circuits of ACC. Optogenetic silencing of ACC decreased BOLD activity in divergent brain regions including defense circuits such as superior colliculus (SC) and periaqueductal gray (PAG). Noxious electrical stimulation caused a positive BOLD response at both the somatosensory circuits (S1, S2) and defense circuits (SC, PAG). However, optogenetic silencing of ACC reduced the positive BOLD response of SC and PAG but did not affect S1 and S2. Anterograde tracers showed dense projections from ACC to SC and PAG. Especially, the projection from ACC to PAG is limited to dl/l PAG associated with an active defensive response. We also demonstrate that ACC-PAG circuit contributes to pain and defensive behaviors. Optogenetic activation of ACC-PAG projections induced pain hypersensitivity without anxiety behavior and enhanced active avoidance behavior, rather than caused analgesia and freezing response (passive defensive behavior). Taken together, our results indicate that ACC is anatomically and functionally connected with PAG, which contributes to pain and defense circuits.

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Poster

P402. Pain Imaging and Perception I

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Program #/Poster #: P402.09

Topic: D.03. Somatosensation – Pain

Title: Investigating the Effects of Flotation Restricted Environment Stimulation Therapy on Neural Networks in Chronic Pain Patients via Functional Magnetic Resonance Imaging

Authors: *T. A. MCGAUGHEY, V. S. FINOMORE, Jr;
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Abstract: Investigating the Effects of Flotation Restricted Environment Stimulation Therapy on Neural Networks in Chronic Pain Patients via Functional Magnetic Resonance Imaging
Authors: Finomore V.S. and McGaughey T.A.
According to the CDC, there are 50 million Americans living with chronic pain from which the majority suffer from chronic lower back pain. Current clinical approaches primarily focus on analgesia via strong opioids or invasive surgical interventions; however, these management strategies fail to consider patient suffering in its entirety while mitigating other key factors of the chronic pain experience, such as higher chronic stress levels, which profoundly affect somatosensory, default mode, and other vital neural networks. Flotation Restricted Environment Stimulation Therapy (REST) is a promising intervention for stress reduction, as it has altered key brain networks of interest in healthy participants. REST flotation requires individuals to fully relax in a sensory deprivation tank specifically designed to reduce auditory, visual, thermal, and tactile stimulation. In the present study evaluating the effects of flotation REST on neural networks impacted by chronic lower back pain, participants underwent resting state and task-based functional magnetic resonance imaging (fMRI) both before and after six flotation REST sessions and compared with control participants' identical fMRI scans conducted both before and after six sessions in a zero-gravity chair, located in a warm, quiet, dimly-lit room as to mimic float tank conditions. All scans were taken on a 3T PRISMA MAGNETOM (Siemens Munich, Germany). Resting state fMRI scans were analyzed via independent component analysis through the CONN toolbox (www.nitrc.org/projects/conn), while general liner modeling through AFNI (R.W. Cox NIH) was used to analyze task-based fMRI scans. The results found significant differences in resting state connectivity in the somatosensory and default mode networks across conditions. Additionally, the experimental group, but not the control group, showed significant differences in the prefrontal cortex over time. These neural changes, coupled with subjective alterations in pain, provide promising support for flotation REST as a supplemental treatment option for chronic lower back pain, demonstrating the importance of stress management in chronic pain treatment.

Disclosures: T.A. McGaughey: None. **V.S. Finomore:** A. Employment/Salary (full or part-time):; West Virginia University.

Poster

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Program #/Poster #: P402.10

Topic: D.03. Somatosensation – Pain

Support: RO1 DK110669
RO1 DK121724

Title: Analytic consistency and neural correlates of peak alpha frequency in the study of pain

Authors: *N. J. MCLAIN, M. S. YANI, J. J. KUTCH;
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Abstract: There is long-standing interest in resting-state peak alpha frequency (PAF) as a summary marker of neural activity. Several studies have found evidence of slowed resting-state peak PAF in chronic pain populations and individuals with high sensitivity to experimentally induced pain. There is some disagreement about how PAF relates to the physiology and experience of pain, and comparison across different types of pain populations is necessary. However, the stability of PAF from different analytic pipelines used in the pain literature has not been determined and underlying neural correlates of PAF have not been sufficiently substantiated in humans. Here we examine a range of analytic pipelines and the relationship of PAF to activity in the thalamus, a hypothesized generator of PAF. We collected resting-state functional magnetic resonance imaging (rs-fMRI) data and subsequently 64 channel resting-state electroencephalographic (EEG) from 48 healthy men. We identified important variations in EEG preprocessing pipelines for PAF from a review of 17 papers investigating the relationship between chronic pain and PAF. We tested three progressively more complex pipelines: Pipeline 1) notch filtering only, 2) Pipeline 1 and data re-referencing, and 3) Pipeline 2 and automatic artifact removal. Data for all three pipelines were then processed by the center-of-gravity (COG) method to determine peak frequency at each electrode. For all pipelines, a single principal component, well-represented by the average PAF across all electrodes (global PAF), explained >95% of the variance across participants. We also found that the global PAF was highly correlated among the analytic pipelines (>0.95). We additionally found interindividual differences in global PAF were significantly correlated with differences in fMRI-estimated activity in the thalamus. These results suggest that PAF is a stable marker with respect to analysis method and reflects interindividual differences in brain function.

Disclosures: N.J. McLain: None. **M.S. Yani:** None. **J.J. Kutch:** None.

Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.01

Topic: D.06. Auditory & Vestibular Systems

Support: Clinical and Translational Science Institute

Title: Neurophysiological improvements in speech in noise task after short-term choir training in older adults

Authors: *S. HENNESSY[1], R. WILCOX[2], A. WOOD[1], A. HABIBI[1];
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Abstract: Perceiving speech in noise (SIN) is important for health and well-being and decreases with age. Musicians show improved speech in noise abilities and reduced age related auditory decline, yet it is unclear whether short term music engagement has similar effects. In this randomized control trial we used a pre-post design to investigate whether a 12 week music intervention in adults aged 50-65 without prior music training and with subjective hearing loss improves well-being, speech-in-noise abilities, and auditory encoding and voluntary attention as indexed by auditory evoked potentials (AEPs) in a syllable in noise task, and later AEPs in an oddball task. Age and gender matched adults were randomized to a choir or control group. Choir participants sang in a 2 hr ensemble with 1 hr home vocal training weekly; controls listened to a 3 hr playlist weekly, attended concerts, and socialized online with fellow participants. From pre to post intervention, no differences between groups were observed on quantitative measures of wellbeing or behavioral speech in noise abilities. In the choir group, but not the control group, changes in the N1 component were observed for the syllable in noise task, with increased N1 amplitude in the passive condition and decreased N1 latency in the active condition. During the oddball task, larger N1 amplitudes to the frequent standard stimuli were also observed in the choir but not control group from pre to post intervention. Findings have implications for the potential role of music training to improve sound encoding in individuals who are in the vulnerable age range and at risk of auditory decline.

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Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.02

Topic: D.06. Auditory & Vestibular Systems

Support: DFG Wo 2371/1-1

Title: Distraction during selective attention induces rhythmically synced neural and behavioral responses

Authors: *T.-Y. LUI, J. OBLESER, M. WÖSTMANN;
Univ. of Luebeck, Lübeck, Germany

Abstract: Attentional sampling of task-relevant sensory stimuli operates in a rhythmic manner. However, the temporal trajectory of distraction by task-irrelevant stimuli is less well understood. We have previously shown that the vulnerability of working memory to distracting speech items fluctuates rhythmically. Here, we investigate the underlying neural responses to auditory distraction, as well as the correspondence of pre-distractor neural phase with behavioral indices of distraction. In the present behavioral and electroencephalography (EEG) study, we probed the temporal dynamics of distraction using a pitch discrimination task. Human participants (N = 30) compared the pitch of two target pure tones and were instructed to ignore an intermittent, task-irrelevant distractor tone sequence with a 25 Hz temporal structure. We systematically varied the onset time of the distractor, which was presented in-

between the two target tones. The degree of distraction was measured behaviorally via the ability to discriminate the target tones (perceptual sensitivity), and neurally via the amplitude of the distractor-evoked response at 25 Hz. Linear mixed-effect models with distractor onset phase as predictor (via sine- and cosine-transformed regressors) showed that distractor onset phase in the delta and theta frequency range (~3.5–5 Hz) modulated both perceptual sensitivity and 25 Hz amplitude. Furthermore, distractor onset phase at similar frequencies co-modulated the behavioral and neural measures of distraction. In order to reveal the underlying neural sources of rhythmic distractibility, we related the pre-distractor phase of 5 Hz source-projected neural oscillations to perceptual sensitivity. The phasic modulation of sensitivity was most prominent in the left inferior frontal cortex. These results suggest that ~5 Hz phasic modulation of neural activity acts as a rhythmically fluctuating attention filter, which alternates between states of higher versus lower distractibility at a frequency of ~5 Hz.

Disclosures: T. Lui: None. **J. Obleser:** None. **M. Wöstmann:** None.

Poster

P449. Auditory Processing: Speech Perception

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant R01DC015462

Title: Age effects on cortical tracking of word-level features of continuous competing speech

Authors: *J. MESIK, L. RAY, M. WOJTCZAK;
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Abstract: Increased difficulty with speech-in-noise (SIN) comprehension commonly arise with aging, yet this deficit is often undetected by traditional speech perception measures. In recent years, electroencephalographic (EEG) studies on young normal-hearing adults identified robust neural signatures of high-level responses to semantic features and lexical predictability. Here we investigated whether these responses vary as a function of age and self-reported SIN perception difficulties. Additionally, we assessed how these measures are affected by the quantity of recorded data. Younger (18-40 yrs., n = 20) and older (41-70 yrs., n = 21) adults participated in a noninvasive EEG recording from 64 surface electrodes, while attending to one of two diotically presented audiobooks (65 dB SPL each). After each ~60 sec block, participants responded to several comprehension questions about the target story. Additionally, participants completed a modified speech, spatial and qualities of hearing (SSQ_m) scale to assess their subjective SIN perception difficulties. Transcripts of the audiobooks were separately used to generate time-resolved four-feature regressors, with each word characterized by its: 1) onset, 2) "semantic" dissimilarity from the preceding context, 3) lexical surprisal, and 4) overall audibility, reflecting the average signal-to-noise ratio. These features were regressed against the EEG signal to estimate the strength of cortical tracking of each feature, and the corresponding temporal response functions (TRF), for both attended and ignored speech. We found robust tracking of all features for attended speech, with surprisal and word audibility showing stronger contributions to neural activity than

dissimilarity. Importantly, older adults showed significantly stronger feature tracking than younger adults, especially at frontal electrode sites, potentially reflecting increased listening effort. Similar trends were observed with TRFs, albeit to a weaker degree. Moreover, we found trends of a negative relationship between SSQ_m and the overall model fit for attended speech, and a positive relationship between task performance and the overall model fit, indicating behavioral relevance of these measures. Finally, while word-level responses were detectable with just minutes of data, both the model fit and TRF estimates monotonically improved with more data up to 40+ minutes (full dataset), indicating that session duration is a critical parameter in multi-feature studies of speech processing. Our results demonstrate the potential for the use of complex, word-level features to study changes in speech processing due to aging and hearing loss.

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Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.04

Topic: D.06. Auditory & Vestibular Systems

Title: Relationship between Temporal Fluctuations in Visual and Auditory Attention and Medial Olivocochlear Reflex

Authors: *M. SUZUKI, Y. ISHIZAKA, S. OTSUKA, S. NAKAGAWA;
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Abstract: The olivocochlear bundle (MOCB) is an efferent neural pathway originating from the brainstem and terminating inside the inner ear. MOCB is activated by sounds and suppresses the amplification of outer hair cells, which is called the medial olivocochlear reflex (MOCR). MOCR is thought to play a role in improving listening in noise and protecting the inner ear from loud sounds. Several studies reported that MOCR is modulated by performing auditory and visual attentional tasks, which was revealed by comparing MOCR strength averaged across time points during each task. However, attention fluctuates from moment-to-moment during sustained performance.
In this study, we quantitatively evaluated the fluctuations in attention by measuring the reaction time to the auditory and visual discrimination task. In the auditory discrimination task, a low- (1-3 kHz) or a high-frequency (3-5 kHz) noise was presented in random order, and listeners were instructed to respond to the low-frequency noise (go signal) as quickly as possible but not to the high-frequency noise (no-go signal). In the visual discrimination task, the go and no-go signal were a cross and a circle displayed on an LCD monitor, respectively. The white noise inducing MOCR was presented simultaneously with the circles and crosses. In both tasks, the probability of appearance of the go and no-go signal was 90 and 10%, respectively. All noises were presented to the left ear at a sound pressure level (SPL) of 60 dB. MOCR was evaluated noninvasively by measuring otoacoustic emission (OAE), which are sounds physiologically emitted from the inner ear. We measured OAEs evoked by clicks presented to the right ear at the rate of 40 clicks per second and at a peak equivalent SPL of 55 dB. The OAE suppression induced by the low-frequency noise (in the auditory task) and the white noise (in the visual task) was

measured. The OAE suppression is reported to reflect MOCR strength.
The reaction time and the MOCR strength (OAE suppression) fluctuated with time on a scale of several minutes. The MOCR strength was negatively correlated with the temporal fluctuations of the reaction time for the auditory task but not with those for the visual task. The results suggest that MOCB activity decreases due to temporary insufficient attention to auditory domain, which would lead to longer response time, but is not affected by visual attention. This suggests that the higher the level of attention to hearing, the stronger the MOCR. In other words, the lack of attention to hearing suggests that MOCR may weaken the inner ear protection and increase the risk for noise-induced hearing loss.

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Poster

P449. Auditory Processing: Speech Perception

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Topic: D.06. Auditory & Vestibular Systems

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Title: Neural representations of acoustic and spatial features interact during auditory object formation.

Authors: *K. VAN DER HEIJDEN[1], P. M. PATEL[2], S. BICKEL[4], J. L. HERRERO[5], A. D. MEHTA[6], N. MESGARANI[3];
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Abstract: In everyday life, human listeners readily extract relevant auditory objects from complex, multi-source auditory scenes. Yet, it is presently unclear how neuronal representations of acoustic and spatial features interact during auditory object formation as prior research typically required listeners to attend to a single sound feature only. Here, we address two central questions about the neuronal transformation of an acoustic-based representation into perceived auditory objects by analyzing invasive intracranial neuronal responses in neurosurgical patients measured with stereotactic electroencephalography. First, when and where in the cortical auditory hierarchy do neuronal representations of spatial and acoustic sound features interact during auditory object formation? Second, how is the transient emergence and decay of - multi-dimensional - feature and object representations affected by attention and by moment-by-moment fluctuations in energetic masking? Participants (N = 7) listened to mixtures of two concurrent, spatially separated speakers (-45° and +45°). Participants were instructed to attend to either the male or female speaker and to report the spatial location of the attended speaker at random moments in between trials to ensure simultaneous attention to spatial and acoustic features. To reveal the transient emergence of neuronal representations of acoustic features (speaker spectral profile), spatial features (location) and auditory objects (speech), we extracted the envelope of the high-gamma band (70-150Hz) and analyzed the time course of neuronal activity in primary and secondary cortical auditory regions. Our findings

show that spatial and acoustic feature representations are transformed from an acoustic-based into an attention-dependent, acoustic-invariant representation at different stages of the cortical auditory hierarchy and come together as an object representation in the superior temporal gyrus. Classifiers trained to identify either location or speaker from distributed neuronal activity patterns, revealed a transient emergence and decay of spatial and acoustic feature representations. The emergence of such representations was affected by the moment-by-moment strength of energetic masking in distinct ways for spatial and acoustic features. Taken together, these findings emphasize the multi-dimensional character of auditory object encoding in the cortical auditory hierarchy and shed new light on the interaction between the ventral and dorsal auditory stream.

Disclosures: K. van der Heijden: None. **P.M. Patel:** None. **S. Bickel:** None. **J.L. Herrero:** None. **A.D. Mehta:** None. **N. Mesgarani:** None.

Poster

P449. Auditory Processing: Speech Perception

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P449.06

Topic: D.06. Auditory & Vestibular Systems

Title: Brain oscillations during degraded speech perception based on prior and acoustic information

Authors: *S. SAIKAN, S. OTSUKA, S. NAKAGAWA;
Chiba University, Chiba, Japan

Abstract: Neural mechanisms underlying speech understanding have been investigated by seeking the brain areas whose activity covaries with the intelligibility of acoustically degraded speech stimuli. Typically, the intelligibility of a stimulus was modulated by giving prior information about the stimulus, e.g., presenting the original clear speech, or by manipulating acoustic information contained in the stimulus. We investigated neural mechanisms underlying the changes in the intelligibility attributed to those two types of information by measuring gamma-band electroencephalogram (EEG) oscillations. Two types of activity in gamma-band can be differentiated: evoked and induced. Whereas the evoked-gamma response is phase-locked to the stimulus onset, the induced gamma response appears with jitter in latency and is reported to be associated with high-level cognitive processes (e.g., short-term memory). Degraded speech stimuli were generated from original phrases in the form of “Ready bear go to (color) (number) now”, with the inclusion of five colors (red, blue, white, peach, rainbow) and nine numbers (0, 1, 3, 4, 6, 7, 8, 9, 10). In total, 45 original phrases were used. The intelligibility of the degraded speech stimuli was manipulated by changing the bandwidth of their formants from 20 to 200 Hz; the narrower the bandwidth of the formants, the lower their intelligibility. Listeners heard the degraded speech stimuli before and after the exposure to the original phrases. In the pre-exposure condition, listeners were required to answer color and number contained in the degraded speech stimulus, and identification performance was assessed as the correct answer rate. The percentage of correct answers was significantly increased as the formant bandwidth increased. No significant changes associated with the formant bandwidth were observed in the evoked- and induced-gamma response. In contrast, the magnitude of the induced-gamma response tended to increase after the original speech presentations regardless of the bandwidth of the formants. The

magnitude of EEG oscillations at slightly higher than gamma band (70-100 Hz) also increased after the original speech presentations. Given oscillations at the frequency range were reported to be associated with short-term memory, the results imply that processes related to short-term memory are prominent during degraded speech perception based on prior information.

Disclosures: S. Saikan: None. **S. Otsuka:** None. **S. Nakagawa:** None.

Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.07

Topic: D.06. Auditory & Vestibular Systems

Support: NSERC Grant RGPIN-2015-05065

Title: Reduced auditory cortical gamma-Aminobutyric acid (GABA) affects gamma-band oscillations and contributes to speech-in-noise (SIN) loss in older age

Authors: *S. DOBRI[1,2], B. ROSS[1,2];
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Abstract: Difficulties in understanding speech in the presence of background noise are a significant concern for aging people. The causes of speech-in-noise (SIN) loss involve aging-related changes at all levels of auditory processing. At the level of perception, deficits in separating the speech sound from noise prevent the older listener from perceiving the target speech as a distinct auditory object and extracting meaningful information from it. The brain uses gamma frequency oscillations to organize acoustical information into auditory objects. Cortical gamma oscillations are generated through reciprocal interconnections between inhibitory interneurons and pyramidal cells, and depend on a fine balance between excitatory and inhibitory connections. Thus, the inhibitory neurotransmitter gamma-Aminobutyric acid (GABA) plays a major role in the generation of gamma oscillations.
This study investigated the associations between healthy aging, behavioural performance in SIN understanding, auditory evoked gamma oscillations, and the concentration of GABA in the auditory cortex. Gamma oscillations were recorded with magnetoencephalography (MEG) in 19 young and 19 older human adults. The level of GABA in their left and right auditory cortices was estimated using MEGA-PRESS magnetic resonance spectroscopy (MRS).
We found bilateral decreases in auditory cortical GABA levels in aging. Decreased GABA in the right auditory cortex was correlated with more severe SIN loss as assessed with QuickSIN. A MEG response suppression paradigm with fast stimulus repetition showed decreased response suppression in aging, indicating reduced ability for response inhibition. Reduced response inhibition was correlated with age but not with SIN loss. However, simultaneously elicited transient gamma-band responses increased in aging and were correlated with SIN loss. In addition, 40-Hz auditory steady-state responses (ASSR) were recorded with and without concurrent multi-talker babble noise. The 40-Hz ASSR amplitude was reduced in the noise condition compared to the no-noise condition. The amount of response reduction was smaller

in aging, and was correlated with SIN loss. The results suggest that an aging-related reduction in auditory cortical GABA impacts functionally relevant gamma band activity, contributing to SIN loss in older age.

Disclosures: S. Dobri: None. **B. Ross:** None.

Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.08

Topic: D.06. Auditory & Vestibular Systems

Support: NIH-NIDCD

Title: Neural tracking of target speech in multitalker speech perception reflects speaker's intelligibility

Authors: *X. HE, V. S. RAGHAVAN, N. MESGARANI;
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Abstract: Neural responses in the auditory cortex track the acoustic envelope of speech, and this tracking is enhanced by attention to a speaker in multi-talker speech. Recent research has shown that neural speech tracking can be used to predict speech intelligibility and is closely linked to intelligibility through a range of influences, such as SNR, speech rate, visual cues, and prior knowledge. However, our current understanding of neural speech tracking is limited either by a narrow set of experimental conditions or a lack of behavioral data. Further, neural speech tracking can be leveraged for auditory attention decoding, a system used in neurally-assisted hearing devices to improve speech understanding in challenging multi-talker acoustic environments. Therefore, it is important to characterize neural speech tracking in a variety of multi-talker experimental conditions and compare it with behavioral intelligibility data.
Here, we recruited 15 native English speakers for a 1.5h EEG experiment. Subjects were presented with 160 trials of 35s stories from 2 speakers spatially separated at ±45° azimuth with background noise. First, word-level speech intelligibility is measured for each subject as a function of SNR. Then, subjects were instructed to focus on a specific speaker in different types and volumes of noise based on their intelligibility-SNR curves. Decoders were then trained to reconstruct the acoustic envelopes of the attended and unattended speakers from 64-channel EEG using regularized linear regression and were tested using leave-one-trial-out cross-validation. Neural speech tracking for both attended and unattended speakers was assessed by computing the correlation between the predicted and true envelopes under each experimental setting.
We identified a minimum threshold of intelligibility for each subject above which the neural tracking of the attended speaker exceeded that of the unattended speaker, and this threshold was consistent across noise types. Below this level, the prediction correlations were similar between speakers due to the competition of top-down attention on the target speech and bottom-up speech saliency of the surroundings. These results support the idea that there is a threshold of intelligibility for successful neural speech tracking and this threshold is not dependent on the type of background noise. These findings deepen our understanding of the relationship between intelligibility and speech tracking and crucially constrain the implementation of auditory attention decoding systems.

Disclosures: X. He: None. **V.S. Raghavan:** None.

Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.09

Topic: D.06. Auditory & Vestibular Systems

Support: Del Monte Institute for Neuroscience Pilot Grant OP346161

Title: The electrophysiological representations of hierarchical speech features vary as a function of background noise

Authors: *S. R. SYNIGAL[1], A. J. ANDERSON[2,3], E. C. LALOR[1,2,3];
[1]Biomed. Engin., [2]Neurosci., [3]Del Monte Inst. for Neurosci., Univ. of Rochester, Rochester, NY

Abstract: Speech is a hierarchically organized form of communication that consists of features that are differentially processed in distinct brain areas, at various timescales. The brain's ability to track each feature, however, may change when background noise is introduced. For example, it has been shown that the cortex continues to track the speech envelope until there is more than twice the amount of noise masking it. Meanwhile, other work has shown that blood oxygen level-dependent (BOLD) activations to syllables decrease in dorsolateral temporal cortex, and BOLD responses to semantically coherent sentences first increase and then decrease in left inferior frontal regions as speech gets noisier. Each of these studies, however, uses different tasks, maskers, and signal-to-noise ratios which can all affect brain activation patterns. Testing each feature in one experiment will show how the encoding of each representation varies across different listening conditions. Although studies have examined how individual speech features are affected by noise, these features are not independent of one another. In fact, it has been hypothesized that higher-level representations can bias perception when incoming stimuli are noisy. The top-down influence of semantic context has been used to bias listeners to hear a specific word even when the critical phoneme of that word is replaced with noise. Recent work also found that semantic context can affect the processing of a word's acoustic and phonetic features. Yet, it is unclear how this bias varies at different hierarchical levels of speech and across different noise levels. Thus, the first goal of this study is to determine how the encoding of various speech features covary across different listening conditions. The second goal is to explore how top-down influences change as speech intelligibility decreases. In this experiment, electroencephalography data was collected while participants listened to a narrative in five different levels of background noise. Subjects also answered comprehension questions and rated speech intelligibility after each trial. Using linear modeling, we find that the encoding of acoustic and linguistic features weakens differentially with increasing levels of noise. Additionally, a second stage regression analysis shows that predictions based on higher-level speech features positively impact the encoding of acoustic-phonetic features for certain noise levels. With this study we seek to extend our understanding of the hierarchical processing of continuous speech under a range of realistic listening conditions.

Disclosures: S.R. Synigal: None. **A.J. Anderson:** None. **E.C. Lalor:** None.

Poster

P449. Auditory Processing: Speech Perception

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Program #/Poster #: P449.10

Topic: D.06. Auditory & Vestibular Systems

Support: NIH-NIDCD

Title: Distinct neural encoding of glimpsed and masked phonetic features in multitalker speech perception

Authors: *V. S. RAGHAVAN[1], J. A. O'SULLIVAN[1], S. BICKEL[2], A. D. MEHTA[2], N. MESGARANI[1]; [1]Electrical Engin., Columbia Univ., New York, NY; [2]Hofstra Northwell Sch. of Med., Manhasset, NY

Abstract: Speech perception in multitalker acoustic environments is a challenging task requiring a listener to extract and group the phonetic features of a target talker from those of non-target talkers. Because speech is a structured sound composed of sparsely distributed regions of energy with redundant information, it is hypothesized that listeners rely on glimpses of spectrotemporal regions in which one talker contains more energy than the others. The glimpsing hypothesis has been tested with computational and behavioral models to show that glimpses contain sufficient information to support speech recognition. While the glimpsing model makes no claims regarding the processing of masked phonemes, one possibility, supported by the phoneme restoration effect, is that masked phonemes may be restored at the acoustic-phonetic level using glimpsed information. Despite the computational and behavioral evidence, the neuroscientific evidence for the glimpsing model is lacking. Specifically, we do not know if glimpsed and masked phonemes of target and nontarget talkers are encoded differently in the human auditory cortical areas. It is also unclear how attention to a talker changes the processing of glimpsed and masked phonemes of that talker. Here, we obtained intracranial EEG recordings in primary and nonprimary auditory cortex, including Heschel's gyrus (HG) and superior temporal gyrus (STG) respectively, while subjects attended to one talker in a co-located two-talker mixture. We used linear encoding models to predict the high-gamma band envelope of neural responses using acoustic, phonetic, and phonotactic features of the target and non-target talkers. We confirmed that linguistic processing beyond phonetic features is only present for the target talker. In processing phonetic features, neural responses were more accurately predicted using separate glimpsed and masked phonetic representations. In particular, we found a robust encoding of glimpsed phonetic features of both target and non-target talkers in HG; however, masked phonemes of either talker were not encoded in HG. We also found that STG represents both masked and glimpsed phonetic features but only for the target talker, with masked phonetics encoded with an additional 100ms delay. Together, these findings provide neural evidence for the glimpsing model, suggesting that the auditory cortex selectively uses glimpses of the target talker to restore masked speech at the acoustic-phonetic level, leading to a complete and invariant representation of target talker phonetic features in the STG that can simplify noise-invariant lexical and semantic processing in downstream auditory cortical areas.

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Poster

P449. Auditory Processing: Speech Perception

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Topic: H.01. Attention

Support: DARPA Grant N660011824024
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Title: Cortical Processing of Arithmetic and Simple Sentences, in an Auditory Attention Task

Authors: *J. P. KULASINGHAM, N. H. JOSHI, M. REZAEIZADEH, J. Z. SIMON;
Electrical and Computer Engin., Unviversity of Maryland, College Park, MD

Abstract: The neural basis of arithmetic and language processing may rely on distinct cortical networks which must also be disentangled from mechanisms underlying the sensory modality of presentation. Here we use spoken equations and sentences to investigate neural processing of arithmetic, compared to general language processing, in an attention-modulated cocktail party paradigm. Magnetoencephalography (MEG) data was recorded from 22 participants listening to simple sentences and arithmetic equations which were presented diotically at distinct word, symbol, sentence and equation rates. This allowed for analysis of neural responses to words and symbols to be largely dissociated from responses to sentences and equations. The sentences and equations were presented either alone, or simultaneously in a competing speaker paradigm and participants were told to attend to only one of the speech streams. Neural responses at the word and symbol rates (which also correspond to repetitive acoustic features), were seen for both speech streams, indicating pre-attentive auditory processing. In contrast, neural responses at the sentence and equation rates (which do not correspond to stimulus acoustics), were present only for the attended stream. Source localized responses in the frequency domain revealed both shared and distinct cortical networks underlying equation and sentence processing. Responses to both sentences and equations were found in temporal lobe, with a left-hemispheric dominance. However, equation responses additionally localized to bilateral parietal areas, possibly indicating distinct networks involved in arithmetic processing. Critically, these higher-level neural responses were significantly correlated with behavioral performance in a deviant detection task. Additionally, the spatiotemporal dynamics of these responses were investigated using Temporal Response Functions. Cortical activity peaked towards the end of the sentence/equation in temporal/parietal areas, possibly indicating processing of sentence/equation completion. Finally, linear decoders trained to classify attention to sentences vs. equations based on MEG responses revealed further differences in these neural responses, with decoding accuracy being highest in superior parietal areas. These results indicate that the cortical networks underlying arithmetic and language processing are well segregated during a competing speaker paradigm, and that these neural responses are linked to comprehension or correct calculations.

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Poster

P512. Cerebellum: Cortex and Nuclei II

Location: Virtual Only

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Topic: E.02. Cerebellum

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NCBS graduate student fellowship to Vandana

Title: The role of Purkinje neuron bistability in cerebellar output and motor behaviour in larval zebrafish

Authors: *V. AGARWAL, S. NARAYANAN, S. CHINTA, V. THIRUMALAI;
Natl. Ctr. For Biol. Sci., Bangalore, India

Abstract: The cerebellum is a brain structure involved in motor control and coordination and its circuitry is well conserved among vertebrates. A lot is known about inputs to the cerebellum, but not much is known about cerebellar output and its effect on motor activity. We looked at 2 neuronal types in the cerebellum - Purkinje neurons (PNs), first place of convergence of multiple inputs to the cerebellum and eurydendroid cells (ECs), which are output neurons of the zebrafish cerebellum and are homologs of the mammalian deep cerebellar nuclear cells. PNs exhibit membrane potential bistability and their activity patterns are distinct in these two states. In the ‘up’ state PNs generate tonic spiking while in the ‘down’ state, they produce burst firing. Multiple PNs converge onto single ECs and inhibit them. We recorded the activity of ECs simultaneously with motor bouts and found that most ECs show correlated spiking during motor bouts. To understand how PN membrane potential bistability and spiking patterns affect EC activity, we used optogenetics to modulate both. While long duration light pulses stably reset PNs to the depolarized ‘up’ state, short pulses triggered synchronized spiking. We used these to modulate the output of PNs while simultaneously monitoring motor output and EC activity during the closed loop optomotor paradigm. We will discuss the results from these experiments.

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Poster

P512. Cerebellum: Cortex and Nuclei II

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Program #/Poster #: P512.02

Topic: E.02. Cerebellum

Support: NIH Grant NS116854

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Title: Modulation of synaptic inhibition in Purkinje cells during sensorimotor integration in vitro and in vivo

Authors: *M. R. HOLLA, S. T. BROWN, I. M. RAMAN;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: In awake mice, suppression of crus I/II cerebellar Purkinje (Pkj) cell firing is the first response to somatosensory input (air puffs) to the whisker pad. This inhibition of Pkj cells briefly disinhibits cerebellar nuclear (CbN) cell targets, increasing cerebellar output and augmenting whisker movement. Sensory-evoked inhibition of Pkj cells is interesting, since trigeminal nuclei mossy fibers excite granule cells whose parallel fiber (pf) axons directly excite Pkj cells and indirectly inhibit Pkj cells via molecular layer interneurons (MLIs). This circuitry raises the questions of how the effect of disynaptic inhibition precedes that of monosynaptic excitation, as well as whether this dominantly inhibitory response is subject to modulation. To investigate these issues, we made whole cell voltage clamp recordings of Pkj cells in cerebellar slices of 4- to 6-week-old mice. Stimulating pf 5x at 50 Hz evoked excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs). Pf-EPSCs were strongly facilitating, whereas pf-MLI-IPSCs were stable (non-facilitating), resulting in a changing E/I ratio over the train of stimuli. Cell-attached recordings of action potentials showed that, with the same pf stimuli, suppression of firing rates was more effective early in the train, suggesting that inhibition strength may depend on pf facilitation status. Since synaptic currents are sensitive to neuromodulators like norepinephrine (NE), we tested the effect of bath application of isoproterenol. With this beta-adrenergic agonist, pf-MLI-IPSC amplitudes nearly doubled, with no changes in short term plasticity; Pkj cell baseline firing rate was reduced; and the frequency of spontaneous IPSCs in Pkj cells increased, consistent with increased firing of MLIs. Also, the mean amplitude and decay rate of spontaneous IPSCs increased, suggesting that activation of beta-adrenergic receptors may differentially recruit basket and stellate cells. Isoproterenol also increased the magnitude of pf-evoked suppression of Pkj firing. The data suggest that neuromodulatory changes in the E/I ratio in Pkj cells in vivo may affect sensorimotor integration. To begin to test if/how different E/I ratios may affect movement, air puffs were applied at different frequencies (5x at 5-40 Hz) to the whiskers of awake head-fixed mice during Pkj cell recordings. The magnitude of suppression of Pkj cells changed with stimulus number and interval and correlated with similar changes in whisker movement. The data illustrate how E/I ratios that dictate Pkj cell output can change with stimulus parameters, context, and/or neuromodulatory state, thereby modulating cerebellar control of movement.

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Poster

P512. Cerebellum: Cortex and Nuclei II

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Topic: E.02. Cerebellum

Support: R01NS112917

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K99EY030528

Title: Circuit-level computations in the cerebellar flocculus: transforming inputs to outputs

Authors: *D. J. HERZFELD, N. J. HALL, S. G. LISBERGER;
Duke Univ., Durham, NC

Abstract: The floccular complex of the cerebellum is crucial for the performance of smooth pursuit eye movements. Leveraging the well-characterized anatomy of the cerebellar circuit, we can begin to investigate the computations performed by the circuit in support of this motor behavior. Here, we recorded from the floccular complex of rhesus macaques using multi-contact silicon probes. Using a combination of waveform, firing rate characteristics, and cerebellar layer, we assigned a putative cell type label to each well-isolated unit. These data allow us to begin to answer how the flocculus performs intrinsic computations.
Mossy fibers (MFs) are the primary excitatory input to the flocculus. In agreement with previous data, our MFs demonstrate diverse pursuit-related responses including modulation due to eye position, velocity, and visual (retinal-slip) signals. MFs synapse onto granule cells, whose axons form the excitatory input to Purkinje cells (PCs), the primary output of the cerebellar cortex. Beyond this feedforward excitatory pathway, the cerebellar circuit features feedback; recurrent and feedforward inhibitory processing elements that may substantially alter the flow of information from MFs to PCs. A crucial first question is whether feedforward excitation from MFs through granule cells to PCs is sufficient to explain PC firing. We constructed an artificial population of 10,000 granule cells with responses during pursuit based on input from our recorded MFs. Each simulated granule cell received four randomly chosen MF inputs with a random positive weight. We then asked whether this simulated population of granule cells was capable of predicting the pursuit-related firing responses of recorded PCs. That is, we asked whether granule cell inputs derived from MFs form a sufficient basis set to explain PC firing during pursuit. Using non-negative linear regression, we found the optimal weights between these simulated granule cells and our recorded PCs. Across the PC population, the feedforward excitatory pathway from MFs to granule cells to PCs was able to explain 55% of the PC response variance. Crucially, this result was largely independent of the number of simulated granule cells.We next asked whether the addition of feedforward inhibition from molecular layer interneurons provided an enhanced basis set to explain PC firing. It did: addition of feedforward inhibition explained 72% of the PC response variance. Taken together, our results demonstrate that processing in the feedforward and recurrent circuitry of the floccular complex is likely to involve significant processing beyond the simple feedforward excitation pathway.

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Poster

P512. Cerebellum: Cortex and Nuclei II

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Topic: E.02. Cerebellum

Support: R01 NS113078
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R21 EY028749

Title: Stimulus and response encoding in a population of Purkinje cells in Crus I and Crus II of the cerebellum during an arbitrary visuomotor association task.

Authors: *A. IPATA[1,2,3], V. FASCIANELLI[3,4], N. SENDHILNATHAN[1,2,5,3], M. E. GOLDBERG[1,2,3,6,7], S. FUSI[1,4,3,6];
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Abstract: We previously showed that when monkeys perform a reinforcement learning arbitrary visuomotor association task, Purkinje cells (PCs) in Crus I and II exhibit an error signal which approaches zero as the monkeys learn the correct associations (Sendhilnathan, 2020). In our previous analysis we showed that the average firing rate of these neurons reflects neither the kinematics of the movements nor the identity of the stimuli. Here we asked if information about the nature of the stimulus or the choice of the movement could be decoded from the activity in the ensemble of PCs. We recorded neural activity of single PCs in the mid-lateral cerebellum while monkeys performed an arbitrary visuomotor association task. Each trial started when monkeys grabbed two bars, after which one of a pair of stimuli appeared at the center of the screen. The identity of each stimulus instructed which bar to release. In the familiar task, their performance was close to 100% in every session. In the novel task we presented a pair of stimuli that the monkeys had never seen, and they had to learn the correct associations between the stimuli and the hand movements through trial and error. Using a linear decoder on the population ensemble, we identified which hand the monkey would release on every trial. In the familiar task and during the later learning trials, the decoder identified the hand 380 ms before the movement. In correct early learning trials, the decoder identified the hand 200 ms before the movement. In early error trials the decoder identified the hand only 100 ms before the movement. Because the hand and stimulus were tied together, we could not dissociate the identities of the stimulus and the movement. To dissociate them, we reversed the associations after the monkeys had learned the novel task. Now the monkeys had to learn the new associations of the same symbols. By combining both novel and reversal trials, where the same symbols evoked opposite movements, we found that the decoder identified movement and symbol at 400 ms after stimulus onset in the early learning trials. In the late learning trials the decoder identified the stimulus at 200 ms after stimulus onset, and the movement at 300 ms after stimulus onset. These results show that the cerebellum has independent access to the movement that the monkey will make, and the identity of the stimulus evoking the movement in a arbitrary visuomotor association task. The cerebellum identifies the stimulus only when the monkey learns the association, and as the monkey learns the association the decoder identifies the movement at a time closer to the stimulus appearance.

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Poster

P512. Cerebellum: Cortex and Nuclei II

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Program #/Poster #: P512.05

Topic: E.02. Cerebellum

Support: NIH NS116854

Title: Cerebellar Purkinje cell responses to regular and irregular trains of somatosensory stimuli in awake mice

Authors: *S. A. GOLDSTEIN, S. T. BROWN, I. M. RAMAN;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: The cerebellum is involved in tasks that require tracking intervals briefer than one second, raising the question of how absolute and/or relative timing is represented in the activity of cerebellar neurons. Recently, we found that with repetitive air puff stimulation (300 ms intervals) of the whiskers in awake mice, Purkinje cell (Pkj) complex spike and simple spike responses changed throughout the course of stimulation. When air puffs were unexpectedly omitted, complex spikes were suppressed during the omission interval. Whether the observed changes in Pkj activity result from the number of repetitive stimuli applied, the duration between stimuli, or the regularity of the stimuli remains an open question, however. We therefore recorded from Pkj cells in awake, head-fixed mice while applying a regular or irregular series of air puffs to the whiskers, interrupted by infrequent and unpredictable stimulus omissions. Each protocol consisted of 1800 stimuli, with intervals of 300 ms for regular stimulation or 100-500 ms (mean, 300 ms) for irregular stimulation, with 120 omissions; the protocol that was run first was varied across cells. As seen before, Pkj cells responded to the air puff with a short-latency, transient, well-timed decrease in simple spike firing (N=8/11) and a longer-latency increase followed by a decrease in complex spike firing (N=9/11). Puff-evoked responses to regular and irregular stimuli were indistinguishable. With repetitive stimulation, the mean simple spike rate as well as the peak puff-evoked complex spike rate decreased, independent of the regularity of the stimuli. These changes therefore appear to be related to the quantity rather than the timing of stimuli. After omissions during regular stimulation, complex spike probability fell below baseline. During irregular stimulation, this omission-associated suppression was absent, indicating that the drop in complex spike probability during the omission interval is not a long-latency response to the preceding puff. Instead, Pkj cell complex spike omission responses appear to be related to the regularity of the stimuli, consistent with participation of the cerebellum in relative (beat-based) timing.

Disclosures: S.A. Goldstein: None. **S.T. Brown:** None. **I.M. Raman:** None.

Poster

P512. Cerebellum: Cortex and Nuclei II

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NRSA F32 MH120887-03

Title: Context-dependent conditioned responses and Purkinje cell activity in cerebellum-dependent associative learning

Authors: *M. KISLIN[1], S. BERGELER[2], G. J. BROUSSARD[1], Y. CHEN[1], J. W. SHAEVITZ[2], S. S.-H. WANG[1];
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Abstract: We studied the context-dependence of delay tactile startle conditioning (DTSC), in which mice learn to withdraw from a conditional stimulus (CS; tone) that predicts an impending unconditional stimulus (US; nosetap). When head-fixed, mice produced progressively more CS-evoked responses (CR) over 6 daily sessions and plateaued with a CR probability of 0.63 ± 0.16 (mean ± sd). In subsequent CS-only experiments, extinction of the response was incomplete: CR probability declined to 0.27 ± 0.09 after 200 trials and remained at that level, higher than the pre-training CR probability (0.07 ± 0.02). Reacquisition of the CR during a second round of CS+nosetap training occurred within 100 trials, resulting in a CR probability of 0.49 ± 0.22 and reaching 0.73 ± 0.18 after 300 trials.
Nosetap-trained mice responded differently when placed in an open arena. We investigated CS-evoked responses in freely-moving mice, monitoring and classifying movements by tracking the pose of the animal over time using SLEAP[1]. CS-alone presentation during locomotion initially led to a rapid deviation in trajectory, but this response disappeared after fewer than seven trials. When subsequently placed in the head-fixed apparatus, the CR returned almost immediately, producing a response within the first few trials of 0.52 ± 0.26 CR probability.
Cerebellar lobule IV/V has a crucial role in acquisition during DTSC[2]. As a second type of US, we expressed the optogenetic probe channelrhodopsin-2 in Ai27 mice and targeted light at central vermal lobule IV/V. Pairing of CSs with direct short-pulse optogenetic stimuli (15 ms) in head-fixed mice led to the acquisition of conditioned startle responses. Continued CS+opto training in the open arena led to ongoing production of CS-triggered startle responses even after many trials.
Finally, we tracked climbing-fiber-driven complex-spike activity using fast-GCaMPs in lobule IV/V Purkinje cell dendrites during learning, extinction, and relearning. We found that CS+nosetap pairing caused a gradual acquisition of CS-triggered calcium transients that appeared with initial learning, diminished with extinction, and re-emerged with reacquisition. We are now testing the hypothesis that calcium signals undergo rapid modulation under changes in behavioral context.
References:
1. Pereira, T. D. et al. SLEAP: Multi-animal pose tracking. bioRxiv 2020.08.31.276246 (2020) doi:10.1101/2020.08.31.276246
2. Yamada, T. et al. Sensory experience remodels genome architecture in neural circuit to drive motor learning. Nature 569, 708-713 (2019)

Disclosures: M. Kislin: None. **S. Bergeler:** None. **G.J. Broussard:** None. **Y. Chen:** None. **J.W. Shaevitz:** None. **S.S. Wang:** None.

Poster

P512. Cerebellum: Cortex and Nuclei II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P512.07

Topic: E.02. Cerebellum

Support: National Science Foundation Grant CNS-1714623
NIH Grant R01-EB028156
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Office of Naval Research Grant N00014-15-1-2312

Title: Synchronous spiking and encoding of eye movements by cerebellar Purkinje cells

Authors: *E. SEDAGHAT NEJAD, J. PI, P. HAGE, M. FAKHARIAN, R. SHADMEHR;
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Abstract: The information that the brain transmits from one region to another is often viewed through the lens of firing rates. However, if the output neurons could vary the timing of their spikes, then they might encode information beyond that which is present in their average rates. A special form of temporal coding is synchronization of spikes among a population of neurons. Indeed, it has been hypothesized that during control of movements, information transfer from the cerebellar cortex to the nucleus might rely on synchronization, as well as modulation of firing rates. Is synchrony among the output neurons a means of transmitting information from one region of the brain to another?

To approach this question, we focused on Purkinje cells (P-cells) because they are the sole output channel from the cerebellar cortex, and because they can be definitively identified via their simple and complex spikes. P-cells are GABAergic, and thus their activity inhibits the downstream nucleus neurons. However, if the spikes produced by P-cells are synchronous, then the P-cells can entrain the nucleus neurons, transforming inhibition into production of spikes. Do P-cells transfer information through synchronization of their spikes?

Here, we recorded from n=143 Purkinje cells (P-cells) while marmosets performed saccadic eye movements. The simple spike firing rates of individual cells exhibited a bewildering assortment of responses, often with modulations that lasted long after saccade end. However, when we organized the cells into populations based on their complex spike response to visual events, the population firing rates of simple spikes varied precisely with saccade direction, velocity, and duration, reproducing our earlier observations in macaques. We analyzed spike patterns in pairs of simultaneously recorded P-cells (n=40 pairs) and found that before saccade initiation, firing rates increased as a function of future saccade velocity, thus inhibiting the nucleus. As the saccade initiated, rates declined below baseline and reached a minimum precisely at the onset of saccade deceleration. Remarkably, during the deceleration period the P-cell spikes became synchronized.

This suggests that the cerebellum controls movements through a combination of rate and temporal codes: nucleus cells are initially inhibited, then released from inhibition precisely at a time when the few remaining spikes from P-cells become synchronized. The fact that this synchrony occurs only during deceleration implies that through entrainment of the nucleus cells, the P-cells are predicting when the movement should be stopped.

Disclosures: E. Sedaghat Nejad: None. **J. Pi:** None. **P. Hage:** None. **M. Fakharian:** None. **R. Shadmehr:** None.

Poster

P512. Cerebellum: Cortex and Nuclei II

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Support: NSF Grant CNS-1714623
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NIH Grant R01-NS078311
ONR Grant N00014-15-1-2312

Title: Saccade related neurons in the fastigial nucleus of the marmoset cerebellum

Authors: *P. HAGE, E. SEDAGHAT-NEJAD, J. PI, M. A. FAKHARIAN, K. POE, R. SHADMEHR; Biomed. Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The cerebellum plays a critical role in control of movements, illustrated by the fact that a hallmark of cerebellar damage is dysmetria. For example, during saccadic eye movements, the ability of the brain to stop the eyes accurately at the target comes about because of the activity of caudal fastigial nucleus (cFN) neurons. The behavioral deficits that follow cerebellar damage imply that firing rates of cFN neurons should encode saccade parameters, particularly the timing of saccade termination. Yet, the firing rate of individual cFN neurons, at least in macaques, is modulated long after the movement comes to an end. How can the cerebellum control saccades if the activity of cFN neurons appear to poorly encode movement parameters? This problem of encoding is not unique to the cerebellar nucleus. In the cerebellar cortex, P-cells in the oculomotor vermis (OMV) also exhibit simple spike (SS) firing patterns that show no obvious relationship to saccade direction, velocity, and duration. Yet, when the P-cells are organized based on their complex spike (CS) response to visual error, the SSs of the population show exquisite modulation with all three parameters. Thus, a key to understanding the cerebellum may be to organize cells based on their response to error. Does this idea generalize to the cerebellar nucleus? To test this, we recorded from the cFN of marmosets. We chose this species because like macaques, they are highly visual animals that rely on saccades to explore their environment. However, being a fraction of the size of macaques, it is possible to accurately target the cerebellum and its deep nuclei with relatively short, high-density probes. These advantages have made it possible to simultaneously record from multiple neurons in the cFN as the animal performs a visually guided saccade task. We recorded the activity of 77 well-isolated cFN neurons, including 138 simultaneous pairs, using multi-contact probes during visually guided saccades. We observed a wide range of spiking patterns during saccades: some neurons produced a burst, some produced a pause, and some did both, with response durations that consistently exceeded saccade duration. Intriguingly, a subset of neurons produced a spiking response at 60-70 ms following onset of visual error, similar to the timing of the CS response in P-cells of the OMV. The cFN response to visual error was tuned to the contralateral direction, which is remarkably similar to

P-cells. We speculate that this tuning may allow for grouping of cFN cells into populations, wherein the combined firing characteristics reflect the encoding of specific saccade kinematic parameters.

Disclosures: P. Hage: None. **E. Sedaghat-Nejad:** None. **J. Pi:** None. **M.A. Fakharian:** None. **K. Poe:** None. **R. Shadmehr:** None.

Poster

P512. Cerebellum: Cortex and Nuclei II

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Topic: E.02. Cerebellum

Support: NIH (5-R01-NS078311)
Office of Naval Research (N00014-15-1-2312)
National Science Foundation (CNS- 1714623)

Title: Encoding of sensory but not motor events via complex spikes of Purkinje cells

Authors: *J. PI, E. SEDAGHAT-NEJAD, P. HAGE, A. FAKHARIAN, R. SHADMEHR;
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Abstract: Input from the inferior olive plays a major role in organizing the cerebellum, carving anatomical modules that bring together groups of Purkinje cells (P-cells) and their downstream nucleus neurons. This input produces complex spikes in P-cells with near 100% probability, yet despite their significance, the question of what is signaled by the complex spikes is strongly debated. On the one hand, unexpected sensory events can modulate the probability of complex spikes, which has led to the theory that complex spikes signal sensory prediction errors, and thus promote learning. On the other hand, complex spikes often precede production of movements, which has led to the theory that they play a role in timing well-learned movements. Disentangling these two possibilities is difficult because a salient sensory event is often followed by a movement. Here, we designed a novel task to separate sensory events from movements. We trained marmosets to fixate a central location and make saccades to a primary visual target (presented randomly in one of 8 locations). During this saccade we displaced the target to a random secondary location, thereby promoting a sensory prediction error. Critically, this secondary target was available only briefly (80 – 250 ms), after which it returned to the primary target location. As a result, following the completion of the primary saccade there was always a sensory prediction error, but only occasionally the animal responded via a movement. At other times, the sensory event was present but did not result in a movement. Finally, we considered a third case in which the animal made spontaneous saccades without externally driven visual cues: movements that were not in response to sensory prediction errors. We recorded from vermis lobules VI and VII in two marmoset monkeys (Callithrix jacchus) and isolated 90 P-cells. Each P-cell exhibited a preference for a particular direction of sensory error. When the sensory event was in the preferred direction of the P-cell, it responded with a complex spike at around 110 ms following the onset of the sensory event. Remarkably, the complex spike response was present even when the sensory event was not followed by a movement. Furthermore, the complex spike response was absent for spontaneous movements that were not driven by the visual cues. Thus, the olivary input to

the cerebellum appeared to signal the onset of a sensory event regardless of whether that event was followed by a movement or not. Indeed, complex spikes were missing from saccades that were not driven by the onset of visual events. These results appear consistent with the idea that complex spikes signal unexpected sensory events to the cerebellum.

Disclosures: J. Pi: None. **E. Sedaghat-Nejad:** None. **P. Hage:** None. **A. Fakharian:** None. **R. Shadmehr:** None.

Poster

P512. Cerebellum: Cortex and Nuclei II

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P512.10

Topic: E.02. Cerebellum

Support: NIH Grant R01 DC002390

Title: Neck muscle activity during active head movements reflects the level of sensory prediction error introduced by unexpected velocity-dependent loads in non-human primates

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Abstract: Passive vestibular and neck proprioceptive stimulation generates reflex responses in neck muscles that function to stabilize the head. However, during voluntary active movements, it is critical that reflexes are suppressed since they would be counterproductive to the intended movement goal. Previous work has shown that vestibular primary afferent input is suppressed during active head movements at the level of the vestibular and deep cerebellar nuclei when the brain's internal model can accurately predict the sensory consequences of motor commands [1]. However, when a perturbation introduces sensory prediction error, these nuclei encode the motion as if it were passive. Importantly, the vestibular and deep cerebellar nuclei provide output to the spinal cord and are well situated to produce reflexes that ensure postural control. Thus, it might be expected that neck muscle activity could reflect errors in the internal model's prediction of the sensory consequences of motor commands.
Here we characterized vestibulo- and cervico-collic reflexes in the splenius capitis muscle with motion in the yaw plane, and then examined muscle responses to sensory prediction error induced by velocity-dependent torques applied unexpectedly while alert rhesus macaques made active head movements. To examine vestibulo- and cervico-collic reflexes, we applied passive yaw movements to the whole body (vestibular stimulation), body under the head (neck proprioceptive stimulation), and head on body (combined vestibular and proprioceptive stimulation) while we recorded indwelling EMG from the right splenius capitis muscle. Vestibulo- and cervico-collic reflexes were observed in rectified EMG and single motor unit activity during whole body and body under head motion, while head on body motion evoked muscle activity that reflected the summation of these reflexes. Next, while the monkey performed active head movements, we applied four levels of velocity-dependent torque that either assisted or resisted the intended movement. While the muscle was acting as an agonist, resistive torque evoked graded excitatory responses in rectified EMG amplitude and increased gain; conversely, assistive torque evoked graded

inhibitory responses in EMG amplitude and decreased gain.
These modulations in neck muscle activity reflect perturbation induced errors in sensory prediction, which would cause a lack of vestibular reafference suppression as well as neck muscle stretch reflexes. Thus, neck muscle activity can provide insight into the functioning of the brain's internal model of the sensory consequences of voluntary motor commands.
[1] Cullen KE. 2019 Nat Rev Neurosci 20(6), 346-363

Disclosures: R.L. Mildren: None. **O. Zobeiri:** None. **K.E. Cullen:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.01

Topic: E.04. Voluntary Movements

Title: Rapid decision-making during human-human sensorimotor interactions

Authors: *R. LOKESH[1], J. CALALO[1], A. ROTH[1], S. SULLIVAN[1], M. J. CARTER[2], J. G. A. CASHABACK[1];
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Abstract: Whether driving a car or playing a sport, humans often make rapid decisions based on the actions of others. Cognitive decision-making is often studied in a single human or animal, where researchers often manipulate the uncertainty of visual information that provides evidence to select the correct action. Despite its relevance, to our knowledge using visual information of another person's actions to perform rapid decision-making remains unstudied. Here we test the idea that humans accumulate evidence about the intended action of others when making a rapid decision. We designed an interactive two-player sensorimotor version of the matching pennies game. Each participant, of a human pair, moved a robotic manipulandum to control a cursor from a start position to one of two potential targets (left or right). Both participants had vision of their opponent's cursor. The two players were assigned as either 'predator' or 'prey'. The predator won the trial by reaching to the same target as the prey. Conversely, the prey won the trial by reaching to a different target from the predator. In Experiment 1, participants performed a symmetric reward condition, where the winner of a trial received 1 point and the loser received 0 points. We manipulated the available time to reach to a target (500ms, 850ms, and 1500ms). In Experiment 2, participants performed both a symmetric and an asymmetrical reward condition. The symmetrical (described above) and symmetrical reward conditions were similar, except in the asymmetrical reward condition the predator received 3 points when both players selected the right target. For each reward condition, participants performed two different timing conditions (500ms and 1500ms). Both experiments used a within subject design, condition order was counterbalanced, and there were 150 trials per condition. Across experiments, participants exploited the additional time in the longer trials. Only near the end of a trial was a participant's hand path predictive of target selection and related to the actions of their opponent. Successful participants delayed their final change in cursor movement direction, suggesting they relied on accumulated evidence of their opponent's intended action to make a rapid decision. Participants proportionally selected targets in a manner that approached an optimal

solution (i.e., Nash equilibrium). Preliminary work shows that a drift-diffusion model does well to capture decision-making during human competition. Taken together, these results suggest that successful participants exploited time to accumulate evidence about their opponent's intended action, and then relied on rapid decision-making to select a target.

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Poster

P527. Reaching Control: Preparation, Selection, and Strategy

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Program #/Poster #: P527.02

Topic: E.04. Voluntary Movements

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GSK Chair in Neuroscience

Title: Shared neural resources influence performance in rapid, interactive behavioural tasks

Authors: *R. H. MOULTON[1], K. RUDIE[1,2,3], S. H. SCOTT[4,5,6];
[1]Dept. of Electrical and Computer Engin., [2]Sch. of Computing, [3]Ingenuity Labs Res. Inst., [4]Dept Biomed. and Mol. Sci., [5]Ctr. for Neurosci. Studies, [6]Dept. of Med., Queen's Univ., Kingston, ON, Canada

Abstract: Sight-reading music highlights the impressive ability for individuals to simultaneously perceive notes on the page, prepare motor actions, and contact keys at the proper time. This task of perceiving, deciding, and acting in parallel becomes particularly challenging as the speed of the performance increases and reaches a capacity limit. Two hypotheses are commonly put forward to explain these limits in capacity: a structural bottleneck model, where processes interfere when they queue to use a particular neural circuit; and a shared resource model, where processes interfere when they compete for resources in a central pool. Here we explore limits in rapid sensorimotor performance to understand which processes are at risk of interference and under which conditions.
We studied the interference of perceptual, decision-making, and motor control processes during behavioural tasks where subjects must rapidly generate upper-limb movements to achieve time-constrained goals. Healthy human subjects (N=487, 212 male, 432 right-handed, age range 18-93) performed Object-Hit (OH) and Object-Hit-and-Avoid (OHA), two related motor decision tasks, in the Kinarm Exoskeleton lab. The goal of each task is to hit as many targets as possible during an ~2.5-minute trial, with OHA adding the requirement to avoid distractor objects that are distinguished by shape. Subjects' performance was measured using their steady-state target hit rate, which represented their peak, sustained level of performance.
We found that subjects with the highest steady-state rates in the OH task are the most affected by the

increased task difficulty in the OHA task, demonstrating that the additional task demands were multiplicative in nature. We also found that the subjects with the poorest performance often demonstrated equal performance between the OH and OHA tasks, seemingly unaffected by the additional task demands. These results are consistent with the shared resource model for process interference and suggests that processes compete for shared resources, such as attention, to mitigate the impact of bottlenecks and maximize task performance. We believe that this shared resource model may be useful when interpreting changes in performance during motor skill learning and physical rehabilitation.

Disclosures: R.H. Moulton: None. **K. Rudie:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SHS is the co-founder and Chief Science Officer of Kinarm, which commercializes the robotic technology used in the present study..

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

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Program #/Poster #: P527.03

Topic: E.04. Voluntary Movements

Support: Banting Postdoctoral Fellowship
BrainsCAN Postdoctoral Fellowship
NSERC Discovery Grant

Title: Long-latency feedback responses reflect explicit sensory priors

Authors: *J. A. MICHAELS[1], J. ZHENG[1], O. CODOL[1], J. WEILER[1], A. PRUSZYNSKI[1,2];
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Abstract: As we move through the world, the brain must constantly integrate sensory information with prior expectations to select the most appropriate actions. Reaching experiments have demonstrated that contextual information can modulate the magnitude of long-latency feedback responses (EMG 50-100ms after perturbation onset) in arm muscles following unexpected mechanical perturbations and that cortical processing plays a key role in these responses. However, it's not known if immediate changes in sensory priors can be integrated into long-latency feedback responses. To answer this, we performed an experiment in which human participants (N = 20) sat in a planar robotic exoskeleton and reached to a target after elbow perturbations that pushed their hand towards or away from the target. For each trial, differently sized arrows randomly cued the relative directional probability (0/25/50/75/100%) of the upcoming perturbation. The trajectory of the hand following perturbations was modulated by the perturbation direction probability, showing the fastest movements for more likely directional perturbations and the slowest responses for unlikely directional perturbations. Crucially, we found that long-latency feedback responses in stretched arm muscles following perturbations that moved the hand away from the target linearly scaled with the cued probability within ~70ms of the perturbation. These results could not be explained by anticipatory muscle contractions before the perturbation nor by participants guessing on individual trials. Training neural networks to control biomechanical models of

the arm with realistic muscles, delays, and noise to perform similar tasks revealed that two key ingredients are necessary to observe scaling of long-latency feedback responses by sensory priors: a penalty on metabolic cost in the muscles and an input signaling the occurrence of a perturbation that precedes perturbation direction specific information. The sensory prior inputs provided to the networks shifted the neural population state along the same axis that differentiated perturbation direction during movement, increasing or decreasing the latency of the muscle response proportional to the probability of the perturbation direction. These findings show that long-latency feedback responses flexibly reflect immediate sensory priors, and suggest that the motor system prepares a single control policy that incorporates these expectations, which is deployed as soon as a perturbation is detected.

Disclosures: J.A. Michaels: None. **J. Zheng:** None. **O. Codol:** None. **J. Weiler:** None. **A. Pruszynski:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

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Program #/Poster #: P527.04

Topic: E.04. Voluntary Movements

Support: European Space Agency (ESA)
PRODEX (Belspo)

Title: Dynamical adjustments of goal-directed feedback control in human reaching movements

Authors: *A. DE COMITE, F. CREVECOEUR, P. LEFEVRE;
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Abstract: Humans execute movements using a goal-directed feedback control policy tuned to the task goal and to the environmental context. For example, the structure of the goal target is considered while planning and executing movements: humans do not reach to a wide target the same way as they reach to a narrow one. Recently, we showed that these goal-directed control policies can be adjusted online in response to an unexpected change in the target structure or in the task environment. However, it is still unknown whether these online adjustments are tuned to dynamical changes such as time-varying changes in target structure. To we investigate this question, we varied the rate of changes in target width to probe whether it evoked gradual adjustments in control policies. Participants (N = 14) had to reach to a rectangular goal target (30 x 2.5 cm) whose structure could unexpectedly change during movement. Three types of changes in target structure were investigated. The first condition was an abrupt switch, where the rectangular target instantaneously turned into a narrow square (2.5 x 2.5 cm). The two remaining conditions were gradual changes whereby the target width decreased continuously during movement at slow or fast rate (respectively 33 and 45 cm/sec). In addition to these changes in target structure, we introduced unexpected mechanical perturbation loads to the hand, orthogonally to the main reaching direction, in order to assess change in control policy associated with the change in target structure. We analysed kinematics of the hand during trial and EMG correlates from the shoulder flexor and extensor muscles to determine whether and how fast the feedback responses to mechanical perturbations reflected

the dynamical changes in target width. We found that the final hand position was dependent on the target change condition, such that more eccentric positions were associated with slower decrease in target width. The analyses of the EMG activities revealed a modulation of long-latency and voluntary responses to the perturbation load with the target condition. Moreover, we observed between trials adjustments of the responses in the dynamical conditions, which could characterize some form of learning. These adjustments were such that the responses to the mechanical perturbations in the dynamical trials were less jerky in the late trials compared to the earlier ones. Altogether, our results demonstrate that the factors that contribute to updates in control consider time-varying changes, suggesting a continuous monitoring of task-related variables allowing dynamic and time varying adjustments in goal-directed reaching control.

Disclosures: A. De Comite: None. **F. Crevecoeur:** None. **P. Lefevre:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.05

Topic: E.04. Voluntary Movements

Title: Sport expertise-dependent movement adjustments impact Go/No-go decision in rapid hitting task

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Abstract: In order for an athlete to achieve high performance, such as hitting a ball on baseball or tennis, both appropriate decision-making and precise motor control are required under tough time constraints. Although recent studies have proposed that motor and decision-making processes interact, often referred to as embodied decision-making, it is still unclear how the embodied decision processes behave under short time constraints and how they depend on sport expertise. We conducted a baseball batting-like Go/No-go hitting task experiment in which Go/No-go judgment and movement execution behavior are assessed simultaneously by collecting movement profiles. Eighteen elite university players with different sport skills (baseball and gymnastics) are required to reach-to-hit a moving target in a strike zone (Go) and not to hit it outside the area (No-go) with different values of time-to-contact (TTC): 400, 500, and 600 ms. We found that the hitting variability was significantly smaller for baseball players at TTC500 and above, but the difference disappeared at TTC400. On the other hand, as TTC decreased, decision success rate (d') decreased, most markedly for the gymnasts, indicating that decision accuracy is more sensitive to sport expertise. Moreover, hierarchical Bayesian estimation based on the Drift-Diffusion Model revealed differences in the decision parameters. Interestingly, movement adjustment for the No-go decision was also distinctive, that is, the participants tended not to move their hand in TTC600, while they started and then stopped their movement in TTC400. We found that the baseball players had a shorter stopping time than gymnasts, and the baseball players had a higher rate of successful cancellation of hitting than gymnasts in TTC400, indicating that the cancellation strategy is effective in maintaining decision success under severe time constraints depending on sport expertise. Our results suggest that motor inhibition, rather than activation, determines rapid embodied decision-making performance.

Disclosures: A. Kobayashi: A. Employment/Salary (full or part-time):; Nippon Telegraph and Telephone Co. **T. Kimura:** A. Employment/Salary (full or part-time):; Nippon Telegraph and Telephone Co..

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

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Program #/Poster #: P527.06

Topic: E.04. Voluntary Movements

Support: National Research, Development and Innovation Fund, Hungary, Grant: GINOP 2.3.2-15-2016-00022.

Title: Arm configuration variance accounts for endpoint jerk in circular arm motion.

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[1]Dept. of Information Technol. and Biorobotics, Univ. of Pecs, Pecs, Hungary; [2]Neurorehabilitation and Motor Control Res. Group, Wigner Res. Ctr. for Physics, Budapest, Hungary; [3]Gannon Univ., Erie, PA; [4]Information Technol. and Bionics, Pazmany Peter Catholic Univ., Budapest, Hungary; [5]Feinberg Sch. of Medicine, Dept. of Physiol., Northwestern Univ., Chicago, IL

Abstract: We investigated the magnitude of endpoint (hand) jerk as function of crank direction during arm cranking movements. The profile of jerk magnitude during a uniform circular motion is theoretically constant. During human arm cranking the neural control tries to approach this motion. It was found that the endpoint jerk performed by the participants is the smallest in two extreme positions: when the hand is closest to the body and when the hand is furthest away from the body. Furthermore between these positions the magnitude of the jerk increased and after reaching a plateau it did not change much until the hand approached the next extreme position. In the vicinity of this hand position the jerk dropped to reach a local minimum. These were found for both of the left arm and right arm for bimanual and unimanual cycling against 3 resistance levels. Participants performed arm cranking movements on an arm cycle ergometer (MEYRA, Kalletal, Germany) with a cadence of 60 revolutions per minute. The crank of the ergometer was 10 cm long. When the handle of the ergometer was at the most distant position (the crank was directed horizontally forward) with respect to the participant, the external angle of the elbow was approximately 10-15 degrees. The cycling task was performed against 3 levels of crank resistance bimanually and unimanually by 15 participants (aged 24 ± 4 years). Arm configuration was defined by the intersegmental joint angles in the shoulder, elbow and wrist. We previously demonstrated that the variance (across cycles) of joint angles as the function of crank direction is the highest when the crank is directed horizontally away from the body (the hand is furthest away from the body) and has two smaller local maxima in each cycle, one during the forward and one durig the backward stroke of the cycling movement. The finding that the jerk is minimal in the positions where the arm configuration variance is the highest, suggests that the central nervous system successfully uses the redundancy of the multi-joint human arm to ensure smooth hand movements in this position (when the hand turns from forward to backward movement). In this hand position the arm is near to singular configuration (the Jacobian of the 3-joint arm is almost singular) but must avoid this configuration to implement a smooth hand movement.

To do this the central control employs more available arm configurations. Our experiment indicates that during the forward and backward phases of the cycles, the arm configuration variance increased and reached local maxima to keep the endpoint jerk magnitude steady as prescribed by the theoretical kinematics of this constrained uniform circular motion.

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Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.07

Topic: E.04. Voluntary Movements

Support: NSERC Discovery
Benno Nigg Chair
NSERC CRC Research Chair Tier 1

Title: A physiological metabolic energetic cost to reaching explains preferred durations and trajectories

Authors: *J. D. WONG, A. D. KUO;
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Abstract: Humans perform upper extremity reaching movements with stereotypical hand trajectories and stereotypical durations. The hand trajectories can be explained by optimal control for kinematic accuracy, for example minimizing error variance for a given duration (Harris & Wolpert, 1998). In contrast, reaching durations are explained by energetics, namely the metabolic cost for moving a given distance traded off against a movement reward (Shadmehr et al. 2016). It seems unlikely that aspects of the same human motion should be governed by such disparate objectives. But the kinematic theory for trajectories is presently incompatible with the energetic theory for durations. Here we show that one objective is sufficient to explain both trajectories and durations simultaneously. We use an energetic cost model informed by recent physiological experiments to resolve the incompatibility of the two models. It includes mechanical work performed by muscle, and a separate "force-rate" term associated with activating muscle to produce rapid changes in force, attributable to calcium transport. The overall minimization also includes a cost for time, equivalent to a reward for briefer reaching durations. Optimal control with this model predicts stereotypical, bell-shaped hand velocity trajectories and reaching durations, which increase approximately linearly with movement distance similar to empirical data (Reppert et al. 2018). The energy cost model also agrees well with empirical metabolic cost of cyclic reaching (Wong et al., 2020, bioRxiv 2020.12.28.424067). The model is also compatible with the previous kinematic theory, because both force-rate and accuracy favor similar bell-shaped velocities under most conditions. We propose that general reaching movements may be governed by energetic cost, accuracy, and a penalty or reward associated with duration.

Disclosures: J.D. Wong: None. **A.D. Kuo:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.08

Topic: E.04. Voluntary Movements

Support: NIH NINDS R01-NS096083

Title: Effort cost of reaching biases reward responsiveness towards reacting faster over moving faster

Authors: *R. COURTER, E. SUMMERSIDE, A. AHMED;
Univ. of Colorado Boulder, Boulder, CO

Abstract: Why is healthy aging linked with a reduction in movement speeds? Older adults tend to walk, reach, and make saccades more slowly, yet the mechanisms underlying this slowing remain unclear. If we approach this question from a neuroeconomics perspective - where choice of movement speed is a consideration of both the effort required and the reward gained - then slower speeds could be due to higher effort costs or lower reward valuation. Indeed, in previous experiments, we found that with greater reward at stake, older adults rely on reacting faster rather than moving faster to acquire it sooner, whereas young adults will both react and reach faster. Faster movements incur a greater energetic cost, and even more so in older adults; perhaps older adults prefer reacting faster as a less costly strategy to obtaining reward sooner.

We asked whether older adults' altered strategy for reward reflected increased movement effort, or reduced reward valuation. Young adults ($n = 20$; 23 ± 4 yrs) performed 10-cm radial, out-and-back reaches to rewarded and non-rewarded quadrants, under high and low effort. In the high effort condition - to simulate the higher effort costs of older adults - reaches were performed with 8 lbs mass affixed to the robotic arm; no mass was added in low effort.

In both effort conditions, rewarded trials exhibited faster reaction times and greater peak speeds ($p < 0.0001$). Higher effort resulted in slowing of these kinematic measures ($p < 0.0001$) and modified the strategy in which this reward was obtained. With low effort, peak speed increased by 2.50 ± 0.184 cm/s towards a rewarded target compared to nonrewarded; when high effort was required, the increase in peak speed was smaller, at 1.21 ± 0.184 cm/s ($p < 0.0001$). Thus, the increase in speed when responding to reward was mitigated by effort. Conversely, subjects reduced reaction time by 5.94 ± 1.413 ms for reward in the low effort condition, compared to 8.22 ± 1.413 ms in the high effort condition. In the high effort condition, rather than react slower, subjects reacted at least as fast, if not faster, to reward ($p > 0.05$). These results were further supported by a computational model, which demonstrated that increased changes in reaction time and reduced changes in movement time for reward are the result of increased effort, not reduced reward valuation.

Effort costs led people to acquire reward sooner by prioritizing reacting earlier more than moving faster. These results suggest that older adults move more slowly largely because of increased effort costs, not because they value reward less. Further, reward-mediated changes in reaction time and movement speed may offer a novel metric to dissociate effort from reward valuation.

Disclosures: R. Courter: None. **E. Summerside:** None. **A. Ahmed:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.09

Topic: E.04. Voluntary Movements

Support: NIH Grant 1R01NS096083

Title: The influence of reward prediction error on reach vigor

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Univ. of Colorado Boulder, Boulder, CO

Abstract: Dopamine cells increase their activity in response to a reward prediction error (RPE). Increased dopaminergic activity has also been linked to greater ensuing movement vigor, indicating that RPE is modulating movement vigor via its influence on reward related dopamine firing. Indeed, saccade reaction times are faster in the instant immediately following a positive RPE, compared to a negative RPE. Here we investigate the vigor of reaching movements and ask whether it is modulated by the magnitude (low vs. high) of the RPE and if this effect is symmetric about the sign of the RPE (+RPE vs -RPE). Subjects (n=42) made 10 cm reaches to one of four cued targets arranged equidistantly on the perimeter of a visible circle. The experiment consisted of four blocks of 180 trials, where each target was cued 45 times in pseudorandom order. Subjects were informed that in each block, every target was associated with a different probability of being rewarded (100%, 66%, 33% and 0%). Reward consisted of a target flash and pleasing tone after reach completion. The probabilistic reward allowed us to categorize reaches in terms of reward prediction error (RPE). Rewarded reaches to the 66% and 33% targets led to a positive RPE, whereas unrewarded reaches led to a negative RPE. Further, rewarded reaches to the 33% target led to a greater positive RPE (high +RPE) than rewarded reaches to the 66% target (low +RPE), and vice versa for the unrewarded reaches. Reaches to the 100% and 0% targets are categorized as having no RPE. We asked whether reach vigor after an RPE event, was influenced by its sign and magnitude. Relative to the previous trial, subjects increased their peak velocity when they experienced a high +RPE ($p = 2.79e-5$) and decreased their peak velocity when they experienced a high -RPE ($p = 9.12e-3$). Interestingly, the magnitudes of these changes in peak velocity were asymmetric ($p = 5.41e-3$), as they increased their velocity more in response to a +RPE than they decreased their velocity following a -RPE. In contrast, subjects did not change their velocity when they experienced no RPE or a low RPE, regardless of it's sign ($p's > 0.05$). Additionally, we observed an effect of the expected value of the reward, i.e. the probability of the reward for each target. Average peak velocity increased with increasing expected value of the reward ($p = 3.00e-7$). Our findings demonstrate that the vigor of movement is modulated by reward prediction errors. Therefore, vigor reflects not only the immediate expectation of reward, but our recent surprise in predicting that reward, providing evidence for an intriguing link between the unpredictability of the outcome of our actions and the vigor of the movements that follow.

Disclosures: D. Apuan: None. **G. Bruening:** None. **A.A. Ahmed:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.10

Topic: E.04. Voluntary Movements

Support: NIH Grant 1R01NS096083

Title: The effects of repetition and reward on the vigor of movements

Authors: *C. KORBISCH[1], S. SUKUMAR[2], A. A. AHMED[3];
[1]Univ. of Colorado, Boulder, Boulder, CO; [2]Univ. of Colorado Boulder, Boulder, CO; [3]Mechanical Engin., Univ. of Colorado, Boulder, CO

Abstract: In tasks emulating foraging, laboratory experiments on humans and animals have shown a consistent tendency to overstay and harvest reward from patches/reward sites long after it is optimal to do so. Similarly, repeating specific actions biases future action to be more similar and have also been accompanied with a reduction in reaction time (RT). (Mawase et al., 2018; Verstynen & Sabes, 2011; Yu & Cohen, 2009). These use-dependent effects could be related to overstaying behavior in foraging and reluctance to switch action, to the extent that harvesting is realized through repeated action. Therefore, to understand the mechanism behind this repetition bias, we seek to first thoroughly understand how the vigor of a movement changes with repetition and how this change is further modulated by the value of action outcomes. We hypothesize that repetition will reduce RT and that this reduction further increases with higher repetition count. Further, while it has been shown that RT reduces with added reward, it is unclear how this phenomenon interacts with repetition count (Reuter et al., 2018). We also expect that an increase in reward will enhance reduction in RT. We believe that these RT reductions afford an improvement in average rate of reward from an environment, thereby rendering bias towards repeating previous behaviors optimal.

We designed an arm reaching study to test these hypotheses. In this study we had subjects perform a series of arm reaching movements towards a cued target (one of two possibilities) under duration constraints. We measured the RT to movement initiation as subjects made either a repeated or alternate movement. The number of repetitions and reward value of successful movements were randomly varied across the subject pool (n=5).

Our preliminary findings show that RT is modulated by both repetition count and reward. We find that after 5 repetitions to a given direction for an added reward of 1 point per accurate reach, subjects on average do not decrease their RT (RT normalized to the first trial in repetition is 1.003). However, after 20 repetitions in the same reward conditions, RT decreased to 88.7% of their RT on the first trial. Further with reward of 5 points per reach, we find that after 5 reaches RT decreases to 93% of that in trial 1 and to 89% of trial 1 RT after 20 reaches. To note, RT towards the initial higher value target was slightly faster than towards the lower value target (0.248 s compared to 0.256 s). Future work involves continued data collection, more detailed analysis of behavioral metrics to determine the effect of repetition. We expect our findings to shed light on the prevalence of repetitive behavior observed in healthy and pathological populations.

Disclosures: C. Korbisch: None. **S. Sukumar:** None. **A.A. Ahmed:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.11

Topic: E.04. Voluntary Movements

Support: NIH-R01NS120579
NIH-R01HD090125
NIH-R01-HD087089
NSF-M3X-1825942

Title: A generative model to assess the behavior of humans and monkeys in a virtual balancing task

Authors: *M. SADEGHI[1], R. SHARIF RAZAVIAN[1], S. BAZZI[1], R. CHOWDHURY[2], P. LOUGHLIN[2], A. BATISTA[2], D. STERNAD[1];
[1]Northeastern Univ., Boston, MA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: A large body of behavioral and neurophysiological studies on primates have attempted to address the computations needed for the control of voluntary movements. Despite numerous insights, these studies mostly relied on simple reaching movements that tended to be short and stereotypic in their kinematic profiles. Much remains unknown about the control mechanisms that govern movements involving continuous interactions with the world. An example of such interactions is balancing a beam, which requires integration of continuous feedback and leads to unique behavior at each attempt. To explore such interactive control, we introduced the Critical Stability Task (CST), where monkeys were trained to balance a linear unstable system in the virtual environment, akin to balancing a beam. Previous analysis of CST behavioral data revealed that despite large trial-by-trial variations, monkeys exhibited consistent features in behavior. For example, as task demands became more difficult, the success rate dropped, and the control response showed shorter lag and lower feedback gains. However, these observations alone could not fully capture the behavioral richness of the task to provide insight into the monkeys' control strategies. To gain more insight, this study adopted a normative approach based on stochastic optimal control theory to develop a generative model. This model produced strikingly similar behavior to the monkeys, both at the aggregate and at the single-trial level of behavior. On average, the model successfully captured how success rate, lag of control response, and magnitude of feedback gains changed as a function of task difficulty. In addition, analysis of single trials provided further insight into different control strategies that the monkey employed for different task demands. Specifically, the model suggested that the behavior in easier trials resembled that of position-based control, while the behavior in more difficult trials exhibited features of a velocity-based control strategy. The proposed model also makes new predictions about the role of different sensory information in task success, which can be later tested in behavioral experiments with both humans and monkeys. Importantly, with available neural recordings from monkeys, this model may inform the analysis of neural data and hence add to the understanding of the neural basis of sensorimotor integration during continuous interactive behavior.

Disclosures: M. Sadeghi: None. **R. Sharif Razavian:** None. **S. Bazzi:** None. **R. Chowdhury:** None. **P. Loughlin:** None. **A. Batista:** None. **D. Sternad:** None.

Poster

P527. Reaching Control: Preparation, Selection, and Strategy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P527.12

Topic: H.10. Human Learning and Cognition

Title: Catch me if you can: task occlusion effects on football catching skills performed in a virtual reality environment

Authors: *K. BURGER[1], M. AUBANEL[2], N. KUZNETSOV[1], M. DALECKI[1];
[1]Sch. of Kinesiology, Louisiana State Univ., Baton Rouge, LA; [2]Digital Media Arts & Engin., Lousiana State Univ., Baton Rouge, LA

Abstract: Virtual reality (VR) is used to train various interceptive tasks as they relate to sports performance. Most research has shown positive learning effects in these environments and has supported VR as a valuable tool for training. A long-used method in motor learning, occlusion training, has been adapted to VR to overload the visual system in a controlled way to understand and improve the learning process. This study aimed to test the learning process of football catching skills in VR and explore if occlusion training in VR affects skill improvement and retention. We hypothesized that the group receiving occlusion training in VR would have lower catching scores through the training session vs. catching without occlusion due to the increased difficulty. However, we also expected that VR occlusion training would lead to higher retention scores due to the increased load on the visual system during practice. Twenty-six healthy young adults (M = 21.2 yrs, 4 males) were placed in a virtual football stadium via a head-mounted display (HTC Vive ProEye) and wore trackers on their wrists that rendered hand motion in VR. A quarterback in the VR environment threw a football and the participant had to catch the ball virtually with both hands. Following a baseline session of 10 catches, the control group practiced catching in VR with 30 throws at 43 mph each. The intervention group also practiced catching with 30 throws at 43 mph for their training session, but the ball disappeared for the middle 40% of its flight trajectory, forcing the participants to react to the ball's reappearance shortly before arrival. 24 hours after the training session, participants returned to test absolute retention consisting of another 10 throws with full visibility of the ball's trajectory.Catching performance at baseline, during the training session, and retention was measured by the percentage of successful catches. The control group significantly improved their catching percentages from baseline to the end of practice (+30% [SD = 17%]) ($p<0.05$), while the intervention group did not (+18% [SD =25%]) ($p>0.05$). Scores recorded 24 hours after the end of training showed good levels of retention in the intervention group (52% [SD = 20%]) ($p>0.05$), and the control group (70%, [SD = 23%]) ($p>0.05$). The results suggest that virtual catching skills can be improved with training, but that partial occlusion, in contrast to our expectation, did not induce any additional benefits to performance. Future studies will explore other intervention settings and the extent to which catching skills learned in VR positively transfer to real world catching skills, which may be useful to improve sport performance.

Disclosures: K. Burger: None. **M. Aubanel:** None. **N. Kuznetsov:** None. **M. Dalecki:** None.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P554.01

Topic: E.05. Brain-Machine Interface

Title: Slow firing single units are essential for optimal decoding of silent speech.

Authors: A. GANESH[1], A. J. CERVANTES[2], ***P. KENNEDY**[1];
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Abstract: *Introduction:* The development of a speech prosthetic for those who are locked-in (paralyzed and mute) requires decoding patterns of individual single units during *silent* speech[1,2]. The aim of this abstract is to provide evidence that fast *and* slow single units recorded from the speech motor cortex of locked-in and intact subjects *speaking silently* are both important in decoding. Slow firing units are essential for *optimal decoding accuracy. Materials, Methods and Results:* The speech motor cortices in two human subjects were implanted with Neurotrophic Electrodes. In both subjects, single units were decoded during audible and silent speaking of phones. The decoding was performed using a Classification paradigm (Matlab). The results indicate that even though fast firing units are important to maintain accuracy (because when fast firing units are excluded, the accuracy drops to 64% as shown), slow firing units contribute to decoding accuracy because when they are removed from the analysis, the accuracy drops from **96.7% to 80%.** *Legend: The accuracy of phone identification during silent speech in subject 6 is 96.7% when ALL UNITS are included (left bar ALL). Excluding each unit (1-23) in sequence may change the accuracy. When the non-firing units (NO) are excluded the accuracy remains the same. When FAST firing units are excluded the accuracy drops to 64%. When slow firing units are excluded the accuracy drops to 80%. The results are similar in the locked-in subject.Discussion:* The slow firing units are important, though not as important as the fast firing units as can be evidenced from the decreases in accuracy shown in the figure. The data is essentially the same for the locked-in subject. The figure above is derived from 23 single units recorded from one electrode in subject 6. Histological analysis after implantation for 13 years in locked-in subject 5 indicates copious numbers of myelinated axons, and no scarring[3] with no loss of functionality[2]. These findings are unique to this electrode. *Significance:* Slow firing units cannot be omitted from analysis as evidenced by these data.

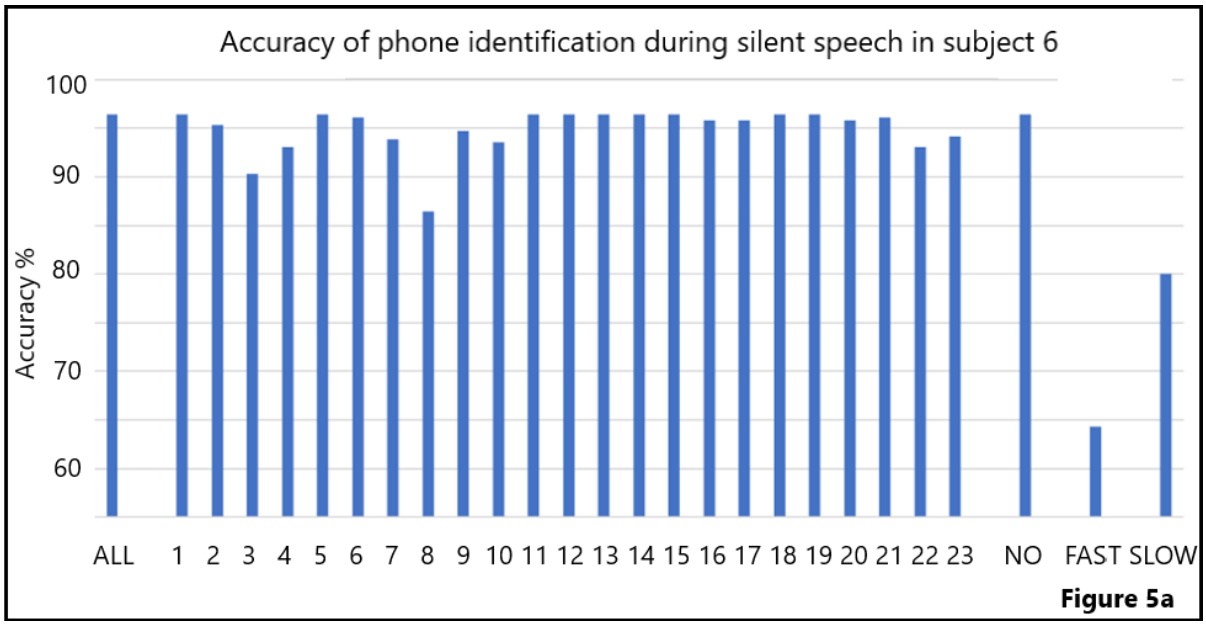


Figure 5a

Disclosures: A. Ganesh: None. **A.J. Cervantes:** None. **P. Kennedy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owns 98% of Neural Signals inc.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P554.02

Topic: E.05. Brain-Machine Interface

Support: DoD Bilateral Academic Research Initiative (DoD BARI), grant number W911NF1810434

Title: Decoding confidence from pre-response EEG enables an augmentative brain-computer interface

Authors: *N. SADRAS[1], O. G. SANI[1], D. VALERIANI[2], C. CINEL[2], R. POLI[2], M. M. SHANECHI[1]; [1]Electrical Engin., USC, Los Angeles, CA; [2]Sch. of Computer Sci. and Electronic Engin., Univ. of Essex, Colchester, United Kingdom

Abstract: Confidence is a cognitive state that reflects a subject's belief in the correctness of a decision. If confidence can be reliably decoded from a subject's brain signals *before* they make a decision (pre-decision), it would then be possible to develop a brain-computer interface (BCI) that could increase a user's decision accuracy. Although prior studies have shown that decision confidence is indeed represented in human brain signals, it remains unclear whether this representation is stimulus-locked (pre-decision) or response-locked (post-decision), and whether pre-decision decoding accuracy is high enough

to enable an augmentative BCI to improve a user's performance. In this work, we investigate the neural representation of decision confidence by collecting electroencephalography (EEG) activity while subjects perform a stimulus discrimination task with realistic stimuli. We use event-related potential (ERP), source-localization, and decoding analyses to characterize the neural correlates of confidence and investigate whether these correlates can be used to reliably decode confidence from single-trial EEG prior to response time. We then develop a simulated BCI to investigate if, and under what conditions, a confidence-based BCI can be used to improve a user's performance. Our ERP and source localization analyses show that the neural representation of confidence is stimulus-locked (pre-decision) in the presence of a post-stimulus gap, and that the absence of this gap can cause the representation to appear as if it is response-locked. This suggests the feasibility of decoding confidence before a decision is made. We then show that decision confidence can be accurately decoded from single-trial, stimulus-locked, pre-decision EEG signals using a nonlinear support vector machine (SVM) classifier. Lastly, our BCI simulation shows that the confidence decoded by the SVM can be used in a BCI to improve a user's performance, specifically when the task is difficult and has a high error cost. These results serve as a proof-of-concept for a non-invasive, confidence-based BCI that can augment human performance.

Disclosures: N. Sadras: None. **O.G. Sani:** None. **D. Valeriani:** None. **C. Cinel:** None. **R. Poli:** None. **M.M. Shanechi:** None.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

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Program #/Poster #: P554.03

Topic: E.05. Brain-Machine Interface

Support: NIH NINDS K99/R00-NS101127
Frank & Evangeline Thompson Opportunity Fund
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Title: Identifying distinct neural features between the initial and corrective phases of precise reaching using autoLFADS

Authors: *W. LEE[1], B. M. KARPOWICZ[3], C. PANDARINATH[3,4], A. G. ROUSE[2,1];
[1]Bioengineering Dept., [2]Dept. of Neurosurg., Univ. of Kansas Med. Ctr., Kansas City, KS; [3]Wallace H. Coulter Dept. of Biomed. Engin., Emory Univ. / Georgia Technol., Atlanta, GA; [4]Dept. of Neurosurg., Emory Univ., Atlanta, GA

Abstract: Reaches to small targets often consist of an initial reach followed by corrective submovements. Thus, when monkeys perform a precision center-out task with small targets and are allowed to make as many corrective submovements as needed, there can be diverse behavior and neural activity on individual trials. We trained two monkeys to perform such a task and used floating microelectrode arrays to record

from primary motor cortex (M1) across multiple sessions. Since the difficulty of the task induces self-generated errors and corrections, each corrective submovement was idiosyncratic and there were a limited number in each session, precluding traditional analyses that use trial-averaging. We used latent factor analysis via dynamical systems (LFADS) to analyze the neural population activity with a non-linear dynamical system, which enabled inference of underlying latent factors and 'denoised' single-trial firing rates. We used automated hyperparameter tuning (autoLFADS) to optimize model fitting and selection. Additionally, we used "stitching" to infer a latent factor space that was common to all sessions, enabling comparison of latent factors across sessions despite changes in the recorded neural population. LFADS improved our ability to predict velocities via linear regression for both initial and corrective movements compared to smoothed firing rates. However, for both LFADS and smoothing, prediction of corrective movements was worse than initial, and the linear mapping that best predicted initial movements did not generalize to corrective movements. When visualized with t-SNE, the neural population state space showed clear clusters for initial movements based on their velocity profiles. In contrast, corrective submovements did not overlap with the clusters of the initial movements, contrary to our expectation if corrective submovements evoked neural activity patterns that were comparable to small initial movements. Instead, corrective submovements formed a separate grouping of neural activity patterns more related to each other than initial movements. Within this separate cluster, the neural factors formed a continuum depending on both velocity and position. Our results highlight how latent neural factors improve the ability to interpret individual trials with variable behavior and design less constrained and more naturalistic tasks. Additionally, it appears that unique differences in neural activity occur during corrective movements making it difficult to decode from a model built from initial movement data alone with a variety of neural patterns encoding the different submovements.

Disclosures: W. Lee: None. **B.M. Karpowicz:** None. **C. Pandarinath:** None. **A.G. Rouse:** None.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

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Program #/Poster #: P554.04

Topic: E.05. Brain-Machine Interface

Support: H2020 MAIA-G.A.N.951910

Title: Deep learning-based decoding of sensorimotor information from superior parietal lobule of macaque

Authors: *M. FILIPPINI[1], D. BORRA[2], M. URSINO[2,3], E. MAGOSSO[2,3], P. FATTORI[1,3];
[1]Dept. of Biomed. and Neuromotor Sci., Univ. of Bologna, Bologna, Italy; [2]Dept. of Electrical, Electronic and Information Engin. "Guglielmo Marconi", Univ. of Bologna, Cesena, Italy; [3]Alma Mater Res. Inst. for Human-Centered Artificial Intelligence, Bologna, Italy

Abstract: To successfully guide our actions, several brain computations are needed. Given the dynamism that the system requires and the inherent delay in collecting sensory feedback, our brain must implement an internal model of our surroundings and body to predict the outcome of our actions in a timely manner.

This feedforward model was proposed running in the posterior parietal cortex (PPC). PPC is implicated in the processing of sensory information coming from surrounding environment and proprioception to guide actions. Yet, little is known about how this integration of different signals can occur and how it is distributed across PPC areas. We investigated how the information is processed in the superior parietal lobule (areas V6A, PEc and PE), belonging to the dorso-medial visual stream that is specialized in planning and guiding reaching movements. We trained two macaque monkeys to perform a delayed reaching task towards 9 positions (distributed on 3 different depths and direction levels) in the 3D peripersonal space. The activity of single cells was recorded from V6A, PEc, PE and fed to convolutional neural networks (CNNs) that exploited the temporal structure of neuronal activation patterns to reconstruct the target positions reached by the monkey. In addition to discrete positions in space (classification problem), we used the same CNN architecture to decode *x,y,z* positions of monkey's index finger during reaching (regression problem). Then, we introduced a positive or negative delay between neural activity (network inputs) and kinematics (network target) to check whether the neural activity was more linked to somatosensory feedbacks (negative delays) or processing of the motor plan (positive delays). CNNs using signals from the most caudal V6A and PEc areas outperformed those using signals from area PE in the reached target and movement trajectories decoding. In all areas, decoding accuracies started to increase when the information about the target to reach was provided, and reached a plateau at movement onset. Results support a dynamic encoding of the different phases and properties of the reaching movement differentially distributed over a network of interconnected areas. Furthermore, decoding accuracies did not change significantly by introducing positive or negative offsets between neuron activity and kinematics, pointing towards a simultaneous presence of feedback and planning signals. This supports the view of an internal feedforward model dealing with in these PPC areas. This study may have implications in the perspective of novel neuroprosthetic devices based on the decoding of these rich signals for reliably carrying out patient's intentions.

Disclosures: M. Filippini: None. **D. Borra:** None. **M. Ursino:** None. **E. Magosso:** None. **P. Fattori:** None.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

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Program #/Poster #: P554.05

Topic: E.05. Brain-Machine Interface

Support: NRF of Korea 2016M3C7A1904987

Title: Non-human primate epidural ECoG analysis using explainable deep learning technology

Authors: *S. LIM[1], H. CHOI[2,1], K.-H. AHN[3], K.-M. LEE[3], D. JANG[1];
[1]Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; [2]Neurol., Univ. of California, San Francisco, CA; [3]Neurol., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: <META NAME="author" CONTENT="임석빈">**Non–human primate epidural ECoG analysis using explainable deep learning technology**

AuthorHoseok Choi[1,2,4], Seokbeen Lim[2,4], Kyoung-ha Ahn[3], Kyoung-Min Lee[3], and Dong Pyo Jang[2*]
1 Department of Neurology, University of California, San Francisco, San Francisco, CA, USA2 Department of Biomedical Engineering, Hanyang University, Seoul, Republic of Korea3 Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea4 These authors contributed equally to this research* Author to whom any correspondence should be addressed. E-mail: dongpjang@gmail.com
AbstractWith the development in the field of neural networks (NN), *Explainable AI* (XAI), is being studied to ensure that AI models can be explained. There are some attempts to apply NN to neuroscientific studies to explain neurophysiological information with high machine learning performances. However, most of those studies have simply visualized features extracted from XAI and seem to lack an active neuroscientific interpretation of those features. In this study, we have tried to actively explain the high-dimensional learning features contained in the neurophysiological information extracted from XAI, compared with the previously reported neuroscientific results. We designed a deep neural network classifier using 3D information (3D DNN) and a 3D class activation map (3D CAM) to visualize high-dimensional classification features. We used those tools to classify monkey electrocorticogram (ECoG) data obtained from the unimanual and bimanual movement experiment. The 3D DNN showed better classification accuracy than other machine learning techniques, such as 2D DNN. Unexpectedly, the activation weight in the 3D CAM analysis was high in the ipsilateral motor and somatosensory cortex regions, whereas the gamma-band power was activated in the contralateral areas during unimanual movement, which suggests that the brain signal acquired from the motor cortex contains information about both contralateral movement and ipsilateral movement. Moreover, the hand-movement classification system used critical temporal information at movement onset and offset when classifying bimanual movements. As far as we know, this is the first study to use high-dimensional neurophysiological information (spatial, spectral, and temporal) with the deep learning method, reconstruct those features, and explain how the NN works. We expect that our methods can be widely applied and used in neuroscience and electrophysiology research from the point of view of the explainability of XAI as well as its performance.
Submitted to the journal of neural engineering.

Disclosures: S. Lim: None. **H. Choi:** None. **K. Ahn:** None. **K. Lee:** None. **D. Jang:** None.

Poster

P554. Neurophysiology: Decoding and Neural Processing IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P554.06

Topic: E.05. Brain-Machine Interface

Support: NIE (R01EY015545, UG1EY032039)
the Tianqiao and Chrissy Chen Brain-machine Interface Center at Caltech
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Title: Fenet feature extraction neural network for brain machine interfaces

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Abstract: Clinical neural prosthetic systems decode brain signals recorded from implanted electrode arrays to enable paralyzed human participants to control external devices. This process occurs in two basic steps. First, electrical signals that convey information about the activity of neurons around the electrode tip are transformed into "neural features". Second, the relationship between neural features and the participant's intent is learned, and subsequently decoded to control external devices. Here, we present FENet, a compact (F)eature (E)xtraction (Net)work that learns an optimized mapping between electrical signals and neural features, which significantly improves decoding performance compare to the classic feature construction methods. FENet is parameterized using a novel architecture that jointly optimizes the feature extraction and feature decoding stages of the neural decoding process, while constraining the feature extraction algorithm to use the same parameterization for all the electrodes used in our training set. This approach is based on the understanding that while the activity of different neurons will contribute to the decoding of the participants' intentions in different ways, the underlying process by which neural activity is translated into electrical fluctuations detected by an electrode is conserved across different electrodes, recording times, and brain regions.
In this work, we validate the FENet architecture by predicting the kinematics of a computer cursor movements using neural data recorded from electrode arrays implanted in human cortex. We compared performance of neural features computed from FENet against two current gold standards: 1) the rate of neural spike events computed by counting threshold crossings of the broadband neural signal; and 2) a wavelet decomposition of the broad band neural data. We found that FENet based features outperformed these two methods by 50 and 47 percent decrease in mean square error, and 51 and 28 percent increase in R2, respectively. We further present an evaluation of the effect of hyperparameter choice on FENet performance, including the amount and quality of training data as well as the choice of parameter initialization. Our results demonstrate that the trained FENet can be used for novel datasets, without modification, and leads to improved performance, generalization, and efficiency of training. Moreover, our approach demonstrates how machine learning techniques constrained by domain specific knowledge can significantly improve generalization performance.

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Poster

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Program #/Poster #: P554.07

Topic: E.05. Brain-Machine Interface

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Title: Adaptive Brain-Computer Interfaces allow credit assignment learning and formation of sparse control strategies

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Abstract: Introduction: In a Brain Computer Interface (BCI), select neurons (readouts) control an external device. There are two key elements to successful BCI control. First, users must produce reliable firing patterns in readout neurons. Second, a decoder translates that neural pattern into a command to achieve the desired movement. Closed-Loop Decoder Adaptation (CLDA) updates the decoder to map learned activity patterns to intended movements to improve performance. However, CLDA still requires the brain to generate reliable activity in readout neurons. Understanding how the brain solves this computation in the presence of adaptive decoders will shed light on learning mechanisms in BCI and inform training protocols to shape user learning. Studies using fixed decoders show that learning produces differential modulation of readout populations compared to non-readout populations, reflecting a credit assignment process. CLDA introduces a moving target for the brain and reduces overall task error, both of which may impact credit assignment learning. Here, we investigate credit assignment in the presence of intermittent CLDA and changes to the readout populations. **Methods:** We analyzed neural activity as a monkey learned to control a 2D BCI cursor with CLDA intermittently performed across 16 days (Orsborn et al, Neuron 2014). 78 motor cortex multi-units were recorded, from which 20 readout units were used in a Kalman Filter decoder. We used a multiclass logistic regression model to quantify how task information is distributed across neural populations over days. **Results**: Consistent with credit assignment learning, readout units became more predictive of task performance than non-readout units over training (*Prediction accuracy on Day 16 (readout, non-readout) : 89.34 ± 3.6%, 52.22 ± 9.8 %; Day 2: 56.69 ± 3.9%, 52.99± 9.4 %*). Model coefficients converged with learning, though changing readout units impacted stability. Within the readout population, neural representations were more sparse after learning, with fewer neurons required to explain 80% of variance (Day 16: 5.5 (mean across targets), Day 2: 7.9). **Conclusion:** Despite reduced task error and decoder instability with CLDA, the brain learns stable representations specific to readout ensembles. Our results further suggest learning may lead to sparse representations within the readout ensemble. This could reflect optimization for low-dimensional tasks or may be incomplete credit assignment. Insights into how and why sparse BCI control strategies emerge will shed light on the neural mechanisms that facilitate and constrain learning BCI.

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Poster

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Title: Closed loop simulation of neural feature selection to accelerate initial brain computer interface decoder training

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Abstract: Advances in neural recording have drastically increased the number of simultaneous neural measurements. This trend could be beneficial for brain-computer interfaces (BCIs) which extract features from neural measurements to decode user intentions. However, increased measurements also introduce new considerations for training closed-loop BCI decoders. Decoders can be trained offline on pre-collected data or online in "closed loop" as the user controls the BCI in real-time. Linear algorithms trained via closed-loop decoder adaptation (CLDA) currently provide the best performance for continuous motor BCIs, and are particularly useful for rapidly calibrating a decoder without requiring initial training data. Increases in the number of parameters to estimate may impact CLDA algorithm convergence for calibration. For instance, inclusion of "noisy" features can reduce performance and slow parameter convergence. Current CLDA methods couple feature selection with decoder parameter estimation. We hypothesize that starting training on a subset of reliable features will accelerate initial decoder training and propose a framework for adaptive feature selection separate from parameter estimation. As an initial test of our hypothesis, we simulated a BCI user with a fixed encoding model relating movement intention to firing rates of neurons. The decoder was a Kalman Filter initialized with random parameters and then trained using SmoothBatch CLDA. To test the role of initial feature selection, we ran simulations with neural populations of varying signal-to-noise ratios (SNR). In a population of neurons, we set 25% as a high SNR feature subset with twice the encoding weights and 40% less noise compared to other neurons. Training on the high SNR subset followed by iterative addition of other neurons allows the user to finish 10% more center-out reaching trials in the same training time compared to a decoder trained with the full set of features from the start. The mean decoder weight of high-SNR neurons also converged faster to the simulated user's encoding model. Future directions include 1) understanding how feature selection scales with the number of neural features, 2) adaptively estimating feature SNRs for closed-loop feature selection, and 3) exploring decoder-encoder interactions using an adaptive encoding model. Our simulations demonstrate the potential utility of initial feature selection for decoder calibration in closed-loop, where user-decoder interactions influence the quality of training data to estimate decoder parameters. Strategic selection of neural features may facilitate initial BCI decoder training and shaping user learning.

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Poster

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Title: Long-term pattern recognition control using Regenerative Peripheral Nerve Interfaces (RPNIs) in humans with upper-limb amputations

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Abstract: Introduction: State-of-the-art control systems can provide upper-extremity prosthetic users greater control, but rely on recording methods limited by low signal-to-noise ratios (SNRs). Consequently, these control systems require frequent recalibration, leading to user frustration and prosthesis abandonment. We developed the Regenerative Peripheral Nerve Interface (RPNI) as a more reliable recording interface for prosthetic control. An RPNI consists of a free muscle graft reinnervated by a transected peripheral nerve and produces SNRs that can be 12x greater than other methods. In this study, we hypothesized that RPNI signal quality can remain stable over time and allow control systems to maintain prediction performance without recalibration. **Materials and Methods**: Two participants with transradial amputations (P1 and P2) underwent surgery to place RPNIs on each of their median and ulnar nerves in 2015 and 2017, respectively. In 2018, intramuscular bipolar electrodes were placed into their RPNIs. Participants were then instructed to volitionally move their phantom limb to mirror 2 finger movements (thumb flexion, small finger flexion). These tasks were repeated in 11 sessions over 276 days in P1 and 14 sessions over 422 days in P2 to track SNRs over time. Additionally, we trained a multi-grip (fist, pinch, point) classifier and tested prediction accuracy in several different arm postures (arm at side, arm raised, arm in front, and arm across body) without recalibration up to 478 days in P2.**Results**: In both participants, SNRs remained consistently high, ranging from 15-250 across sessions, and showed no significant decreasing trend over time ($p = 0.92$). However, signals did vary substantially from session to session. Specifically, P1's median RPNI SNRs ranged between 65-250 across days for thumb flexion, whereas the ulnar RPNI SNRs ranged between 15-55 for small finger flexion. P2's SNRs ranged between 20-40 for the median RPNI and 15-80 for the ulnar RPNIs. The multi-grip classifier predicted greater than 94% accuracy across all arm postures with no significant decrease in performance across sessions ($p = 0.26$). Of the 1,179 trials performed, 85% of trials had prediction speeds of less than 250 ms, which is well below the 300 ms threshold of perceived delay between muscle activation and prosthetic hand movement.**Conclusions**: RPNIs provide high signal quality and stability (SNRs > 15), allowing them to be used as prosthetic control systems to maintain prediction performance without recalibration for up to 478 days. As a result, RPNIs have the potential to increase prosthetic use satisfaction and decrease prosthetic abandonment.

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Title: Investigation of the most informative electrocorticography features for speech decoding

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Abstract: Brain-computer Interfaces (BCI) can provide new means of communication for those who lost the ability to vocalize speech due to severe paralysis, caused by e.g. amyotrophic lateral sclerosis. The most intuitive way to control a BCI would be by attempting or silently producing speech, with words being decoded in real-time from the sensorimotor cortex (SMC). We have previously shown we are able to detect four different individually spoken phonemes from SMC electrocorticography (ECoG) recordings (Ramsey et al. 2018). However, to decode phonemes that are spoken within a word and are thus subject to coarticulation, it is crucial to know which ECoG features are most informative. Here, we conducted an investigation of ECoG features that may be used for speech decoding. In specific, we aimed to assess which time window around phoneme pronunciation contains the most information for decoding.
We recorded ECoG data from subdural high-density (HD) electrode grids over the SMC in three patients with epilepsy who were chronically implanted for presurgical diagnostic purposes. Patients performed overt speech tasks, producing isolated phonemes. We analyzed their high frequency band (HFB) power change in a window of 2s centered on phoneme onset time, which was determined manually by the experimenter as the time the phoneme could be acoustically detected. For each phoneme, the mean HFB response over trials was calculated for all electrodes and for all timepoints in the 2s time window, creating a spatiotemporal template per phoneme. This template was divided in non-overlapping sub-templates of equal time window sizes. Each of these sub-templates of a specific phoneme was tested for correlation to the full spatiotemporal templates of all phonemes, to determine how informative each phoneme specific sub-template was for decoding that phoneme.
Using this method, we identified a sub-template that is most informative about the full spatiotemporal template of its own phoneme compared to the other three phoneme templates. However, this sub-template differed per phoneme. For some phonemes the highest correlating sub-template was found prior to phoneme onset time, while for other phonemes this was found after phoneme onset time.
These results suggest that for accurate detection of phonemes from ECoG signals, there is a need for phoneme specific spatiotemporal templates. The method proposed in this study is able to identify the most informative ECoG features and may thus be applied to increase phoneme decoding accuracies. We hypothesize that the most informative time period for each individual phoneme can also be used to decode words, since every word is a unique combination of phonemes.

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Poster

P859. Timing and Temporal Processing III

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Program #/Poster #: P859.01

Topic: H.08. Learning and Memory

Support: T90DA043219

Title: A biophysical counting mechanism for keeping time

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Abstract: The ability to estimate and produce appropriately timed responses is central to many behaviors including speaking, dancing, and playing a musical instrument. A classical framework for estimating or producing a time interval is the pacemaker-accumulator model in which pulses of a pacemaker are counted and compared to a stored representation. However, the neural mechanisms for how these pulses are counted remains an open question. We present a biophysical model of how to keep count of a pacemaker using a system of bistable Wilson-Cowan units asymmetrically connected in a one-dimensional array; all units receive the same input pulses from a central clock but only one unit is active at any point in time. With each pulse from the clock, the position of the activated unit changes thereby encoding the total number of pulses emitted. This neural architecture maps the counting problem into the spatial domain, which in turn translates count to a time estimate thus allowing our mechanism to be used in time interval production and estimation. We show that our mechanism allows encoding of count that is robust to two sources of stochasticity: noise internal to the neural units themselves and variability that arises from using a stochastic oscillator as the pacemaker. Finally, we extend the model to a hierarchical structure to be able to robustly achieve higher counts.

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Topic: H.08. Learning and Memory

Support: NIH R01 NS086947

Title: The persistence of time cell sequences during delay intervals does not depend on ongoing theta oscillations

Authors: *L. YUAN[1], J. FIGUEROA[1], A. KHAN[1], C. HSU[1], G. NARAYAN[1], J. K. LEUTGEB[1], S. LEUTGEB[1,2];
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Abstract: Working memory (WM) retention over periods of seconds is essential for cognitive tasks. Many studies have reported sequential firing of hippocampal cells which represent intervals of time (time cells) in WM tasks as a possible mechanism for memory maintenance. The sequential firing patterns of time cells are thought to be internally generated, and time compression during theta oscillations is a potential mechanism to generate time cell sequences on the behavioral time scale. Consistent with this notion, hippocampal sequential firing patterns were abolished when theta was reduced by inactivating the medial septal area. However, time cells have also been reported in tasks in which there was no sustained theta during WM retention. We therefore asked whether the emergence or stability of time cells during a delay interval in a WM task depends on ongoing theta oscillations. While recording hippocampal CA1 ensembles in rats (n=4) that performed a delayed spatial alternation task with delay intervals of 10 s and 30 s, differences in the occurrence of theta oscillations during the delay period were generated by taking advantage of the link between movement and the emergence of hippocampal theta. The task included blocks of trials when rats were either forced to run on a treadmill or were allowed to rest during the delay interval, and theta power was significantly lower during resting compared to running. Despite the substantial differences in theta power, the proportion of time cells in CA1 did not differ between running or resting during delay intervals [running: n=138 of 280 cells (49.3 %), resting: n = 125 of 280 cells (44.6 %)]. In both running and resting trials, reliable time cells with a short time field were limited to the first few seconds of the delay regardless of its duration (10 s or 30 s). In addition, a second population of late-firing cells were observed in 30 s delays, which were silent during the first few seconds, but then constitutively active across the remainder of the delay period. Taken together, our results show that consistent theta oscillations are not required for the emergence or stability of hippocampal time cells. These results support the hypothesis that other mechanisms, such as network activity that can temporally organize firing patterns over several seconds, are required for supporting time cell sequences. In addition, with WM lasting 30 s in our experiment (percent correct trials: 84.0 % for running, 86.7 % for resting) and time cell sequences only lasting for the initial seconds of the delay, WM retention likely requires mechanisms other than the sustained activity of hippocampal time cells.

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Topic: H.08. Learning and Memory

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Title: Propofol differentially modulates early consolidation of ego- and allocentric spatial navigation

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Abstract: Successful navigation in familiar environments can be achieved by reproducing previously travelled path sequences and by using the remembered positions of environmental landmarks. It is currently unclear, whether the substrates supporting the corresponding egocentric and allocentric memory representations can be dissociated at the neural level and regarding the temporal dynamics of their consolidation. Here, we investigated possible differential contributions of hippocampus-dependent networks to early consolidation of egocentric and allocentric spatial memory by using a neuropharmacological approach in neurologically normal human subjects. We used the $GABA_A$-ergic anesthetic propofol to transiently modulate hippocampal neural activity during the early stage of spatial memory consolidation. A total of 52 patients undergoing minor ear-nose-throat surgery learned to navigate to a target in a five-armed maze derived from animal experiments immediately prior to injection of propofol (early group) or more than 60 minutes before injection (late group). Two hundred and forty minutes after anesthesia, subjects were tested for egocentric and allocentric memory-guided navigation. Our results show a selective impairment of memory-guided navigation in the early group and near-normal performance in the late group. Both egocentric and allocentric navigation were affected, albeit with distinct error patterns. In the egocentric condition, early group patients navigated significantly more often to a wrong alley but showed otherwise efficient navigation, suggesting a deficit for path sequence memory. By contrast, in the allocentric condition, early group patients mostly navigated to the correct alley but showed a significant increase in detours and prolonged navigation times, thus suggesting a weakened representation of the relationship between landmarks. We conclude that hippocampus-dependent networks contribute to early consolidation of representations underlying both egocentric and allocentric memory-guided navigation. Distinct aspects of these representations are susceptible to $GABA_A$-ergic modulation within a brief time window of less than 60 minutes, indicating an early redistribution and reconfiguration of hippocampus-dependent memory networks.

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Poster

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Program #/Poster #: P859.04

Topic: H.08. Learning and Memory

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Title: Tracking elapsed time: contrasting striatal vs. hippocampal neural activity

Authors: F. ROLANDO[1], T. W. KONONOWICZ[2,1], J.-R. DUHAMEL[1], V. DOYERE[2], *S. WIRTH[1]; [1]Inst. des Sci. Cognitives, CNRS-UMR 5229, Bron, France; [2]Univ. Paris Saclay, CNRS-UMR 9197 Neuro-Psi, Saclay, France

Abstract: Processing time gives a sense of continuity and allows to order events throughout days to years. Yet, at a smaller scale, during daily events, we can also tell when a blank in a conversation is too long, or that the metro door is going to close shortly. Here we asked how neural regions previously

involved in timing represent different durations scaling from sub second to supra second range. We focused on the striatum (caudate and putamen) and the hippocampus, as time cells were discovered in both regions. We designed an ongoing 3 intervals discrimination task, where the durations to be timed changed from 0.25s to 8s. Cross-species comparison showed that humans performed better at durations above the second range, whereas rhesus macaques were accurate at both, sub-second and supra-second timing. Time related activity was found in all 3 neural regions. To further characterize the nature of time representation in each region, we performed a decoding analysis using the activity of the population of neurons through time. We asked how any individual point in time differed significantly from any other time points of the interval. This analysis allowed for each region to determine the evolution of the discrimination through time and its temporal resolution. Below 2s, the decoding analysis based on the population of caudate neurons suggests that this region discriminates time accurately in a continuous manner with a fine time resolution. This contrasted with putamen-based decoding, for which specific intervals corresponding to expected events were represented. Finally, despite the presence of time cells, decoding based on hippocampus activity performed poorly compared to the other two striatal regions. The results highlight strong differences across neural structures, despite the presence of time cells in all 3 regions. We attempt to interpret these differences in light of the different role of each regions in motivation, motor planning and memory.

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Title: Hedonic and semantic modulation of subjective temporal duration in healthy ageing

Authors: *M.-C. REQUENA-KOMURO[1], J. JIANG[1], C. J. D. HARDY[1], F. N. BADER[2], M. WIENER[2], J. D. WARREN[1];
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Abstract: Our ability to perceive time supports our everyday living. Our brain should therefore keep track of the physical time in an accurate and precise way in order to guide us in our interactions with the external world. However, our common experience tells us that our perception of time is highly subjective and constantly modulated by our internal states. Previous research suggests that the important role of hedonic valence in modulating the perceived duration of external events and stimuli may reflect both attentional and arousal effects on internal clock mechanisms. However, to our knowledge, the influence

of the semantic identity of perceived objects has not been investigated. Moreover, some evidence suggests that ageing itself modulates our awareness of time passing. How the interaction between affective and semantic stimulus characteristics impacts subjective time perception is not well understood however, and how healthy ageing affects this interaction is not clear. Here we addressed this issue using an online auditory temporal bisection paradigm in which we manipulated the pleasantness of natural sounds of several seconds duration as well as their semantic category (human versus environmental sounds). Healthy young adults (n=106, 57 female; aged 18 to 30) and healthy older adults (n=83, 44 female; aged 50-75) were recruited through a third-party recruitment platform known as Prolific. They were first asked to rate the pleasantness of the sounds before completing the time experiment on a different day. Psychometric curves were fitted to participants' responses to extract time perception parameters (temporal bisection task and weber's ratio) which were then statistically compared using repeated measures ANOVA. Choice and reaction time data were further analysed using a hierarchical drift-diffusion model. We found no evidence of an ageing effect on the bisection point, while older adults showed a higher discrimination sensitivity for environmental unpleasant sounds compared to younger adults. Both groups perceived the human pleasant and unpleasant sounds as shorter in duration than the environmental pleasant sounds, which were in turn perceived as shorter than the environmental unpleasant sounds; both groups also showed lower discrimination sensitivity for human unpleasant sounds compared to other sounds. Those differences were further reflected in the decision-making parameters. The findings further our understanding of subjective temporal experience in everyday life and how it may change in healthy ageing.

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Topic: H.08. Learning and Memory

Title: Pharmacological inactivation of the rat mediodorsal thalamus but not lateral cerebellar nucleus impairs supra-second timing performance

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Abstract: While cortical regions like the prefrontal cortex have long been associated with cognitive function, less is known about how subcortical structures like the cerebellum and thalamus contribute to cognitive processing. Supra-second interval timing relies on cognitive functions such as attention and working memory, mediated by the frontal cortex. However, the extended neural circuit necessary for successful supra-second timing has not been fully defined. We used a supra-second interval timing task to probe whether two subcortical structures, the mediodorsal thalamus (MD) and the lateral cerebellar nuclei (LCN), are necessary for temporal processing in rats. Male Long Evans rats learned to time 4- and 12-second intervals in an operant dual-interval peak procedure. In Experiment 1, we used a disconnection

design to determine whether the MD and LCN work together to influence timing performance. We used focal pharmacology to inactivate either half the LCN-MD circuit, or the full LCN-MD circuit during the timing task. In Experiment 2, we assessed the contribution of the MD and LCN independently in our task, with respective bilateral pharmacological inactivations. Preliminary results of these experiments suggest that inactivating the MD impacts the ability to respond in the correct response location for a given cue-duration pairing, but not timing precision or accuracy. LCN inactivations appear to have no effect on timing performance measures nor response location accuracy. Future directions will include performing analyses of inter-trial intervals to examine if the incorrect responding is exploratory in nature or tied cue onset. Additionally single-trial analyses may provide insights into when incorrect responding is occurring during a given trial.

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Title: The role of movement in optimal multimodal timing

Authors: *R. DE KOCK[1], P. DATTA[1], W. ZHOU[1], K. A. GLADHILL[2], W. M. JOINER[1], M. WIENER[2];
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Abstract: Time perception research spans a variety of paradigms to understand how we perceive and time sensory events. However, a gap exists between our understanding of sensory timing and motor timing, as these processes can robustly influence each other. We previously found that motor activity enhanced timing precision of auditory intervals when participants manipulated a robotic arm, compared to participants held in place. We propose that this improvement is achieved via optimal cue combination, whereby movement introduces a new channel of sensory information that is more precise than auditory information, and as such, the combination of the two produces an estimate that is more precise than either alone. In the current experiment, participants timed durations of isolated arm movements, isolated auditory tones, and a combination of both. We hypothesized that precision would be highest for the combined estimates (in line with optimal integration), and that movement estimates would be similar or more precise than auditory estimates. We administered a temporal reproduction task in which participants encoded one of seven durations (1000-4000 ms, linearly spaced). Participants performed the task using a robotic arm manipulandum with a flat workspace. There were three trial types: “movement”, “auditory”, and “auditory-movement”. In “movement” trials, participants began in a randomized location and were cued to begin moving freely until they were interrupted by a “brake” to signify duration offset. In

"auditory" trials, participants were held in place in a randomized location while passively listening to an auditory tone. In "auditory-movement" trials, they simultaneously timed a movement and auditory interval, with aligned onsets and offsets (i.e., the brake aligned with the tone offset). After encoding, in all conditions the duration was reproduced by holding and releasing a button attached to the handle. We analyzed timing accuracy for each condition via estimation means, and to test our hypothesis, we examined the coefficient of variation for each condition (standard deviation/mean). Results demonstrated that subjects exhibited similar accuracy between conditions in reproducing durations. Additionally, the variability for movement and auditory-only conditions were equivalent, with the combined auditory-movement condition exhibiting superior precision over both conditions. These preliminary results suggest that movement can provide a timing signal that is at least as good as auditory timing, and that the combination of these signals leads to improved timing performance, in line with cue combination predictions.

Disclosures: R. De Kock: None. **P. Datta:** None. **W. Zhou:** None. **K.A. Gladhill:** None. **W.M. Joiner:** None. **M. Wiener:** None.

Poster

P859. Timing and Temporal Processing III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P859.08

Topic: H.08. Learning and Memory

Support: NIH Grant MH112143

Title: Cerebellar interactions with the cerebral cortex in healthy and ataxic mice

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Abstract: Long known for its role in motor control, it is increasingly clear that the cerebellum is also involved in numerous cognitive behaviors. Though the neuronal mechanism for the role of the cerebellum in cognition is still unclear, there is a consensus that it involves cerebellar interactions with the cerebral cortex. Recent studies from us and other groups suggest that the cerebellum monitors, and possibly coordinates, the precise phase alignment or coherence of neuronal oscillations in cerebral cortical areas. Specifically, we previously showed that Purkinje cells in right lobulus simplex (LS) and Crus I of healthy mice represent the instantaneous phase and phase differences of local field potential (LFP) oscillations in the medial prefrontal cortex (mPFC) and the dorsal hippocampus (dHC). Here, we asked how loss of cerebellar function affects the coherence of oscillations between the cerebellum and the mPFC or dHC and between the mPFC and dHC. We used multisite *in vivo* extracellular recordings in freely moving mice to measure neuronal oscillations in the LFPs of the cerebellar LS, mPFC, and dHC in a home cage environment. We compared a mouse model of cerebellar ataxia and their littermate controls. The ataxic mice were designed to have a genetically induced loss of Purkinje cell neurotransmission, resulting in an expected repertoire of cerebellar motor deficits. The question we asked here is whether these mice also

have neurophysiological defects that are indicative of cognitive circuit dysfunction. We quantified power spectra of LFP oscillations in each structure and the magnitudes of coherence of oscillations and Granger causality (GC) between each pair of structures using a nonparametric spectral method. Resting-state coherence of gamma oscillations between LS and mPFC was increased in ataxic mice relative to their control littermates and trended towards significance. GC analysis revealed direction and frequency band specific differences between ataxic and control animals. For example, ataxic animals showed significantly larger GC from the mPFC to cerebellar LS in the high gamma band compared to littermate controls. Loss of Purkinje cell neurotransmission also affected GC between the dHC and mPFC where ataxic mice showed significantly lower GC from the dHC to mPFC than control mice in the low gamma frequency range. Our findings reveal that Purkinje cell neurotransmission is required for normal functional interactions between the cerebellum and cerebral cortex and between cerebral cortical areas involved in cognitive functions, suggesting an involvement of the cerebellum in the modulation or coordination of functional communication between brain areas.

Disclosures: B.L. Correia: None. **M. Dhamala:** None. **R.V. Sillitoe:** None. **Y. Liu:** None. **D.H. Heck:** None.

Poster

P859. Timing and Temporal Processing III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P859.09

Topic: H.08. Learning and Memory

Title: Mice Rapidly Update Timed Behaviors in a Serial Fixed Interval Task

Authors: N. AGGADI, R. K. VAN DER MERWE, R. I. ALBERT-LYONS, O. LU, G. MALAKI, C. J. MADDOX, M. GHANEM, J. R. SCOTT, C. R. MOREHOUSE, P. SIMEN, C. D. HOWARD; Oberlin Col., Oberlin, OH

Abstract: Almost all cognitive functions rely on temporal information and perception, though brain circuits encoding timing processes have remained elusive. Much work has investigated how animals time fixed interval durations, but far less work has investigated how animals learn to update behavior to mirror new time intervals, and very little is known about brain circuits contributing to this process. The aim of this study is to investigate whether mice can rapidly update responding in a serial Fixed Interval (sFI) task. In this task, mice are rewarded for presses made after a fixed duration ranging from 12 and 60 seconds, and this fixed interval is updated after a randomly chosen number of trials (ranging from 13-21 trials). Updating of timed behaviors was inferred through three metrics: 1. the time when mice first press the lever in each trial, 2. the time of the first bout of presses in each trial (3 presses, each separated by <0.5 sec), and 3. the time when mice reach 63% of their maximum press rate in each trial. We found that mice are capable of rapidly updating their responding in new blocks, and the average time of first press, time of first bout, and time reaching 63% maximum press rate are all linearly related to fixed interval duration. This updating is often rapid and can take place in only a few trials after the start of a new block. Now, pilot studies are underway to determine how manipulation of secondary motor cortex (M2) using optogenetics in GAD-Cre and CAMKII-Cre mice modifies the speed of updating in this task, and the

performance within fixed interval blocks. Our findings provide a platform for investigating the updating of temporal behavioral patterns in a dynamic timing task and will provide new insights into brain circuits involved in this process.

Disclosures: N. Aggadi: None. **R.K. van der Merwe:** None. **R.I. Albert-Lyons:** None. **O. Lu:** None. **G. Malaki:** None. **C.J. Maddox:** None. **M. Ghanem:** None. **J.R. Scott:** None. **C.R. Morehouse:** None. **P. Simen:** None. **C.D. Howard:** None.

Poster

P859. Timing and Temporal Processing III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P859.10

Topic: H.08. Learning and Memory

Support: Simons Foundation Autism Research Initiative
Hock E. Tan and K. Lisa Yang Center for Autism Research at MIT
James and Patricia Poitras Center for Psychiatric Disorders Research at MIT
Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard

Title: Wireless EEG recordings in freely behaving marmosets reveal potential neuronal correlates of temporal expectation.

Authors: *T. DRAGOI[1], H. SUGIHARA[1], J. SHARMA[1], G. FENG[2], R. DESIMONE[2], M. SUR[1]; [1]Picower Inst. for Learning and Memory, [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Environments constantly undergo change and the brain often needs to dynamically adjust stimulus-response-reward associations due to varying contexts and stimuli. Amongst changing environments, the prioritization of relevant incoming information helps animals generate optimal internal models of their environment to help predict future outcomes. Previous studies have implicated fronto-parietal circuits as playing a key role in generating predictions. The predictive coding hypothesis posits a progressively increasing fronto-parietal influence as an animal utilizes an internal model of prediction. To test whether neural responses in marmosets follow predictive coding models, we designed a simple timing task in which freely behaving marmosets were required to make a timed response prompted by a visual stimulus change with a uniform distribution of stimulus durations. We implanted a wireless EEG system in one marmoset to simultaneously record from occipital, parietal, and frontal cortices while he learned the simple timing task. We found that once the animal had learned the task, there was a clear ramping up of EEG signal, consistent with the animal using an internal prediction model of stimulus offset timing that qualitatively followed similar changes in its behavioral performance. An analysis of oscillatory dynamics during learning revealed that in general, low frequency oscillations increased in power across cortical regions but especially in occipital cortex, and high frequency oscillations broadly decreased in power for sessions when the marmoset had learned the task. These findings are consistent with a model in which low frequency oscillations carry top-down predictions which inhibit high frequency oscillations in sensory areas. Altogether, our preliminary results demonstrate distinct changes in brain activity as the

animal learns and uses an internal model of prediction. Our data also suggests that temporal prediction may be facilitated by top-down effects mediated by fronto-parietal circuits.

Disclosures: T. Dragoi: None. **H. Sugihara:** None. **J. Sharma:** None. **G. Feng:** None. **R. Desimone:** None. **M. Sur:** None.

Poster

P859. Timing and Temporal Processing III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P859.11

Topic: F.08. Biological Rhythms and Sleep

Title: Temporal reversibility of neural dynamics as a signature of consciousness

Authors: *L. DE LA FUENTE[1], F. ZAMBERLAND[2], H. BOCACCIO[3], E. TAGLIAZUCCHI[4]; [1]Facultad De Ciencias Exactas y Naturales, UBA, CABA, Argentina; [2]COCUCO/DF-IFIBA/UBA, CABA, Argentina; [3]DF-IFIBA-UBA, CABA, Argentina; [4]Univ. of Buenos Aires, Buenos Aires, Argentina

Abstract: The brain is capable of constructing representations of the physical world, which might include the temporal asymmetry manifest due the preferred direction of time (thermodynamic arrow of time). In this work, we investigated whether the direction of time can be decoded from electrocorticography (ECoG) recordings in non-human primates in different states of consciousness (awake, sleep and under ketamine), and how the accuracy of this decoding relates to the level of consciousness. Time courses of the 3 first principal components (PC) of ECoG data were epoched and transformed to frequency and phase spectrograms. This information was used as the input of a convolutional (1, 3 and 5 blocks) network trained to distinguish original vs. time reversed epochs. In total, 16,200 models were fitted for 81 conditions (3 levels of model complexity, 3 types of data, 3 PCs, in 3 states of consciousness) with 100 iterations each. This was repeated after randomizing data labels to construct a null model. Unshuffled models yielded a significantly higher performance ($p < 0.001$). For wakefulness, the AUC in the validation set was always above .75. In the case of sleep, the best performance was observed for the models that included the phase information of the 2nd PC. For the ketamine condition, significant performance was only observed for the most complex models and/or those that included frequency information of at least 2 PCs. The probabilities for each data sample were consistent among models ($p < 0.001$), this consistency was especially high for the awake condition. To analyze which characteristics of the data were most relevant, gradient images were calculated. In the frequency domain, a greater relative importance was observed for high frequencies, most marked in the 2nd PC. Particularly in sleep, the importance was highest for the phase data of the 2nd PC. In summary, deep convolutional network models were able to predict the direction of time from ECoG data during wakefulness, but this prediction was hindered in states of reduced awareness such as deep sleep or under ketamine anesthesia. This suggests that conscious representations of information encode the arrow of time. Thus, this may indicate that in active states the ordering of events is given by external information and/or is an intrinsic property of neural activity, being present mostly in high and low frequencies. Finally, the possibility of decoding the direction of time from

sleep using phase domain information is consistent with the presence of cortical waves travelling between pairs of cortical regions, as shown by experiments in sleeping human and non-human primates.

Disclosures: L. de la Fuente: None. **F. Zamberland:** None. **H. Bocaccio:** None. **E. Tagliazucchi:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.01

Topic: I.04. Physiological Methods

Support: Max Planck Society

Title: Implantable nanophotonic neural probes for simultaneous patterned photostimulation and electrophysiology recording

Authors: *F.-D. CHEN[1,2], T. XUE[1,2], Y. JUNG[1], J. N. STRAGUZZI[1], H. WAHN[1], S. S. AZADEH[1], A. STALMASHONAK[1], A. WENZEL[1], X. LUO[3], G.-Q. LO[3], W. D. SACHER[1], J. K. S. POON[1,2]; [1]Max Planck Inst. for Microstructure Physics, Halle, Germany; [2]Dept. of Electrical and Computer Engin., Univ. of Toronto, Toronto, ON, Canada; [3]Advanced Micro Foundry Pte. Ltd., Singapore, Singapore

Abstract: Optogenetics enables precise interrogation of brain circuits by combining genetically specific cell-type targeting with deterministic neuron actuation. Despite the cellular precision of the technique, most light delivery systems used in optogenetic experiments, such as fibers and light-emitting diodes, do not offer control on the directionality or pattern of the light beam. Patterned light can precisely target a tissue region with micron-scale resolution, thereby addressing highly specific populations of neurons. To deliver patterned light in brain tissue at depth, we are developing implantable nanophotonic neural probes with specially designed gratings that emit light beams. Our probes are fabricated in a semiconductor foundry on 200mm diameter silicon wafers to ensure the technology can be broadly disseminated to the scientific community in the future.

In this work, we report the characterization of silicon neural probes that integrate together electrophysiology electrodes and nanophotonic waveguides. Each probe contains up to 72 titanium nitride (TiN) electrodes with 16 optical emitters distributed across 1 to 4 shanks each about 100 to 154 um wide. The electrodes are chemically treated post-fabrication to reach the impedance for electrophysiology recording. A custom optical scanning system and multicore fiber are used to couple laser light into the neural probe and to address the light emission sites. We have realized a variety of emission patterns including beams that are low-divergence, planar sheets, or steerable. Each probe is packaged onto a custom printed circuit board compatible with the Intan recording headstage. These probes show how silicon nanophotonic and microelectronic technologies can create new disseminable tools for precision brain activity mapping.

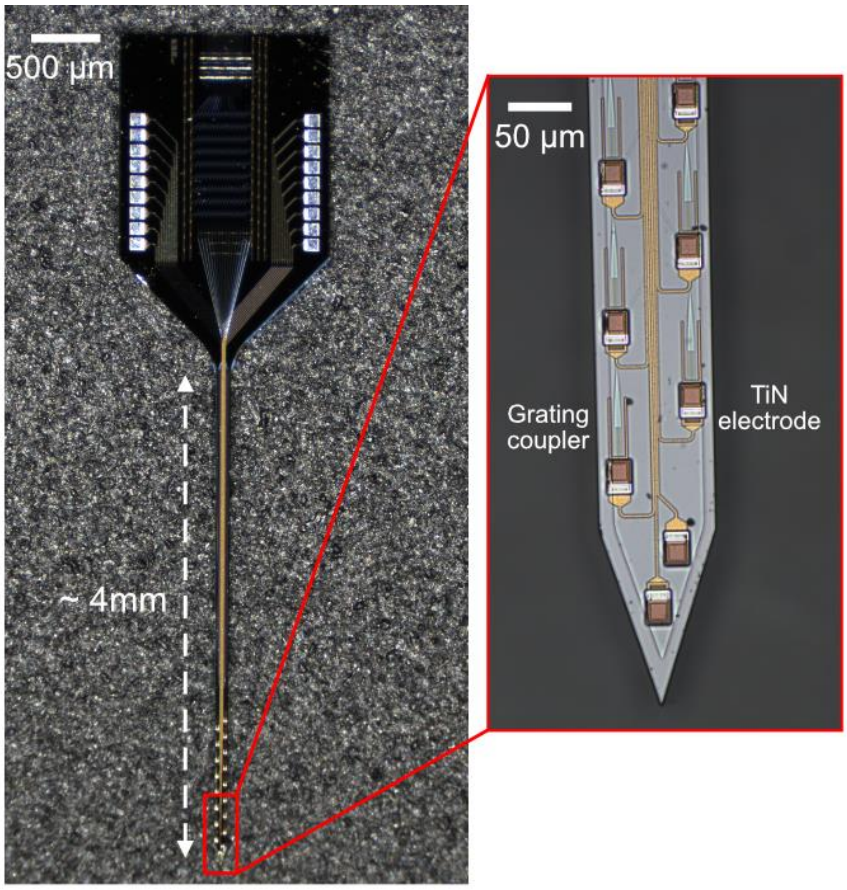


Figure 1. Top-down microscope images of an example implantable probe with integrated waveguides and recording electrodes. The probe contains 18 TiN electrodes and 16 grating couplers that emit low-divergence light beams.

Disclosures: F. Chen: None. **T. Xue:** None. **Y. Jung:** None. **J.N. Straguzzi:** None. **H. Wahn:** None. **S.S. Azadeh:** None. **A. Stalmashonak:** None. **A. Wenzel:** None. **X. Luo:** None. **G. Lo:** None. **W.D. Sacher:** None. **J.K.S. Poon:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.02

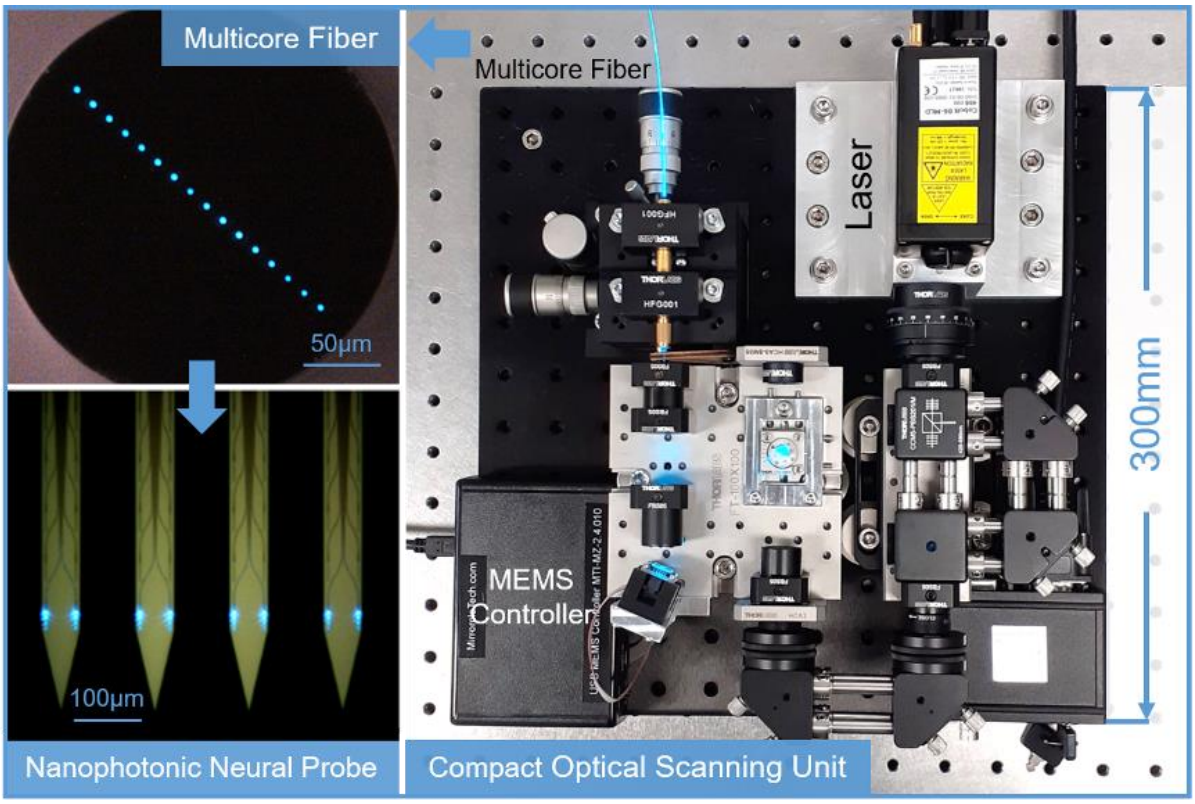
Topic: I.04. Physiological Methods

Support: Max Planck Society

Title: Implantable nanophotonic neural probe system with compact scanning optics and custom visible light multicore fiber

Authors: H. WAHN[1], F.-D. CHEN[1,2], S. S. AZADEH[1], A. STALMASHONAK[1], W. D. SACHER[1], *J. K. S. POON[1,2];
[1]Max Planck Inst. of Microstructure Physics, Halle, Germany; [2]Dept. of Electrical and Computer Engin., Univ. of Toronto, Toronto, ON, Canada

Abstract: To overcome the optical scattering limitation to light penetration in brain tissue for optogenetics and functional optical imaging, implantable photonic neural probes are an emerging technology that delivers patterned illumination at depth in brain tissue. We have been developing neural probes that are manufactured in a semiconductor foundry on 200mm diameter silicon wafers to ensure scalable production. The neural probes integrate nanophotonic waveguides onto long (3-6mm) thin (50-100µm) implantable shanks. The probes are passive to reduce heating, and the light emission sites on the probes are addressed spatially using a multicore fiber connected to the on-chip waveguides. Though several prototypes have been demonstrated for light-sheet imaging and beam-steering optogenetic stimulation, for the wide deployment of this technology as a practical system for neuroscience laboratories, the peripheral optics must be reduced in size and optimized.
Here, we combine our neural probes with a newly developed multicore fiber and a compact scanning optical unit. The optical unit has a portable footprint of 300mm x 300mm, including the laser, a fiber alignment stage and other components. The first-of-its-kind multicore fiber is specially designed to be single-mode over the visible spectrum. It has an outer diameter of 300µm and a linear array of 16 cores of 3µm diameter at a 16µm pitch. The custom scanning optics transfer a collimated laser beam of 0.7mm diameter via a micro-electromechanical system (MEMS) mirror to a steerable focused spot addressing the cores of the fiber. Currently, 50% of the optical power at a wavelength of 488nm is coupled from the scanning system to the fiber. To improve the power stability of the optical emission from the probe, the scanning optics and the neural probes have been co-designed such that the emission is independent of polarization fluctuations in the fiber. The progress described in this work is important for the deployment of implantable nanophotonic neural probes. Our future work includes the simultaneous operation at several laser wavelengths.



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Poster

P934. Probe Design and Engineering: New Methodologies

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Program #/Poster #: P934.03

Topic: I.04. Physiological Methods

Support: NIH NINDS R01NS089688
NIH R01NS110564

Title: Integration of microprism and micro-electrode array for long-term in vivo two-photon imaging of the intracortical neural interface

Authors: *Q. YANG, B. WU, E. CASTAGNOLA, A. L. VAZQUEZ, T. X. CUI;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical electrodes have long been used for communicating with neural tissue in both clinical therapies and research studies, but exactly how the brain cells interact with the electrodes has not been fully elucidated, especially for chronic implants. Two-photon microscopy (TPM) has been a

valuable tool for monitoring cellular activities at high resolutions *in vivo*. However, in chronic setups, conventional TPM maintains the best imaging quality only in the superficial brain regions (up to ~150μm) due to skull bone regrowth, meningeal thickening, and foreign body responses. Microprism implants bypass the above issues at the superficial regions by reflecting lights at 90 degrees and directly presenting a vertical view of the brain-implant interface (down to ~1mm deep). Here we integrate optical microprisms with microelectrode arrays (MEA) in order to chronically visualize the brain cell activities in all cortical layers near the intracortical neural electrode. The flexible and mostly transparent 4x4 MEA is fabricated by patterning Pt onto an ultrathin SU8 substrate using a standard photolithography process. To further improve the electrochemical properties of the electrodes, we electrically deposit nanostructured Pt or PEDOT onto each site. The MEA is then adhered to the microprism and coverglass using optical glue. In vivo electrochemical characterizations of the MEAs show an initial drop in the performance but then stabilize in one week. By implanting the microprism/MEA assembly into the cortex of Thy1-GCaMP6s mice, we achieve reliable electrophysiological recordings and calcium imaging of neuronal activities in all cortical layers on the same animal for more than 10 weeks. Additionally, by implanting the microprism/MEA assembly into CX3CR1-GFP mice, the inflammatory cell responses to different electrode regions and materials can be tracked over time. This microprism/MEA assembly technology enables longitudinal TPM imaging and electrophysiological studies of the neural interface across all cortical depths.

Disclosures: Q. Yang: None. **B. Wu:** None. **E. Castagnola:** None. **A.L. Vazquez:** None. **T.X. Cui:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.04

Topic: I.04. Physiological Methods

Support: AIA Grant 25A575
AIA Grant 211812
NSF CBET-16631912

Title: Initial development of a GRIN endoscopic probe for neurosurgery

Authors: *T. WELTON[1], B. N. OZBAY[4], S. OJEMANN[2], A. ABOSCH[5], D. RESTREPO[3], E. A. GIBSON[1];
[1]Bioengineering, [2]Neurosurg., [3]Cell & Developmental Biol., Univ. of Colorado Denver - Anschutz Med. Campus, Aurora, CO; [4]3i, Denver, CO; [5]Neurosurg., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Microendoscopy, the use of miniature optical probes to access and image deep brain areas, in combination with optogenetics is a popular technique for studying neuronal activity *in-vivo*. In recent years, there has been a push to apply this type of technology to the operating room to quickly evaluate the diagnostic viability of tissue samples, visualize blood vessels and other morphology, and potentially aid in surgical navigation. For example, Deep Brain Stimulation (DBS) surgery is an FDA approved

treatment for the motor symptoms of Parkinson's Disease (PD). The success of this surgery largely depends on the accurate localization of implanted electrodes at deep brain targets of interest like the subthalamic nucleus (STN). In the United States, a combination of stereotactic surgical techniques and microelectrode recordings (MER) are typically utilized to ensure accurate placement of the electrode(s). Even with these methods, the rate of electrode revision or removal in North America is between 15% and 34%. Furthermore, the use of sharp needles, microelectrodes, requires specialized training and increases the cost, duration, and risk of intracranial hemorrhage during the procedure. Therefore, there is a need to reduce or eliminate the use of MER during DBS and not forfeit the targeting accuracy of deep brain nuclei. Our group proposes to use two-photon microendoscopy to access and image deep brain locations in real time along the surgical trajectory. In this work, we present the initial design and testing of a long endoscopic probe composed of gradient refractive index (GRIN) lenses and perform some preliminary *in-vitro* tissue imaging as a proof of concept.

Disclosures: T. Welton: None. **B.N. Ozbay:** None. **S. Ojemann:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Fellowship grant support from Medtronic, Abbot, and Boston Scientific. **A. Abosch:** None. **D. Restrepo:** None. **E.A. Gibson:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.05

Topic: I.04. Physiological Methods

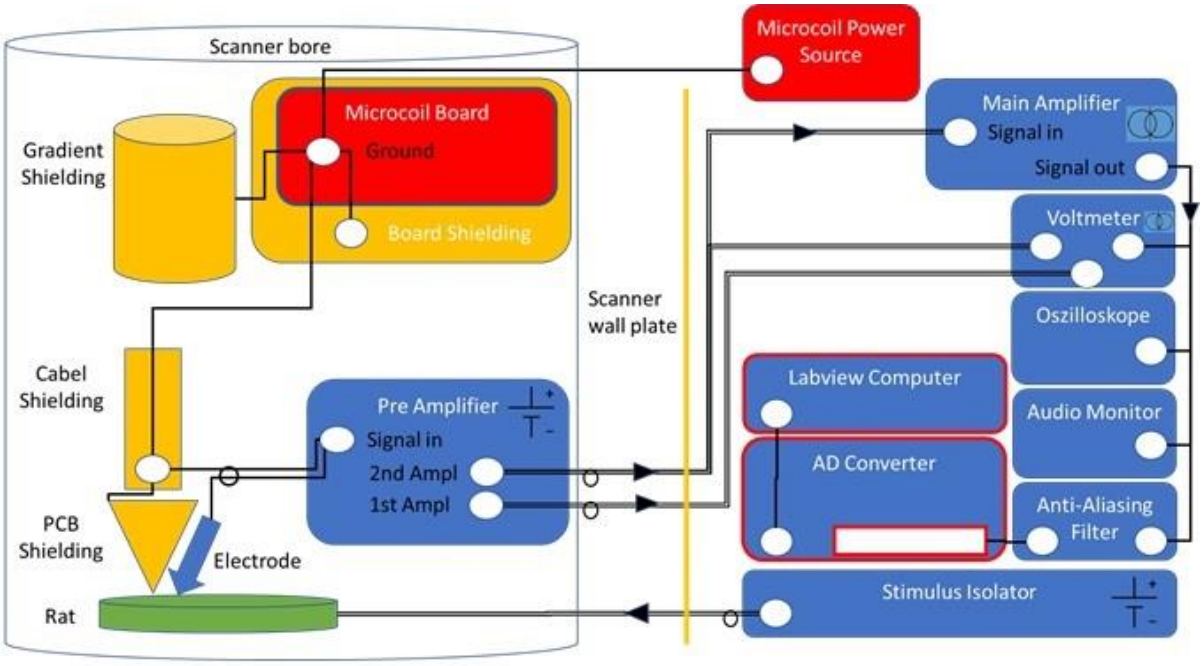
Support: BMBF 01GQ1702

Title: Electrophysiological setup for simultaneous microscale BOLD response and multi-unit activity recording at 14.1 Tesla

Authors: *A. VON RAVEN[1], A. OELTERMANN[2], M. BEYERLEIN[2], K. SCHEFFLER[1];
[1]High Field Magnetic Resonance, [2]Physiol. of Cognitive Processes, Max Planck Inst. for biological cybernetics, Tuebingen, Germany

Abstract: Introduction. Performing fMRI and electrophysiological measurements simultaneously offer a better understanding of the hemodynamic response function due to the high temporal and spatial resolution of the combination of these methods. In 2020 we introduced a monolithically integrated NMR chip on a needle for local in vivo measurements (Handwerker et al., 2020). As the NMR needle achieved a similar spatiotemporal resolution as electrophysiology while offering the specificity and versatility of NMR, an electrophysiology setup has been developed to detect multi-unit activity (MUA) as well as local field potential (LFP) simultaneously to the NMR needle measurements, potentially closing the gap between these complementary modalities. **Methods**. The electrophysiological electrode was based on carbon monofilament, causing low susceptibility distortions in a 14 Tesla MR scanner close to the NMR needle. Furthermore, it was electroplated with PEDOT:pTS to be able to record MUA additional to LFP

activity (Chuapoco et al., 2019). In order to prevent SNR loss, the non-magnetic, custom-made preamplifier was placed inside the magnet close to the recording electrode. We used a custom-designed galvanically separated main amplifier. We added several shielding applications to work under high magnetic-field conditions and to minimize interferences between the transmission pulse of the NMR needle and the microelectrode inside the tissue. (Image 1) **Results**. The electrophysiological electrode including magnetic field proof electronics was designed and constructed to detect stimulus-evoked neuronal signals with simultaneous NMR needle recordings. First experiments outside the magnet have shown its ability to detect multi-unit activity. **Conclusion**. This combined experimental setup will allow capturing localized BOLD activity within distinct cortical layers. It will enable to observe neurovascular coupling directly at high temporal and spatial resolution. We aim to detect the hemodynamic response of different non-evoked neuronal activities at distinct locations with this setup.



Disclosures: A. von Raven: None. **A. Oeltermann:** None. **M. Beyerlein:** None. **K. Scheffler:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.06

Topic: I.08. Methods to Modulate Neural Activity

Support: HSFP project fund RGP0004/2019

Title: Manipulation of network activity in the spinal cord by single cell stimulation via nanoscale photodiodes

Authors: *M. FONTANINI[1], A. THALHAMMER[1], B. TIAN[2], D. SCAINI[1,3], L. BALLERINI[1]; [1]SISSA, Trieste, Italy; [2]Univ. of Chicago, Chicago, IL; [3]ELETTRA, Trieste, Italy

Abstract: The aim of this project is to exploit nanoscale photodiodes (nPDs) to achieve selective and minimally-invasive manipulation of neural activity with high spatial and temporal resolution. Upon light stimulation a charge separation is induced on nPD surfaces that is able to depolarize cell membranes. We used near-infrared (NIR) light activation of nPDs at the single cell level in organotypic slice cultures (OSCs) of the spinal cord, where the 3D structure of neuronal networks is preserved while allowing easy access for molecular, pharmacological and optical manipulation. In order to record activity at a network level, we made use of neuronally expressed genetically encoded Ca^{2+} indicator GCaMP7f.We found that stimulating nPDs (1hr incubation) attached to the cell body of a visually identified neuron in the dorsal horn (DH) area of 2-3 weeks old OSCs, with a temporal pattern of illumination of 100 stimuli at 25Hz, induced a long lasting (>20min) increase (35%) in spontaneous network activity. Conversely illumination of the ventral area was not effective in inducing long term changes of spinal networks, nor was illuminating DH in absence of nPDs. This suggests that selective stimulation of a single excitatory DH neuron can cause potentiation of network activity. Light stimulation of single excitatory neurons live labelled for transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors confirmed that the increase in network firing observed occured mainly via capsaicin-sensitive pathways. These findings are reminiscent of 'Central Sensitisation' in chronic pain signaling, the molecular mechanism underlying pain hypersensitivity.In summary, our nanoscale photo-activatable material allows for non-genetic and minimally-invasive stimulation of single neurons, resulting in diverse changes of activity in intact neuronal networks depending on type and location of neuron stimulated. Considering that aelective stimulation of the spinal cord has been in use for decades as treatment for chronic pain, future experiments will be critical to reveal if activation of inhibitory interneurons of the DH can dampen the effect of nociceptive fiber input, paving the way for potential therapeutic application of nPDs *in vivo*.

Disclosures: M. fontanini: None. **A. Thalhammer:** None. **B. Tian:** None. **D. Scaini:** None. **L. Ballerini:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

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Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.07

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant UF1NS107694
NSF TANMS ERC Award 1160504

Title: Ultra-compact Magnetoelectric Antennas for Sub-mm Brain Implants to Record and Stimulate the Activity of Neurons

Authors: *M. NASROLLAHPOUR[1], A. KHALIFA[2], I. MARTOS-REPATH[1], M. ZAEIMBASHI[1], X. LIANG[1], H. CHEN[1], H. LIN[1], Z. XU[1], D. DAS[1], A. MITTAL[1], M. ONABAJO[1], A. SHRIVASTAVA[1], S.

CASH[2], N.-X. SUN[1];
[1]Northeastern Univ., Boston, MA; [2]MGH, Boston, MA

Abstract: Emerging healthcare applications require the contribution of wireless implantable devices to manage the neural recording and brain stimulation. The current technologies with the micro-coils provide low power transfer efficiency, which often implies the need for transmitted power in excess of the requirements defined by the Federal Communications Commission (FCC), especially for deep brain stimulation where the tissue loss and field attenuation is significant. Recent brain implant technologies operate based on voltage and current sensing, which brings two major issues: 1) direct contact of the electrode and the tissue degrades over time due to the electrochemical fouling, and 2) the differential recording across space. Two different ultra-compact non-electrochemical magnetoelectric (ME) antennas, Film Bulk Acoustic Resonator (FBAR) and Solid Mounted Resonator (SMR), were designed for wirelessly powered implants to stimulate the neurons while providing small magnetic field measurements for neural activities. The proposed FBAR antenna resonates at 2.51 GHz with the size of 0.0435 mm^2 and the SMR antenna resonates at 2.61GHz with the size of 0.04 mm^2, both showing power transfer efficiency of 1~2 orders of magnitude higher than the conventional micro-coils. This allows to operate within the FCC's specific absorption rate (SAR) limit. The proposed hybrid FBAR antenna provides the lower frequency resonance of 63 MHz that provides the magnetic sensing capability within the nano-Tesla range at frequencies more than 100 Hz, allowing the implant's neural recording without differential recording. The results demonstrate that the ME antenna provides efficient energy harvesting in case of transmitter coil misalignment or a rotated structure. Energy harvesting integrated circuits (ICs) were designed and fabricated in 180nm XFAB SOI technology. The first version of the energy harvesting circuit is considered for an ME antenna providing 50Ω matching, and the other design is considered for an ME antenna having an input resistance of more than 50Ω to improve the power transfer efficiency during energy harvesting. The recorded field potentials from a rat hippocampus slice in response to a 200 µs monopolar stimulus are shown while a stimulating stereotrode was connected to the rectifier output while a recording glass micropipette was connected to an external amplifier and data acquisition system (DAQ) to display the field response.

Disclosures: M. nasrollahpour: None. **A. Khalifa:** None. **I. Martos-Repath:** None. **M. Zaeimbashi:** None. **X. Liang:** None. **H. Chen:** None. **H. Lin:** None. **Z. Xu:** None. **D. Das:** None. **A. Mittal:** None. **M. Onabajo:** None. **A. Shrivastava:** None. **S. Cash:** None. **N. Sun:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.08

Topic: I.04. Physiological Methods

Support: NIH Grant K01EB027184
NIH Grant DP2NS122605

Title: Transduction of neural activity to magnetic signals by nanofabricated inductors, quantified via finite element analysis

Authors: *J. PHILLIPS[1], M. GLODOWSKI[1], Y. GOKHALE[1], A. ASHTIANI[1], M. DWYER[2], A. HAI[2];
[1]Biomed. Engin., [2]Biomed. Engineering, Electrical and Computer Engin., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Methods for the detection of neural signals involve a trade-off between invasiveness, spatial resolution, temporal resolution, and the number of neurons or brain regions recorded. Electrode-based probes offer excellent spatial and temporal resolution but usually require transcranial wiring and capture small portions of the brain. Noninvasive methods such as electroencephalography (EEG) and magnetoencephalography (MEG) offer fast readouts of field potentials or biomagnetic signals, respectively, but have spatial constraints that prohibit recording from single neurons. A device that can enhance neural magnetic fields can be used as an *in situ* sensor for MEG and increase the ability to detect signals from deeper brain regions. We have designed a device capable of forming a tight electrical connection with a neuron, and of using changes in cellular potential to drive current through an inductor, which transduces neuronal electrical activity into magnetic signals. Here, we present detailed quantification of the device performance using realistic finite element simulations with signals and geometries taken from patch-clamped neurons *in vitro,* and demonstrate the device's capability to produce magnetic signals readable via existing modalities from a single neuron. We compare the magnetic output of this device to that of a single neuron, and show that the transduced magnetic signal is not only higher at its peak (1.70 nT vs 0.39 nT), but importantly, is spread over a larger volume, making the transduced magnetic field output within a carefully chosen voxel (40x40x10 microns) over 250 times higher than the native signal (0.64 nT vs 2.5 pT).

Disclosures: J. Phillips: None. **M. Glodowski:** None. **Y. Gokhale:** None. **A. Ashtiani:** None. **M. Dwyer:** None. **A. Hai:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.09

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA Contract No. N66001-19-C-4020
NSF Neuronex innovation award 1707562
Welch Foundation Grant C-1963
NIH Grant RO1MH107474

Title: Optimization of Fast Multiplexed Magnetogenetics

Authors: *C. SEBESTA[1], D. TORRES[1], B. WANG[3], Z. LI[4], G. DURET[2], K. JIANG[1], Z. XIAO[6], Q. ZHANG[1], V. COLVIN[6], S. GOETZ[4], A. V. PETERCHEV[5], H. DIERICK[7], G. BAO[1], J. T. ROBINSON[2,8];
[1]BioEngineering, [2]Electrical and Computer Engin., Rice Univ., Houston, TX; [3]Psychiatry and Behavioral Sci., [4]Electrical and Computer Engin., [5]Psychiatry & Behavioral Sci., Duke Univ., Durham, NC; [6]Chem., Brown Univ., Providence, RI; [7]Mol. and Human Genet., [8]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Precisely timed activation of genetically targeted cells is a powerful tool for investigating neural circuits and controlling cell-based therapies. Magnetic control of cell activity or "magnetogenetics" using magnetic heating of nanoparticles to activate temperature-sensitive ion channels enables remote, non-invasive activation of neurons for deep-tissue applications and studies of freely behaving animals. However, the *in vivo* response time of thermal magnetogenetics is currently tens of seconds, which prevents the precise temporal modulation of neural activity achieved by light-based optogenetics. Moreover, magnetogenetics has not provided a means to selectively activate multiple channels to drive behavior. Here we demonstrate that by combining magnetic nanoparticles with a rate-sensitive thermoreceptor (TRPA1-A) it is possible to achieve sub-second behavioral responses in *Drosophila melanogaster*. Additionally, we have identified novel TRPA1 channels that show promise of translating this work to mammalian systems. Furthermore, by tuning the properties of magnetic nanoparticles to respond to different magnetic field strengths and frequencies, we can achieve fast, multi-channel stimulation, analogous to optogenetic stimulation with different wavelengths of light. These results bring magnetogenetics closer to the temporal resolution and multiplexed stimulation possible with optogenetics while maintaining the minimal invasiveness and deep-tissue stimulation enabled by magnetic activation.

Disclosures: C. Sebesta: None. **D. Torres:** None. **B. Wang:** None. **Z. Li:** None. **G. Duret:** None. **K. Jiang:** None. **Z. Xiao:** None. **Q. Zhang:** None. **V. Colvin:** None. **S. Goetz:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Magstim. **A.V. Peterchev:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Rogue Research, Tal Medical/Neurex, Magstim, MagVenture, Neuronetics, BTL Industries, Advise Connect Inspire. **H. Dierick:** None. **G. Bao:** None. **J.T. Robinson:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.10

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant AG065914
NIH Grant AG065914-01S1

Title: Cellular resolution, volumetric recording of neuronal activity over a large cortical area in freely-moving mice

Authors: *A. DAS[1], S. HOLDEN[2], J. BOROVICKA[1], D. PATEL[1], J. RABER[2,3], H. DANA[1];
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Abstract: Genetically-encoded calcium indicators (GECIs) are widely used to record neuronal activity *in vivo*. GECIs are mostly used in one of two configurations: 1) Fixing the animal's head under a microscope, or 2) Implanting a recording device onto the animal's skull. Both options have limitations. Head fixation imposes unnatural posture and behavioral performance and the implanted device puts a

relatively heavy weight on the head of the animal, especially for mice, that also restricts natural behaviors. To address these limitations, we show that Calcium-Modulated Photoactivatable Ratiometric Integrator (CaMPARI) can be used to record single-neuron, cortical activity in freely-moving animals without any implanted device or head fixation during the experiment. The fluorescence signal of CaMPARI undergoes an irreversible change from green to red when the increased intracellular calcium concentration coincides with light illumination at 400nm. We show that this activity-dependent photoconversion can be used in freely-moving mice to detect large-scale activity as deep as Layer V of the cortex during behavioral tests. Moreover, we show that the red signal decays within 7 days and therefore allows recording multiple times from the same mice. Thus, CaMPARI-based recording expands the capabilities of "traditional" GECIs and can be used to selectively detect cortical neuronal activity under minimally-restricted experimental conditions.

Disclosures: A. Das: None. **S. Holden:** None. **J. Borovicka:** None. **D. Patel:** None. **J. Raber:** None. **H. Dana:** None.

Poster

P934. Probe Design and Engineering: New Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P934.11

Topic: I.08. Methods to Modulate Neural Activity

Title: Long-term, cortex-wide neural interfacing in single-cell resolution via SomaGCaMP8f and 3D-printed transparent skull combined with polymer electrodes.

Authors: *Y. WANG[1,2], Y. ZHENG[3], K. D. PIATKEVICH[1];
[1]Westlake Univ., Hangzhou, China; [2]Xi'an Jiaotong Univ., Xi'an, China; [3]Dept. of NanoEngineering, Univ. of California San Diego, La Jolla, CA

Abstract: Imaging neuronal activities at single-cell resolution at mesoscopic levels in multiple brain regions are critical for studying how neural activity in specific cortical regions contributes to behavior. Progress has been made in developing transparent "See-Shells", that allows for optical access to a larger area of the dorsal cerebral cortex in the mouse. However, this "See-Shell" is lacking the long-term ability to perturbing and recording neural activities. In addition, one-photon methods used in mesoscopic imaging with this "see-shell" usually suffer from higher levels of crosstalk among neuropils, resulting in a decreased signal-to-noise ratio and artifactual correlations of neural activity. To address these problems, we engineered a new version of soma-target GCaMP8f, with improved signal-to-noise ratio and increased brightness, combined with 3D-printed, digitally designed, biocompatible, and stable polymer electrodes on the See-Shell, to achieve long-term cortex-wide neural interfacing in single cell resolution.

Disclosures: Y. Wang: None. **K.D. Piatkevich:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.01

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Fisher Center for Alzheimer Research Foundation
JPB Foundation

Title: The use of DEL (DNA-encoded library) drug discovery platform for neurodegenerative diseases

Authors: Y. K. SUNKARI, V. K. SIRIPURAM, T.-L. NGUYEN-MEDRIHAN, W. WANG, ***M. FLAJOLET**;
rockefeller university, new york, NY

Abstract: The DNA-encoded library (DEL) technology, conceptualized by Drs. Brenner and Lerner in an article published in PNAS in 1992, started to emerge in 2005 and has been considerably developed and optimized over the last 10 years. While relatively rare in the academia, this technology is particularly suited for academic research due to its extremely compact nature. Indeed, the screening activity is totally lab compatible and does not require any specific large equipment, handling robots, large storage spaces, etc. For several reasons it is especially suited for Neuroscience and neurodegenerative diseases. Briefly, the methodology implies that drug-like compounds are made in a combinatorial way and barcoded with unique and specific DNA sequences. Because each compound is barcoded with a unique and specific DNA sequence all tagged compounds can co-exist in a single tube. Due to the combinatorial nature of the process, very large number of compounds are being made following this approach; we will introduce one of our DEL libraries that combines over 100 millions compounds and several applications directed toward Alzheimer's disease dysfunctions. The protein target of interest is expressed, purified and immobilized onto a solid support using a classical tagging system. Because very little of the protein target is required for 1 tube/1 screening campaign, it allows for the target to be purified from other sources than *E. coli*, from more physiological sources, such as mammalian cells or even brain tissue. This methodology will open up new screening avenues, especially when the protein target has a complex post-translational modification pattern and that it is often not fully identified (e.g., tau phosphorylation). Furthermore, several screens can be performed in parallel, for example comparing WT versus mutants, or comparing the same target protein expressed in stimulated and non-stimulated conditions. We will further detail some of these concepts and present specific examples of screening campaign results, focusing on Alzheimer's disease, and especially in the context of sTREM2 and tau.

Disclosures: Y.K. Sunkari: None. **V.K. Siripuram:** None. **T. Nguyen-Medrihan:** None. **W. Wang:** None. **M. flajolet:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.02

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: GATE Graduate fellowship

Title: Design and development of Heterobifunctional peptide molecule against neurodegenerative proteins

Authors: *K. BHAVSAR[1], S. GUPTA[2];
[2]Biol. engineering, [1]Indian Inst. of Technology, Gandhinagar, Gandhinagar, India

Abstract: Neurodegenerative disorders (ND) are increasingly recognized as the major cause of disability and deaths, currently affecting 47.5 million people globally with dementia in people aging 60 or above. One common feature linked to mostly all ND is the misfolding and aggregation of certain proteins, which generates the cascade of pathological events leading to failure to protein homeostasis in the physiological state. TAR DNA binding protein 43 (TDP-43), is one such protein responsible for Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal lobar degeneration (FTLD). Physiologically TDP-43 is a regulator of gene expression, RNA processing, etc. However, the mutation in TDP-43, leads to the excess deposition and formation of misfolded toxic protein aggregates in the cytoplasm of the cell, leading to disease. The aggregation-prone proteins are pharmacologically difficult to target because of their misfolded and disordered structure. To tackle this stumbling block, we contemplated Targeted Protein Degradation approach and developed a peptide-based Proteolysis Targeting Chimera (PROTAC) against aggregated TDP-43 degradation. PROTAC is a heterobifunctional molecule, composed of two different binding domains connected by a linker. One is for engaging an E3 ubiquitin ligase and other for the binding to targeted protein. E3 ligase recruitment leads to the ubiquitination of targeted protein, and recognition by the Ubiquitin proteasome system for the degradation. As a protein quality control system, the UPS plays a key role in the degradation of misfolded or aggregated proteins and maintaining protein homeostasis. Our objective is to study the degradation potential of cytoplasmic mutated TDP-43 utilizing synthesised peptide-PROTAC Synthesis of the peptide-PROTACs was done via Fmoc-base solid phase peptide synthesis methodology. Purity and characterization of the molecule was checked using RP-HPLC and MALDI mass spectrometer. TDP-43 recombination protein expressed and purified in *E.Coli* bacterial culture was performed. The Cell penetration study of the synthesized PROTAC was performed in SH-SY5Y neuroblastoma cell line using confocal microscopy. Further the cell viability assay was done using MTT Assay and analysed. Further experiments including the protein expression in SH-SY5Y cell lines are currently in process. The preliminary studies performed on peptide-PROTAC was seen to be promising and further evaluation needs to be done. Conclusion: We believe that the synthesized novel PROTAC will regulate the aggregated cytosolic TDP-43 towards the selective degradation, utilizing inherent cellular UPS.

Disclosures: K. Bhavsar: None. **S. Gupta:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.03

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Identification of the cellular origin of brain-derived exosomes by combined reflectance and fluorescence microscopy

Authors: C. BAGCI, N. BELDER, M. SEVER-BAHÇEKAPILI, **S. ERDENER**, *T. DALKARA; Hacettepe Univ. Inst. For Neurolog. Sci. and Psychiatry, Ankara, Turkey

Abstract: Exosomes are endosomal membrane vesicles commonly found in tissues and biological fluids. They have a diameter of ~40–150 nm and are produced by nearly every cell. Exosomes carry a variety of cargo from the cell that they are released, including RNAs, DNAs, proteins, and lipids. Exosomes are taken up by local and distant cells, hence, play a role in intercellular communication. Their content varies during pathological and physiological processes; therefore, exosomes may be used as reporters of intracellular milieu of the cell of origin.There are several methods available for efficient exosome isolation, but no standardized techniques for quick characterization of their cellular origin following their extraction from the brain tissue except complex sorting approaches. Exosomes originate from a number of different CNS cells in vivo. This heterogeneity together with their small size makes their characterization challenging. Exosomes can be fluorescently labelled by using antibodies against their surface markers or payloads. Fluorescent emission from them can be detected by confocal microscopy despite their actual size being below the optical resolution (approximately 200 nm at 532 nm wavelength; Van Der Pol et al., 2010). However, fluorescent speckles corresponding to single or aggregated exosomes is confounded with non-specific particulate-like emissions from the tissue or in vitro medium. We found that confocal reflectance microscopy, which is readily available in almost all commercial equipment, enabled detection of exosomes and their clusters owing to high refractive index mismatch with the medium, provided by their lipid content (Ter-Ovanesyan et al., 2017). In the present study, we describe a reproducible and practical method combining fluorescence and reflectance modalities to overcome the above imaging limitations. For this, exosomes isolated from the mouse brain tissue were immuno-labelled with antibodies against the cell-specific intracellular and surface proteins such as ALDH1L1 and s100β (astrocyte markers), CD171 (neuronal marker) and Iba1 (microglia marker) to determine their cellular origins. Combining fluorescent and reflectance signals correctly identified the exosomes and eliminated the false fluorescent speckles. With double or triple immunofluorescence staining and reflectance microscopy, we were able to determine payloads of exosomes along with their cellular origins (i.e., neuronal, astrocytic, etc.). The combined reflectance and fluorescent microscopy can therefore be employed to identify the cellular origin of isolated exosomes and their payloads as a practical method.

Disclosures: C. Bagci: None. **N. Belder:** None. **M. Sever-Bahçekapili:** None. **S. Erdener:** None. **T. Dalkara:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.04

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Lysolecithin (LPC) induced demyelination of the optic chiasm as a model to evaluate remyelinating agents

Authors: *G. EDU, A. LORENZANA, M. POON, D. LORRAIN;
Pipeline Therapeut., San Diego, CA

Abstract: Myelination of axons is necessary for faithful, long-distance conductance of electrical impulses. Multiple sclerosis (MS) is characterized by immune mediated myelin injury and progressive axonal loss. Many patients with MS exhibit myelin-dependent slowing of neuronal transmission in the optic nerve which can be measured through visual evoked potentials (VEP). VEP is a clinically translatable endpoint used to quantify myelin damage in MS patients and in animal models of MS. Demyelination is characterized by a significant latency shift in the VEP waveform signal (Toussaint et al., 1983, Green et al., 2017). While current MS therapies primarily address the immune mediated component of the disease, there has been recent interest in mechanisms that promote remyelination. To evaluate mechanisms that directly impact remyelination, mouse models using acute demyelinating agents, such as, lysolecithin injection into the spinal cord or corpus callosum are used with a histological endpoint to assess the cellular and structural aspects of remyelination. Because of its focal nature, however, attempts at a reliable functional endpoint, such as a behavioral score is difficult to evaluate. While other MS models, like MOG-EAE provide the benefit of both a histological and functional endpoint - the model evaluates compounds that could impact the immune component, oligodendrocyte differentiation, or both. Moreover, the model can at times vary with respect to onset and severity of the demyelination. This model evaluates the myelination component specifically. Recently, a group described a model whereby lysolecithin was directly injected into the optic chiasm (Mozafari et al., 2010). Here we validate this model, show a progression from demyelination to remyelination, and importantly, show a correlation between VEP latency and histology across time points. Peak latency delays were seen by 7 days post-lysolecithin suggesting an optimal timepoint to evaluate remyelinating compounds. We further show that the VEP delay and recovery are not caused by differences in inflammation. Because both histological and VEP endpoints can be measured, acute, focal lysolecithin induced demyelination in the optic chiasm provides a rapid, comprehensive method for evaluating remyelinating agents.

Disclosures: G. Edu: A. Employment/Salary (full or part-time):; Pipeline Therapeutics. **A. Lorenzana:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. **M. Poon:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. **D. Lorrain:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.05

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Characterization of M1-Selective and Brain-Penetrant [11C]-PIPE-307 PET Radiotracer in Cynomolgus Monkeys

Authors: A. CHEN[1], A. L. AMENTA[2], C. BACCEI[1], G. BOSCUTTI[3], B. P. BURKE[3], C. PLISSON[3], C. SANDIEGO[3], L. WELLS[3], *D. LORRAIN[1];
[1]Pipeline Therapeut., San Diego, CA; [2]Invicro, New Haven, CT; [3]Invicro, London, United Kingdom

Abstract: Recent preclinical and clinical research have suggested that the selective antagonism of M1 in the CNS should facilitate the remyelination of denuded axons by effectively promoting the differentiation of oligodendrocyte precursor cells (OPCs) into oligodendrocytes. In this regard, we have identified PIPE-307, a novel, potent and selective M1-antagonist, as a potential treatment of demyelinating diseases such as multiple sclerosis (MS), that is complementary to currently known immunotherapies. To support the clinical development of PIPE-307, a carbon-11 labelled PIPE-307 ([^{11}C]-PIPE-307) radiotracer suitable for imaging M1 receptors using positron emission tomography (PET) was synthesized and characterized. [^{11}C]-PIPE-307 was prepared using [^{11}C]-CH_3OTf after 34 ± 3 min of synthesis, with isolated radiochemical yield of 10 ± 2 %, radiochemical purity greater than 99%, and molar activity of 253 ± 85 GBq·µmol^{-1}The CNS pharmacokinetics of [^{11}C]-PIPE-307, its binding to the M1 receptors, and its displacement *in vivo* by cold PIPE-307 as a function of dose and plasma exposure, was assessed in non-human primate (NHP) brain. Two cynomolgus NHPs underwent dynamic PET imaging, acquired over 90 min post-injection of [^{11}C]-PIPE-307, at baseline and after I.V. administration of cold PIPE-307 (0.01 to 2 mg/kg) 5 min prior to radiotracer injection. [^{11}C]-PIPE307 demonstrated excellent brain uptake, reversible kinetics, and regional distribution consistent with M1 expression. Specific binding (BP_{ND}) in brain regions were estimated using Logan graphical analysis, with the cerebellum as the reference region. At baseline, BP_{ND} range was 1.30 ~ 1.49 in caudate and putamen, and 0.56 ~ 0.90 in amygdala, hippocampus, frontal, occipital, and temporal cortices. Unlabeled PIPE-307 decreased BP_{ND} dose-dependently from baseline levels, and the resulting change in regional BP_{ND} was used to estimate occupancy. An Emax model was used to derive the relationship between occupancy with dose (ED_{50} = 0.032 mg/kg) plasma concentration (EC_{50} = 7.14 nM). BP_{ND} test-retest variability was 2 ± 8%, averaged across regions and animals.These favorable results support the translation of the novel radiotracer [^{11}C]-PIPE-307 to clinical imaging studies for the assessments of human M1 dose-occupancy in the CNS.

Disclosures: A. Chen: A. Employment/Salary (full or part-time):; Pipeline Therapeutics. **A.L. Amenta:** A. Employment/Salary (full or part-time):; Invicro. **C. Baccei:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. **G. Boscutti:** A. Employment/Salary (full or part-time):; Invicro. **B.P. Burke:** A. Employment/Salary (full or part-time):; Invicro. **C. Plisson:** A. Employment/Salary (full or part-time):; Invicro. **C. Sandiego:** A. Employment/Salary (full or part-time):; Invicro. **L. Wells:** A. Employment/Salary (full or part-time):; Invicro. **D. Lorrain:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P942.06

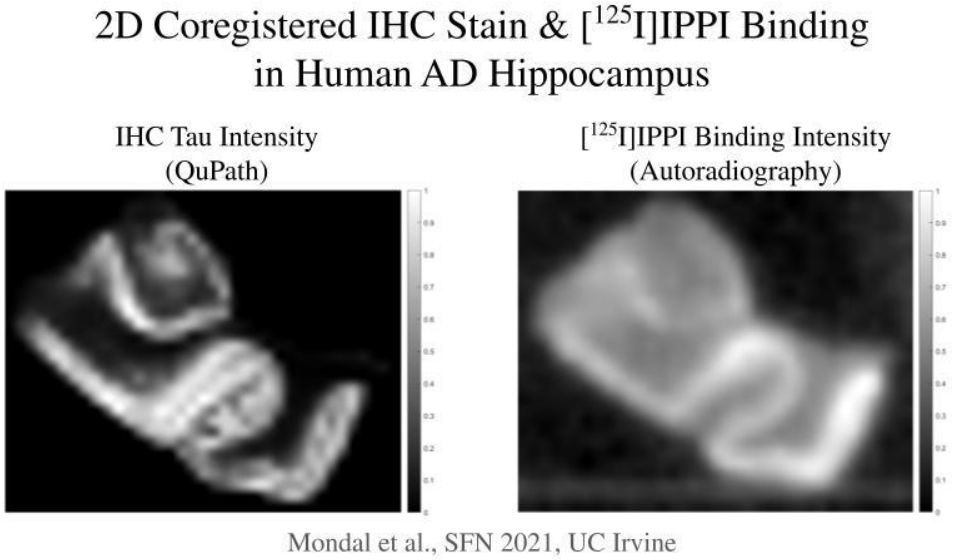
Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH/NIA RF1 AG02979

Title: [^{125}I]ippi: a novel tau radioligand for assessing neurofibrillary tangles in human hippocampus of postmortem alzheimer's disease subjects

Authors: R. MONDAL, R. M. LADWA, C. LIANG, *J. MUKHERJEE;
Radiological Sci., Univ. of California, Irvine, Irvine, CA

Abstract: Title: [^{125}I]IPPI: Novel Tau Radioligand for Assessing Neurofibrillary Tangles in Human Hippocampus of Postmortem Alzheimer's Disease Subjects
Objective: Alzheimer's disease (AD) is a neurodegenerative disease characterized by aggregation of Tau protein into paired helical filaments causing neurofibrillary tangles (NFT) in the brain. We have developed a Tau selective radioligand, [^{125}I]IPPI which is suitable for autoradiographic studies of NFT accumulation in AD brains. Here we report binding of [^{125}I]IPPI in hippocampus (HP) in postmortem AD (n=29) and compared to cognitively normal (CN, n=32) brains.
Methods: Hippocampus from well-characterized subjects were used in the study. All brain sections were obtained from Banner Health Research Institute, Sun City, Arizona. Brain slices with [^{125}I]IPPI in 10% ethanol PBS buffer pH 7.4 (60 mL; 0.1 μCi/mL) were incubated at 25 oC for 1.25 hr. The slices were then washed with cold PBS buffer, 50% ethanolic PBS buffer twice, PBS buffer and cold water. The brain sections were air dried and extent of binding of [^{125}I]IPPI was measured in DLU/mm2. Adjacent slices were immunostained with DAKO polyclonal antibody to total Tau which detects all 6 six isoforms of Tau. QuPath was used for analysis of the IHC images. The pixel thresholder and pixel classifier functions were used to detect percent and area of Tau, based on DAB staining intensity.
Results: All AD subjects exhibited high [^{125}I]IPPI binding in the HP grey matter (GM) regions. In comparison CN subjects had significantly lower binding as expected. Ratio of average GM [^{125}I]IPPI in AD versus CN was found to be 7.31. All AD subjects IHC were positively stained for the presence of NFT. A more detailed correlative analysis of [^{125}I]IPPI with IHC intensity using coregistered images is currently being carried out using Qupath as shown in Figure 1.
Conclusion: [^{125}I]IPPI is a novel radioligand well suited for autoradiographic studies of NFT in AD. The autoradiography binding profile of IPPI to Tau matches the QuPath generated profile from 2D coregistered IHC and IPPI images.



Disclosures: R. Mondal: None. **R.M. Ladwa:** None. **C. Liang:** None. **J. Mukherjee:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

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Program #/Poster #: P942.07

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH Grant NS093127

Title: Development of a selective ELISA for pre-formed alpha-synuclein fibrils over alpha-synuclein monomers

Authors: J. T. WONG, *R. S. AKHTAR;
Northwestern Univ., Chicago, IL

Abstract: Fibrillar α-synuclein (α-syn) is hypothesized to be central in the pathogenesis of Parkinson disease (PD). However, there are no clinical assays or biomarkers capable of tracking fibrillar α-syn in patient samples. Such biomarkers are necessary to evaluate putative disease-modifying treatments designed to interrupt α-syn fibrillization. Adequate biomarkers for α-syn fibrils are particularly challenging to develop since the assays must exclude the normally folded, non-fibrillar monomeric form of the protein. Here, we developed and optimized an enzyme-linked immunosorbent assay (ELISA) to detect recombinant human α-syn monomer and distinguish it from pre-formed α-syn fibrils (PFFs). We selected a 96-well ELISA platform for its ability to perform simultaneous assays on many samples. Recombinant human α-syn was prepared as PFFs by templated recruitment reaction. Fibrillar nature of α-syn was confirmed using thioflavin T assay and sedimentation assay. ELISA plates were coated with commercially available antibodies for α-syn. We systematically tested multiple blocking agents to optimize sensitivity and reduce nonspecific background signal. The plates were then incubated sequentially with either α-syn monomer or PFFs, a secondary α-syn antibody of differing host species, and an HRP-antibody conjugate. We systematically tested antibody concentrations, diluents, incubation times and temperatures, pH, and chromogen parameters to enhance fibril detection over monomer. We found that a combination of rabbit monoclonal antibody MJRF1 (Abcam) and mouse monoclonal antibody S5566 (Sigma) adequately detected α-syn PFFs while excluding α-syn monomer. Of several blocking agents, Blockace (Bio-Rad) allowed adequate sensitivity while reducing nonspecific background signals. Varying diluent composition minimally affected sensitivity of PFFs over monomer. Lower pH and increased incubation times resulted in higher sensitivity for both species but no change in selectivity of PFFs. We developed an ELISA using commercially available α-syn antibodies to detect both α-syn monomers and PFFs. Selectivity for the fibrillar form can be achieved using optimized assay conditions and antibody concentrations. Our next step is to leverage this assay to detect fibrillar α-syn in patient samples, coupled with high quality clinical data. These analytic measures have potential as diagnostic and / or prognostic biomarkers for PD.

Disclosures: J.T. Wong: None. **R.S. Akhtar:** None.

Poster

P942. Neurodegenerative Diseases: Methods and Tools

Location: Virtual Only

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Program #/Poster #: P942.08

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: AveXis GRT00054231

Title: Continual Cerebrospinal Fluid Sampling in the Neonatal Domestic Piglet for Biomarker and Discovery Studies

Authors: *M. PINO[1], R. GANGULY[2], K. RICH[1], A. FOX[1], L. MATTOX[3], E. KECKLEY[3], M. JOSEPH[4], R. MALBRUE[3], V. KRISHNA[2], B. YOUNGBLOOD[3], S. KOLB[1,5];
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Abstract: Background: Continual access to cerebrospinal fluid (CSF) is useful when studying neurological disorders or diseases affecting CSF composition. For longitudinal studies, there is a need for reliable and safe permanent intrathecal access. Large animal models provide opportunities to discover and characterize CSF contents. In this study, we tested a new method for insertion of a permanent intrathecal catheter, facilitating longitudinal collection of CSF.
Methods: Postnatal day (PND) 4 domestic piglets received broad-spectrum antibiotics, steroids, and isoflurane-induced anesthesia prior to surgery. Piglets were placed in prone position over a towel roll with the hips flexed. Following sterile surgical preparation, an incision was made over the lumbosacral area. Soft tissue was dissected and a laminectomy made at the L5 spinal level. The dura was exposed, a micro-incision was made, and CSF egress was visualized. A barium-impregnated, fenestrated catheter was inserted into the thecal sac under direct visualization, then advanced superiorly under fluoroscopic x-ray guidance until the tip reached the cisterna magna. Iohexol contrast dye was injected in the catheter and visualized in the cisterna magna under fluoroscopy. The catheter and access port were flushed with sterile saline and sutured in place subcutaneously. Immediately after surgery, CSF flow through the catheter and port was assessed via needle aspiration. Beginning three days post-surgery, CSF samples were drawn from the port at regular intervals (every 2-4 days) under light anesthesia and analyzed for neurofilament light chain, a biomarker of axonal injury.
Results: Frequent, longitudinal sampling of CSF was achievable in PND 4-60 pigs. CSF was readily accessible through the catheter and port multiple times per week during the two-month study period. Post-mortem dissections confirmed proper catheter placement. Catheterized pigs demonstrated slowed, but normal, weight gain compared to control pigs. Post-procedural complications included elevated white blood cell count and limb weakness but were manageable with medications. Levels of CSF neurofilament light chain at multiple time points will be presented.
Conclusion: We have developed a reliable and minimally invasive method for repeated CSF collection in the piglet that is both safe and effective for long-term, intrathecal use. Our methodology enables the biomarker, pharmacodynamic, and discovery studies of central and peripheral nervous system conditions where continual access to CSF is desired.

Disclosures: M. Pino: None. **R. Ganguly:** None. **K. Rich:** None. **A. Fox:** None. **L. Mattox:** None. **E. Keckley:** None. **M. Joseph:** None. **R. Malbrue:** None. **V. Krishna:** None. **B. Youngblood:** None. **S.**

Kolb: F. Consulting Fees (e.g., advisory boards); SJK has received compensation for consultation from AveXis, Biogen and Genentech..

Poster

P986. New Techniques Related to Optogenetics

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Program #/Poster #: P986.01

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH-NIDA Intramural Research Program
NIH Grant ZIA000069

Title: PET compatible opsins for translational optogenetics

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Abstract: Optogenetic technologies enable the manipulation of target neuronal populations and circuits with precise spatiotemporal control. This capability offers preclinical and therapeutic utility, but a major translational obstacle is the need to monitor the location and function of opsins without invasive procedures. Positron emission tomography (PET) is a versatile molecular imaging technique that can be used to visualize transgenic constructs with compatible radiotracers (e.g. chemogenetic receptors). To adapt this approach for optogenetics, we developed the first PET compatible opsin - ChRERα - by attaching the ligand binding domain (LBD) of the estrogen receptor alpha (ERα) to the excitatory channelrhodopsin-2 (ChR2). In vitro validation experiments in HEK-293 cells show ChRERα retains the original ERα-LBD affinity for binding estradiol and fluoroestradiol. In addition, blue light stimulation (473 nm) of cells transfected with ChRERα elicited photocurrents indistinguishable from cells transfected with ChR2, thus ChRERα retains the functional properties of the original excitatory opsin. To test whether ChRERα expression can be visualized with PET in vivo, we performed scans with the FDA approved radiotracer [^{18}F]-fluoroestradiol (FES) before and after intracranial injections of a ChRERα adeno-associated viral vector (AAV2/5-hSyn-ChR2-V5-ERαLBD) in the motor cortex (M1) of rats (Sprague Dawley, n=8) and squirrel monkeys (*Saimiri sciureus*, n=2). FES-PET scans in rats post-AAV (3-5 weeks following surgery) and monkeys (5-7 weeks following surgery) showed localized increases in FES-PET signal (measured as standard uptake value (SUV) and SUV ratios) near the M1 injection site (~2x SUV ratio of baseline) as well as in established motor cortical projection areas. Interestingly, these localized increases were still observed in monkey FES-PET scans performed 1-1.5 years after the AAV injection, although to a lesser extent than observed 5-7 weeks post-AAV. Immunofluorescence microscopy (with anti-ChR2 primary antibody) was used as post-mortem confirmation of ChRERα expression and coincided with brain areas showing localized increases in FES-PET signal post-AAV. This project demonstrates the application of the first transgenic opsin designed for compatibility with a PET radiotracer. Importantly, FES-PET was capable of localizing ChRERα in rodents and nonhuman

primates, and repeated within subject scans revealed longitudinal changes in opsin expression. This approach may be adaptable for visualizing a variety of opsins (and other transgenic constructs) to advance the translational potential of optogenetics and related technologies.

Disclosures: M.A. Boehm: None. **J. Bonaventura:** None. **H.P. Jedema:** None. **O. Solís:** None. **E.A. Stein:** None. **C.W. Bradberry:** None. **M. Michaelides:** None.

Poster

P986. New Techniques Related to Optogenetics

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R21 EY030278
Pfizer/NCBiotech 2020-GTF-6908
Duke Institute for Brain Sciences Research Germinator Award
Hartwell Biomedical Research Fellowship

Title: Epifluorescent assessment of viral mediated gene expression is unreliable compared to immunostaining in neuronal populations of the primate model: implications for neuronal actuator use

Authors: *T. DAW[1], H. G. EL-NAHAL[2], M. A. BASSO[3], E. J. JUN[3], A. R. BAUTISTA[3], R. J. SAMULSKI[4], M. A. SOMMER[2], M. O. BOHLEN[2];
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Abstract: Neuronal actuator technologies are increasingly used in rodent research, but their utility in non-human primates (NHP) remains limited. The lack of robust physiological and behavioral results in NHP suggests a fundamental issue with translating these techniques from rodents to primates. In the present study, following viral injections in the brain, epifluorescent assessment of transduction and expression patterns consistently failed to reveal adequate transgene labeling, whereas immunofluorescence and immunohistochemical assessment reliably provided visualization of robust transgene expression. Using epifluorescent assessment, viral gene expression was typically restricted to neuronal cell bodies and large processes, such as apical dendrites. In contrast, following immunostaining, viral mediated labeling was visualized in cell bodies, apical dendrites, and small neuronal processes, including dendritic and axonal terminal fields. Thus, it is likely that, although many viral constructs successfully transduce neurons in NHP, the transgene is not necessarily being expressed in targeted cells. Epifluorescence is therefore inadequate for assessment of viral mediated expression in NHP, and immunostaining is necessary to avoid false negative conclusions about transduction. Furthermore, the findings suggest a need for reagent optimization specifically in the NHP model. Reagent optimization in the primate for the primate will drastically improve the efficacy of neuronal actuator techniques in NHP behavioral studies.

Disclosures: T. Daw: None. **H.G. El-Nahal:** None. **M.A. Basso:** None. **E.J. Jun:** None. **A.R. Bautista:** None. **R.J. Samulski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Asklepios Biopharmaceutical Inc. **M.A. Sommer:** None. **M.O. Bohlen:** None.

Poster

P986. New Techniques Related to Optogenetics

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Program #/Poster #: P986.03

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH U01 NS099702
NIH RO1 EY019743
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NSF IOS 1355075
NSF EAGER 1649923
Research To Prevent Blindness

Title: A Novel Device for Spatiotemporally Precise Large-Scale Optogenetic Stimulation of Deep Cortical Layers in Non-Human Primates

Authors: *A. ANGELUCCI[1], A. INGOLD[1], D. CUNDY III[1], C. REICHE[2], J. L. BALSOR[1], F. FEDERER[1], N. MCALINDEN[4], J. ROLSTON[3], L. RIETH[5], K. MATHIESON[4], S. BLAIR[2], **A. M. CLARK**[1];
[1]Ophthalmology and Visual Sci., [2]Electrical and Computer Engin., [3]Neurosurg., Univ. of Utah, Salt Lake City, UT; [4]SUPA, Inst. of Photonics, Dept. of Physics, Univ. of Strathclyde, Glasgow, United Kingdom; [5]Feinstein Inst. of Med. Res., Manhasset, NY

Abstract: Optogenetics is a powerful tool for studying neural circuit function. While widely applied in rodents, a significant obstacle to applying optogenetics in non-human primates is spatially precise stimulation of deep cortical layers across large volumes. Here, we describe a novel device, the Utah Optrode Array (UOA), that meets this critical need. The UOA is a 10x10 array of glass needle shanks tiling a 4 x 4mm area. For photostimulation, a custom µLED array is integrated to the device, with an individual, electrically addressable, 80µm^2 µLED delivering light through each individual shank. A pinhole layer at the µLED/array interface and an optically opaque interposer on the backplane eliminates surface illumination. Shank length and tip profile are customizable, in order to target different layers and vary the spatial profile of light spread, respectively. The UOA is capable of delivering irradiances far exceeding activation threshold across a range of opsins. We used *in vivo* linear electrode array (LEA) recordings to assess the utility of UOAs for precise modulation of neural activity in deep layers of monkey cortex expressing the excitatory opsin *Channelrhodopsin-2* (ChR2). We also employed *ex vivo* imaging of immediate early gene (cFos) expression to determine the downstream consequences of focal deep layer optogenetic activation. Comparison of surface and UOA stimulation revealed a sharp difference in laminar activity patterns. Surface stimulation of ChR2-expressing regions via a laser-coupled collimated optical fiber evoked responses spanning layers 2-4. Conversely, ChR2 activation via a UOA inserted so shank tips terminated in layer 4 evoked responses across layers 4-6. At lower intensities, UOA-evoked neural responses were localized to the layer nearby the UOA tips. Varying the pattern of

UOA stimulation revealed a preference on each LEA contact for stimulation at particular sites (optrode receptive fields - ORFs). ORF centers varied smoothly across contacts and generally increased in size with stimulation intensity. Differences in response latencies across layers were consistent with localized optogenetic activation followed by synaptic spread. cFos imaging revealed downstream consequences of this deep layer optogenetic activation at the scale of inter-connected cortical regions. These results demonstrate the capacity to utilize the UOA, in tandem with new vectors for targeting opsin expression, to isolate the role of deep cortical layers in complex intracortical and corticocortical circuits. We recently integrated a second µLED array to the device, capable of delivering light between UOA shanks for photostimulation of superficial layers.

Disclosures: A. Angelucci: None. **A. Ingold:** None. **D. Cundy III:** None. **C. Reiche:** None. **J.L. Balsor:** None. **F. Federer:** None. **N. McAlinden:** None. **J. Rolston:** None. **L. Rieth:** None. **K. Mathieson:** None. **S. Blair:** None. **A.M. Clark:** None.

Poster

P986. New Techniques Related to Optogenetics

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Topic: I.08. Methods to Modulate Neural Activity

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Title: Network-level modelling of stimulation-induced functional connectivity change: An optogenetic study in non-human primate cortex

Authors: *J. BLOCH, A. GREAVES-TUNNELL, E. SHEA-BROWN, Z. HARCHAOUI, A. SHOJAIE, A. YAZDAN-SHAHMORAD;
Univ. of Washington, Seattle, WA

Abstract: The ability to shape network-level inter-area synchronization of the brain would be a profound accomplishment for developing treatments for neural disorders. Large-scale inter-area synchronization, termed “functional connectivity,” has been repeatedly shown to underlie healthy brain function. Brain stimulation has been established as a promising method for modifying large-scale functional connectivity, but the mapping from stimulation to the resulting modification remains unclear.
The prevalent framework for inducing targeted connectivity change is neural stimulation informed by Spike-Timing Dependent Plasticity (STDP), a mechanism which relates a change in synaptic strength to the delay between the spiking times of pre- and post-synaptic neurons. Although STDP governs neural connectivity change at the single-synapse level, translation from its original controlled in vitro setting to

more challenging and clinically relevant in vivo settings required targeting multi-synapse level connectivity. While researchers could adapt to this change such as by measuring functional connectivity instead of individual synapse connection strength, the use of STDP-informed stimulation in its non-native context yielded inconsistent results. First, studies reported that the stimulation often failed to induce desired connectivity changes. Second, although STDP only predicts connectivity changes between stimulated sites, studies reported widespread connectivity changes between unstimulated sites. Taken together, these results highlight the need for an updated framework for modeling widespread stimulation-induced functional connectivity change in vivo.
Here, we successfully develop a model which accurately predicts stimulation-induced functional connectivity changes over a large-scale (~1cm2) network of non-human primate sensorimotor cortex. We arrive at this model through a large-scale optogenetic brain interface for simultaneous stimulation and recording, graph theory tools for network-level analysis, and an interpretable machine learning model for accurate prediction and inference. Our model is accurate over multiple days of stimulation, subjects, and for both stimulated-state functional connectivity changes and resting-state functional connectivity changes. From our model we observe that STDP-informed protocol features alone poorly predict stimulation induced functional connectivity changes, whereas the structure of the pre-existing functional connectivity network is an accurate predictor. Our model and insights represent a promising new framework for targeted network-level functional connectivity change.

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Poster

P986. New Techniques Related to Optogenetics

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Program #/Poster #: P986.05

Topic: I.08. Methods to Modulate Neural Activity

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AMED 21wm0525003h0001
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Takeda Science Foundation

Title: Remapping of Adult-Born Neuron Activity during Fear Memory Consolidation in Mice

Authors: P. VERGARA, D. KUMAR, S. SRINIVASAN, I. KOYANAGI, T. NAOI, S. SINGH, *M. SAKAGUCHI;
Univ. Tsukuba WPI-IIIS, Tsukuba, Japan

Abstract: Adult-born neurons (ABNs) in the dentate gyrus (DG) are constantly being integrated into the hippocampal circuit. These ABNs undergo a process of maturation that ultimately leads to synaptic and electric properties that are equivalent to those of developmentally born granule cells. However, when ABNs are still immature, they display properties that largely differ from their mature counterparts, such as increased synaptic plasticity and excitability, and weaker inhibitory inputs. These properties may bestow ABNs with unique roles during memory processing; indeed, several studies indicate that ABNs contribute to each of the three main stages of memory: encoding, consolidation, and retrieval. However, the exact mechanism by which ABNs contribute to each of these stages is unknown. One possibility is that ABNs operate as engram cells. If this is the case, ABNs activity dynamics should satisfy at least two conditions: 1) A specific population of ABNs should be activated during learning, and 2) this same population should be reactivated when animals remember the encoded memory. Nonetheless, the activity dynamics during memory encoding, consolidation, and retrieval are unknown. To address this issue, we imaged ABNs calcium activity across a 6-hour-long contextual fear conditioning memory paradigm. This revealed two fundamental notions about how ABNs operate during memory processing: First, ABNs active during memory encoding do not overlap with the cells active during memory retrieval. Indicating that, at least at the population level, ABNs do not behave as putative engram cells. Second, ABNs underwent a constant process of activity remapping through time, in such a way that at different time points, different populations of ABNs were predominantly active. These results suggest that ABNs support the establishment of a fear memory trace in a different manner to directly holding the memory. Moreover, this activity remapping process in ABNs may support the segregation of memories formed at different times. These results provide new insight into the role of adult neurogenesis in the mammalian memory system.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

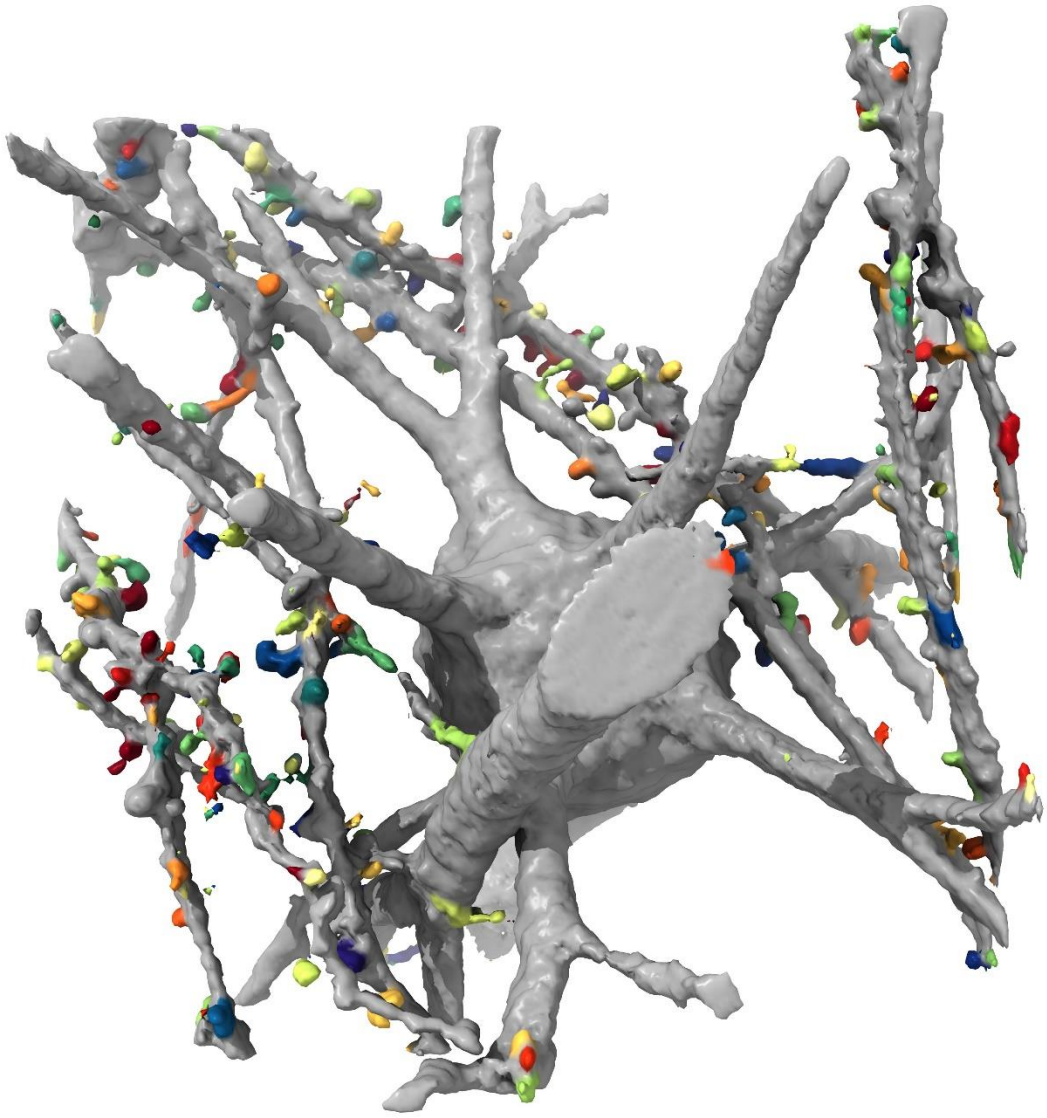
Support: 1R01DK127589
1R01MH120131
1R21HD105189

Title: Whole-brain imaging at synaptic-scale resolution with axially swept light-sheet microscopy.

Authors: R. FIOLKA, ***K. M. DEAN**;
Lyda Hill Dept. of Bioinformatics, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Large-scale interdisciplinary efforts aim to comprehensively map the functional architecture of neuronal cells and circuits. To date, this has largely been performed with serial sectioning-based approaches such as Focused Ion Beam Scanning Electron Microscopy (FIB-SEM). Nonetheless, while

such efforts provide incredible detail, imaging a select brain region is prohibitively expensive and takes months to years, thereby limiting the acquisition of important biological replicates. Furthermore, unlike fluorescence, FIB-SEM fails to provide molecular specificity. To circumvent these limitations, we developed a scalable imaging platform that delivers isotropic sub-cellular resolution throughout intact volumes of chemically cleared tissues. The system, referred to as cleared-tissue Axially Swept Light-Sheet Microscopy (ctASLM), combines high-speed aberration-free remote focusing and residual aberration correction to achieve an isotropic imaging resolution of 360 and 310 nm laterally and axially after deconvolution, in aqueous and BABB-cleared samples, respectively, throughout a ~330 micron field of view. Owing to ctASLM's performance, we can resolve and automatically detect synaptic spines in any spatial dimension while also evaluating long-range projections with trans-synaptic tracers throughout centimeters of tissue. Furthermore, when combined with expansion and iterative expansion microscopy, ctASLM provides ~80 and ~20 nm isotropic resolution, respectively. ctASLM is affordable, easy to assemble, has a better axial resolution than Lattice Light-Sheet Microscopy, and is orders of magnitude faster than leading confocal microscopes. Thus, ctASLM serves as an ideal imaging system for next-generation connectomic studies in both health and disease.



Disclosures: R. Fiolka: None. **K.M. Dean:** None.

Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: 1DP2GM146247-01

Title: Mammalian Directed Evolution of Allosteric Optobodies

Authors: C. WOODS[1], A. ZAHM[2], ***J. ENGLISH**[2];
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Abstract: Found in every cell, G-protein coupled receptors (GPCRs) mediate neurotransmission and are the functional targets of most drugs of abuse and psychiatric therapeutics. The past one-hundred years of biochemical research on GPCRs has produced over 500 structural determinations, >100,000 confirmed ligands, and a wealth of signaling assay platforms. Absent from this impressive roster are any tools for the discrete, cell-type specific tuning of endogenous receptor activity. Without such tools, we lack the ability to directly connect discrete GPCR signaling events to cell-type specific physiological outputs. Such tools are essential if we are to understand how GPCRs dictate human health and disease.
I have previously developed a platform for the directed evolution of protein sequences in mammalian cells (VEGAS). My lab has advanced this platform to enable the evolution of optogenetic tools in mammalian cell contexts. We are now using this platform to engineer optogenetically activated, GPCR allosteric intrabodies to directly engage with and control GPCR signaling events in the brain. I will share these advances, including improvements on the VEGAS platform and our strategy for developing these optogenetic intrabodies.

Disclosures: C. Woods: None. **A. Zahm:** None. **J. English:** None.

Poster

P986. New Techniques Related to Optogenetics

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Program #/Poster #: P986.08

Topic: I.08. Methods to Modulate Neural Activity

Support: F31MH122137
R01MH115900

Title: Holographic imaging and stimulation of deviance detection ensembles in auditory cortex

Authors: *Y. SHYMKIV, R. YUSTE;
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Abstract: Perception of sensory information by the brain is highly dependent on context, where responses to the most informative, or deviant (novel), stimuli are selectively amplified. Deficits of deviance detection appear in patients with schizophrenia, suggesting its importance for normal information processing and cognitive function.Here we use a holographic two-photon microscope with a spatial light modulator (SLM) integrated on both imaging and stimulation paths, to do aberration-free simultaneous volumetric imaging and stimulation. We imaged awake mice in the auditory cortex (AC) undergoing passive auditory oddball paradigm. We found novelty detection cells across all imaged areas of auditory cortex, in both primary (A1 and AAF) and secondary (A2 and UF) areas, with higher density and selectivity than cells responding in neutral (control) context. To analyze multineuronal activity, we developed a NMF-based pipeline to 1) compute data dimensionality, 2) extract neuronal ensembles and 3)

evaluate ensemble quality with a cross-validation prediction model. The analysis of ensemble dynamics suggests that the stimulus-evoked single trial activity is higher dimensional than expected, with more dimensions than the number of unique stimuli presented. That is, for seemingly identical trials, including deviant trials of oddball, there are often multiple distinct stimulus-tuned ensembles responding individually, but not at the same time. In addition, 30% of extracted ensembles were not tuned to any presented stimuli or locomotion, corresponding to ongoing cortical activity. We hypothesize that ensembles are context-coding units and to test this we are using our holographic setup to imprint (optically train) enhanced evoked responses to deviant stimuli, by stimulating deviance detection ensembles. A method to improve perception of deviance may be important for rescuing the deficits associated with schizophrenia.

Disclosures: Y. Shymkiv: None. **R. Yuste:** None.

Poster

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National Institute of Neurological Disorders and Stroke of the National Institute of Health (1R01NS116464-01)

Title: Optimized, large-scale optogenetic interface for non-human primates

Authors: *D. GRIGGS, W. K. S. OJEMANN, J. BLOCH, S. FISHER, A. YAZDAN-SHAHMORAD; Univ. of Washington, Seattle, WA

Abstract: High spatial and temporal precision and cell type specificity make optogenetics a powerful tool for studying fundamental neural mechanisms and developing neurorehabilitation techniques. To these ends, we introduced an optimized large-scale optogenetic interface for non-human primates (NHPs) [1] and we acutely validated our novel, semi-transparent electrode array [2].
This interface consists of a flexible, semitransparent recording and stimulating miniature-electrocorticography (ECoG) array called a multi-modal artificial dura (MMAD) which we have integrated into a transparent silicone artificial dura for chronic use. We have surgically implanted the MMAD which provides both optical access to about 2.7 cm^2 of the brain and ECoG recording capability to about 1 cm^2 of the brain which collectively enable large-scale cortical optogenetic experimentation.

This interface improves upon the stability and scale of our previous interface iterations [3]. Previously, optical access to the brain was limited to 2-3 weeks due to the optical window being clouded with opaque tissue growth which required resection before continued use, μECoG recording hardware was prone to corrosion, and the setup was limited to 2-3 simultaneous optical stimulation channels. Here, we will validate our optimized design allows for months of optical access, is corrosion resistant, and supports up to 15 LEDs for simultaneous optical stimulation, thus improving the stability and scale of the interface. We have performed convection enhanced delivery (CED), an efficient pressure-based viral delivery approach, to genetically modify cortical neurons of the NHP with uniform, widespread viral delivery [3-4]. After optogenetic expression, various optical and electrical stimulation protocols will be employed to modulate neural activity and the results will be recorded by the MMAD.
If successful, our experiments will validate the stability and scale of the interface design by (1) increasing the length of time of optical access to neural tissue from a few weeks to several months, (2) demonstrating no significant corrosion to electrical recording hardware, and (3) demonstrating neural modulation via various optogenetic and electrical stimulation protocols as measured by ECoG recordings. This work will set the stage for the development of stable, large-scale, multi-modal neural modulation protocols for the purpose of studying cortical organization and plasticity, and developing neurorehabilitation techniques.
References:
[1] DJ Griggs et. al., *SPIE,* 2019.
[2] DJ Griggs et. al., *J. Neural Eng.*, 2021.
[3] A Yazdan-Shahmorad et. al., *Neuron,* 2016.
[4] K Khateeb et. al., *J. Vis. Exp.*, 2019.

Disclosures: D. Griggs: None. **W.K.S. Ojemann:** None. **J. Bloch:** None. **S. Fisher:** None. **A. Yazdan-Shahmorad:** None.

Poster

P986. New Techniques Related to Optogenetics

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Program #/Poster #: P986.10

Topic: I.08. Methods to Modulate Neural Activity

Support: samsung science and technology foundation under project number SSTF-BA1602-11

Title: Translational control of a specific gene by light-induced liquid-liquid phase separation

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Abstract: Translational control of a specific gene by light-induced liquid-liquid phase separation
Hyeonjeong Jeong, Hyungseok Moon, Min Lee, Yongdae Shin, Hyeyoon Park
Biological asymmetry originates from differential orchestration of gene expression. One of the ways to introduce cellular asymmetry is precise spatiotemporal control of translation. For example, mRNA

localization with regulated translation is known to be essential for long-term plasticity in neurons. However, there lacks a tool which recapitulates this nature's ability to precisely control the translation of a specific gene. Here, we implemented a technique to control translation by light using a recently developed OptoDroplet system. We demonstrate that the OptoDroplet system can be applied to control translation of β-actin mRNA in neurons. Analysis of structural long-term potentiation (s-LTP) of dendritic spines during chemical long-term potentiation (c-LTP) revealed the role of newly synthesized β-actin in sculpting synaptic strengths in neurons.

Disclosures: H. Jeong: None. **H. Moon:** None. **M. Lee:** None. **Y. Shin:** None. **H. Park:** None.

Poster

P988. New Methods for Manipulating Neural Activity

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIMH R01MH108729

Title: A comparison of DREADDs agonists using fear conditioning in a rodent model

Authors: *T. B. WISE, D. L. POETA, J. G. LEE, M. M. MAZUMDER, R. D. BURWELL;
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Abstract: Designer receptors exclusively activated by designer drugs (DREADDs) is an increasingly popular chemogenetic technique used in neuroscience to temporarily and selectively modify neuronal activity. Currently, clozapine-*N*-oxide (CNO) is the most widely used DREADDs agonist, but due to concerns regarding off-target effects of CNO, deschloroclozapine (DCZ) has been proposed as a possible alternative. In vitro studies indicate that DCZ has a high affinity for common muscarinic-based DREADDs that may be comparable or greater than that of CNO. Evidence from these studies also suggest that DCZ may be faster acting and permeable at lower doses than CNO, therefore providing an argument for broader use of DCZ as an alternative to CNO (Nagai et al 2020). Studies investigating the potential of DCZ, however, remain limited in scope. To our knowledge, the effectiveness and possible behavioral impact of DCZ have not yet been examined in rats.
In this study, we compared the effectiveness of DCZ to CNO using DREADDs manipulation of the basolateral amygdala (BLA) in rats. Utilizing a standard signaled contextual fear conditioning paradigm, we measured the behavioral effects of silencing the BLA during training using either DCZ or CNO. Freezing behavior was also measured during both context extinction and tone extinction phases as well as during reactivation of fear conditioning. Rats were euthanized and brains were taken immediately after the reactivation procedure. We verified DREADDs virus placement using fluorescent microscopy, and we analyzed c-fos expression in the BLA. This examination for differences between DCZ and CNO may provide support for or against using DCZ as a CNO alternative, guiding future research and potentially motivating the transition to a more accessible and targeted DREADDS agonist.

Disclosures: T.B. Wise: None. **D.L. Poeta:** None. **J.G. Lee:** None. **M.M. Mazumder:** None. **R.D. Burwell:** None.

Poster

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Program #/Poster #: P988.02

Topic: I.08. Methods to Modulate Neural Activity

Support: KAKENHI JP21K07268
JP21dm0107146

Title: Chronic behavioral manipulation via orally delivered chemogenetic actuator in macaque monkeys

Authors: *K. OYAMA[1], Y. HORI[1], Y. NAGAI[1], N. MIYAKAWA[1], K. MIMURA[1], T. HIRABAYASHI[1], K.-I. INOUE[2], M. TAKADA[2], M. HIGUCHI[1], T. MINAMIMOTO[1];
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Abstract: The chemogenetic technology referred to as designer receptors exclusively activated by designer drugs (DREADDs) offers reversible and less invasive means to control neuronal activity for investigating its functional correlation with behavioral action. Deschloroclozapine (DCZ), a recently-developed highly potent and selective DREADDs actuator, displays a capacity to expand the utility of DREADDs for chronic manipulation without side-effects in non-human primates, which has not yet been validated. Here we investigated the pharmacokinetics and behavioral effects of orally administered DCZ in macaque monkeys. Pharmacokinetic analysis and positron emission tomography (PET) occupancy examination demonstrated that oral administration of DCZ yielded a slower and prolonged kinetics, and that its bioavailability was 10-20% of that in the case of systemic injection. We then examined the chemogenetic effect of oral DCZ administration on behavior in two monkeys that expressed hM4Di in the bilateral dorsolateral prefrontal cortex (dlPFC) around the principal sulcus (Brodmann's area 46), a brain region known to be responsible for spatial working memory. Orally administered DCZ (300-1000 μg/kg, 3-10 times higher doses than systemic injection) induced significant working memory deficits for at least 4 h. The oral DCZ doses did not cause any detectable behavioral changes in control monkeys without vector injection. We also found that repeated daily oral doses of DCZ consistently caused similar deficits over two weeks without discernible desensitization. Our results indicate that orally delivered DCZ affords a less invasive strategy for chronic but reversible chemogenetic manipulation of neuronal activity in non-human primates, which has potential for clinical application.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: BRAIN initiative grant R01MH117040
Takeda Science Foundation Overseas Research Fellowship

Title: The effect of Deschloroclozapine on fMRI functional-connectivity.

Authors: *A. FUJIMOTO[1], C. ELORETTE[1], S. H. FUJIMOTO[1], L. FLEYSHER[2], P. H. RUDEBECK[1], B. E. RUSS[3,4,1];
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Abstract: Chemogenetic techniques such as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) enable transient, reversible, and minimally invasive manipulation of neural activity *in vivo*. Their development in non-human primates is essential for uncovering how specific cell types, neural circuits, and areas contribute to behavior as well as potentially enabling their translation to humans. Recently, deschloroclozapine (DCZ) has been shown to be a selective, high affinity ligand that reliably activates DREADD receptors at dosing levels that do not cause behavioral alterations in normal controls. However, it is unknown whether low dose DCZ causes subtle changes in brain activity. To address this issue, we acquired resting-state fMRI scans from lightly anesthetized macaque monkeys (N = 8) that were administered with either 0.1, 0.3 mg/kg of DCZ, or vehicle systemically (i.v.) halfway through an imaging session. As 0.1 mg/kg DCZ does not impair performance of control monkeys in a working-memory task (Nagai et al., *Nat Neurosci*, 2020), we hypothesized that fMRI functional-connectivity patterns will be similar between pre and post DCZ injections, whereas 0.3 mg/kg DCZ will cause significant changes in connectivity. Whole brain functional images were acquired on a Siemens MAGNETOM Skyra 3T scanner (TR/TE 2100/16ms, voxel size 1.6x1.6x1.6mm) while animals were lightly anesthetized. We found that 0.1 mg/kg DCZ, as predicted, did not lead to any consistent or specific changes in whole-brain functional connectivity. Notably, a higher dose of DCZ (0.3 mg/kg) known to cause behavioral impairments (Upright and Baxter, *Neuropsychopharm*, 2020) was associated with changes in whole brain functional connectivity patterns. Our findings show that at dose levels that are not associated with behavioral effects, DCZ does not alter whole-brain resting-state functional connectivity. Because fMRI is non-invasive and has higher spatial/temporal resolution than other whole-brain measures such as FDG-PET, it is a powerful tool for a drug-screening of individual animals especially for chemogenetic experiments in non-human primates.

Disclosures: A. Fujimoto: None. **C. Elorette:** None. **S.H. Fujimoto:** None. **L. Fleysher:** None. **P.H. Rudebeck:** None. **B.E. Russ:** None.

Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 MH119814

Title: Assessing differing DREADD construct effectiveness in prelimbic cortex-projecting neurons.

Authors: *A. GLORIUS, P. MAHBOD, B. PACKARD, D. BUESING, Y. M. ULRICH-LAI, J. P. HERMAN;
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Abstract: Chronic stress is associated with the development of affective disorders. Prior work from our group indicates that performing pleasurable behaviors can ameliorate the negative effects of stress on behavior. This study was designed to identify neural circuitry underlying the beneficial effects of palatable food intake, focusing on connection between the basolateral amygdala (BLA) and the prelimbic (PL) division of the medial prefrontal cortex. In these exploratory experiments, we used differing constructs of Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) to specifically target chemogenetic activation/inhibition of this connection and assess the optimal construct to conduct large-scale experimentation. Male rats underwent stereotaxic surgical procedures to receive an ipsilateral dual region-injection (no sex differences were assessed). In the initial study rats received a unilateral stereotactic injection of a retrograde AAV (adeno-associated virus) construct expressing Cre recombinase (rgAAV2-Cre) in the BLA and ipsilateral injection of Cre-dependent mCherry-tagged excitatory (AAV8 or AAV2 Gq-DREADD) or mCherry-tagged inhibitory (AAV8 or AAV2 Gi-DREADD) constructs into the PL in the same surgical session. CNO was used to actuate DREADD constructs, either alone (Gq-DREADD) or in combination with restraint stress (Gi-DREADD)(a manipulation known to activate PL neurons). The ability of the Cre-inducible DREADD to modulate PL◊BLA activation was measured by cell counts of Fos activated cells bodies expressing mCherry and/or Cre recombinase. Our results indicate that Fos was highly expressed in mCherry/Cre labeled neurons following CNO in Gq-DREADD animals, and the % Fos colocalization was significantly higher than that observed in mCherry negative, Cre positive neurons. In contrast, activation of Gi-DREADD almost entirely prevented restraint-induced Fos activation in mCherry/Cre positive cells. Broader analysis of mCherry expression revealed occasional mCherry/Cre-expressing in regions outside the PL, including the paraventricular thalamus and BLA, suggesting retrograde trans-neuronal spread of AAV8 virus. In contrast, we did not observe spread of mCherry, Cre outside the PL in AAV2 treated animals. These results suggest we have sufficient control of the PL◊BLA projections, via DREADDs, to examine the role of these connections in stress resilience. More so, these results suggest that use of AAV2 vectors may be preferable to avoid retrograde transmission of viral DREADD constructs.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIH 5K00MH123667
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Title: Development and Validation of Photo-caged Oxytocin Analogs

Authors: *I. A. AHMED[1], J. LIU[2], C. J. BAIR-MARSHALL[1], B. E. HETZLER[3], A. ADEEWAKUN[1], C. ARP[3], D. TRAUNER[3], R. TSIEN[2], R. C. FROEMKE[1];
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Abstract: Oxytocin is an evolutionarily conserved neurohormone that regulates fundamental physiological processes involving reproduction, childbirth, and milk ejection[1,2]. More recently, oxytocin has been shown to play a key role in social behavior such as pair-bonding and maternal behavior[3,4]. Deficiencies in oxytocin signaling have been linked with several neuropsychiatric disorders affecting social interaction, such as autism spectrum disorder and postpartum depression[5]. At the molecular level, oxytocin activates its respective G-protein-coupled receptor (OXTR), which is expressed in various regions of the brain and throughout the rest of the body. For example, in the brain, oxytocin modulates neuronal excitability and synaptic transmission. However, methods to precisely deliver and activate neuropeptides like oxytocin within specific anatomical regions of the brain and periphery with spatiotemporal specificity are lacking. To achieve spatiotemporal activation of oxytocin in mammalian tissue, we developed photocaged analogs of oxytocin. These caged-oxytocin peptides are functionally inert prior to photolysis, and irradiation with ultraviolet (UV) light causes the release of native oxytocin. We validated the caged compounds in vitro using a fluorescent calcium flux assay and calcium imaging in cell culture. We further demonstrated its utility in brain tissue by performing whole-cell electrophysiological recordings in acute brain slices of mouse auditory cortex. We demonstrated that photorelease of the caged-oxytocin cause significant ($p = 0.0299$, unpaired t-test) membrane depolarization of OXTR+ neurons (n= 9) but not OXTR- neurons (n=5). The effect of photolyzed caged-oxytocin compares well with the pharmacological application of oxytocin peptide, which produces significant ($p = 0.0014$, unpaired t-test) membrane depolarization of OXTR+ neurons (n= 13) but not OXTR- neurons (n=9). Furthermore, we show that caged-oxytocin is relatively inert in brain slices. We show both caged-oxytocin (n= 10) and artificial cerebrospinal fluid (n= 7) show no significant (unpaired t-test) change in the cell resting potential of OXTR+ hippocampal CA2 neurons. Conversely, uncaging of the caged-oxytocin (n= 10) induces membrane depolarization of OXTR+ hippocampal CA2 neurons to a similar extent (n.s., unpaired t-test) of pharmacologically applied oxytocin (n=7). Together, these results demonstrate that photo-caged peptides are useful tools for spatiotemporal control of the release of neuropeptides like oxytocin in the mammalian brain.
1. Burbach et al. 2006 2. Valtcheva & Froemke 2019 3. Insel and Young 2001 4. Marlin et al. 2015 5. Cochran et al. 2013

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Poster

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Program #/Poster #: P988.06

Topic: I.08. Methods to Modulate Neural Activity

Support: AEI/FEDER PGC2018-095895-B-I00

Title: Effect of near infrared-laser stimulation in single neurons and electrically coupled cells

Authors: A. GARRIDO-PEÑA[1], P. SÁNCHEZ-MARTÍN[1], R. LEVI[1], J. CASTILLA[2], J. TORNERO[2], *P. VARONA[1];
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Abstract: Near-infrared lasers can be used as a non-invasive stimulation technique for studying neural dynamics. Such optical stimulus elicits changes in single neuron dynamics with little or no cell damage and have a potential use for medical purposes. However, the detailed biophysical basis of the effect of this stimulation is not yet known. In this work, we quantified the outcome of infrared laser stimulation both on single cells and on electrically coupled neurons. To explain the effect of the stimulation we employed a combined experimental and modeling approach in the nervous system of Lymnaea stagnalis. We first characterized the activity recorded with intracellular electrodes comparing the amplitude, duration, depolarization and repolarization slopes of individual spikes before, during and after the infrared-laser stimulation. In these experiments, the laser beam was focused on one of the neurons being recorded. Spike duration was reduced under the laser stimulation, along with a change in the repolarization slope. The effect was reversible after termination of the stimulation. The analysis was repeated on well-known electrically-coupled cells of the right parietal and visceral ganglia of Lymnaea. For electrically coupled cells, the activity was simultaneously recorded in both neurons while the laser was illuminating only one of them. The experimental protocols were reproduced in a conductance-based model that considered multiple explanations for the observed effect of the laser stimulation, and we tested which ones best reproduced all observations. Our study unveiled several factors underlying the source of the infrared-laser effect and supports the use of this stimulation in multiple experimental protocols.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: NSF EPSCoR 1632881

Title: Using LITE-1 for X-genetic control of behavior in C. elegans

Authors: K. E. CANNON[1], M. RANASINGHE[2], L. DOBRUNZ[1], J. ANKER[2], *M. BOLDING[1];
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Abstract: “X-genetics” proposes to replace visible light stimulation used in optogenetics with X-radiation, which penetrates bone with higher efficiency, avoiding the need for surgical implantation of optic fibers. Finding a receptor protein sensitive to X-rays or the biochemical products of X-radiation is crucial for the development of the X-genetics technique. Here we report that LITE-1, an unusual UV-sensitive photoreceptor protein found in C. elegans, functions as an X-ray receptor, mediating X-ray induced behavioral responses in wild type and transgenic worms. Videos were obtained of behavioral avoidance responses of adult hermaphrodite wild type and LITE-1 mutant nematodes exposed to focused X-ray stimulation. Nematode activity was quantified using WormLab tracking software. Videos were obtained of paralysis responses of swimming wild type and pmyo-3::lite-1 transgenic nematodes exposed to unfocused X-ray stimulation. Body bend frequency was tallied manually by an individual blinded to the experimental condition and worm strain. Wild type and LITE-1 intact nematodes were found to respond to focused 0.5, 0.7, and 1 Gy/s X-radiation with a short-latency avoidance response (within ~2 s), seen as a robust increase in activity, that was absent in strains deficient for LITE-1 (N = 20, 10, 10, 10, and 17 for wild type at 0, 0.2, 0.5, 0.7, and 1 Gy/s; N = 10 for each mutant strain at 0 and 1 Gy/s). Additionally, transgenic expression of LITE-1 in C. elegans myocytes was found to elicit a paralysis response, seen as a increase decrease in body bend frequency, and egg ejection to unfocused X-radiation administered at dose rates of 0.56 and 0.74 Gy/s (N = 10, 9, 11, 11, and 12 for pmyo-3::lite-1 strain at 0, 0.19, 0.38, 0.56, and 0.74 Gy/s; N = 12 for wild type at 0 and 0.74 Gy/s). The paralysis experiments were replicated in two labs using different X-ray sources. Together, these results suggest that LITE-1 can function as an X-ray sensitive receptor, playing a critical role in the transduction of X-ray signals into neural activity to produce behavioral responses. As such, LITE-1 shows strong potential for use in X-genetics to transduce transcranial X-ray signals for precise minimally invasive manipulation of neural activity in mammals.

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Poster

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Title: Resistance heating can selectively block small-diameter axons similar to IR inhibition

Authors: *J. ZHUO[1], C. E. WEIDRICK[2], Y. LIU[1], M. A. MOFFITT[1], E. D. JANSEN[3], H. J. CHIEL[4], M. W. JENKINS[1];
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Abstract: Small-diameter nerve fibers carry various sensory signals (e.g., pain, heat/cold, pressure) and play an important role in the autonomic regulation of normal biological processes. An implantable device for the selective block of small-diameter nerve fibers is an unmet medical need. Our group has shown that Infrared (IR) neural inhibition can selectively inhibit the small-diameter nerve fibers by IR-induced heating. Furthermore, the power threshold for IR inhibition can be lowered by isotonic extracellular ion replacement or by varying the IR application length. Based on our previous modeling and experimental work, we hypothesize that resistance heating via a heating cuff can induce the selective heat block of the small-diameter nerve fibers, similar to the IR inhibition effect. We tested our hypothesis on the pleural-abdominal connective nerve of *Aplysia californica* in vitro. The nerve was placed in a chamber filled with *Aplysia* saline, in which both the heating cuff and the IR optical fiber were immersed to mimic an in vivo thermal condition. The resistance heating and the IR light were applied on the same segment of the nerve where the temperature increase (ΔT) at the nerve surface was measured by a 200 μm thermocouple. For each nerve, both heating modalities were applied with a range of power levels that covered a similar range of ΔT. Suction electrodes were used to electrically stimulate and record compound action potentials (CAPs) at 2 Hz with a 2 ms pulse width and 0.3 - 0.5 mA current range to ensure full recruitment of all CAP components. The rectified area under the curve (RAUC) of the CAP or its subcomponents were used to characterize the inhibition strength. The latency of different subcomponents in the CAP corresponded to the different nerve diameters and conduction velocities, which permitted the analysis of the response from different nerve subgroups (large *vs.* small). The dose-response curve of the RAUC versus ΔT for both IR and resistance heating showed a similar trend. When looking at the response on different nerve size subgroups, resistance heating showed a selective block on the small-diameter nerve fibers that was similar to IR inhibition. The results demonstrated that other heating modalities, such as resistance heating via a heating cuff, can be used as a selective neural inhibition modality. In addition, the resistance heating system's energy efficiency is high enough to allow further development of a battery-powered, implantable, selective, nerve-block device.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: Microtransponder

Title: Vagus Nerve Stimulation Paired with Upper Limb Rehabilitation After Chronic Stroke: Cross-over Results from the VNS-REHAB Pivotal Trial

Authors: *I. VORA[1], J. DAWSON[2], C. Y. LIU[3], G. FRANCISCO[4], S. L. WOLF[5], M. W. O'DELL[6], K. BELL[7], A. DIXIT[8], J. REDGRAVE[9], D. L. TURNER[10], W. FENG[11], L. DEMARK[12], D. PIERCE[13], C. N. PRUDENTE[13], B. TARVER[13], N. ENGINEER[13], T. J. KIMBERLEY[1];
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Abstract: A common outcome after chronic stroke is long term loss of arm function. Vagus Nerve Stimulation (VNS) paired with intense rehabilitation is a promising intervention that may reduce arm impairment after chronic stroke. The VNS-Rehab trial was a randomized, triple-blinded, sham controlled study. In total, 108 participants across 19 sites were implanted at the start of the study and randomized to Active-VNS (n=53; VNS group) and Sham-VNS (n=55; Control group) in conjunction with rehabilitation. During the randomized phase, participants received 6 weeks of in-clinic therapy followed by 3 months of home therapy paired with Active or Sham-VNS. After the completion of home therapy, participants in the VNS group showed a significant and clinically meaningful improvement in arm impairment (Upper Extremity Fugl-Meyer Assessment: FMA-UE $\geq$ 6 points) compared to the Control group. Participants, therapists, and assessors were unblinded at the end of the randomized phase and the Control group then crossed over to receive 6 weeks of in-clinic Active-VNS followed by a 3 month Active-VNS home exercise program. Here we report the results from the cross-over phase of the study, where 49 participants who were initially randomized to the Control group crossed over to receive Active-VNS with rehabilitation.
No adverse or serious adverse events were attributed to the Sham or Active-VNS paired with rehabilitation. FMA-UE outcomes were determined at baseline, after the Sham-VNS phase, after in-clinic Active-VNS and after the 3 month Active-VNS home exercise program. Following 3 months of home-based therapy during the Sham-VNS phase, FMA-UE score increased by 3.06 (SE 0.76) points from 35.65 to 38.71 (n=49, $p<0.0002$). FMA-UE score increased by an additional 2.82 (SE 0.46) points from 38.71 to 41.53 after in-clinic Active-VNS (n=49, $p<0.0001$), and 2.42 (SE 0.73) points from 38.71 to 41.13 after the 3-month active-VNS home exercise program (n=43, $p<0.002$). 24% of participants showed a clinically meaningful response after the control therapy which increased to 44% after receiving Active-VNS in the cross-over phase.
Participants initially receiving Sham-VNS with rehabilitation demonstrated further improvement in arm impairment after receiving Active-VNS. Moreover, an additional 20% of participants achieved a clinically meaningful improvement after completing the Active-VNS cross-over phase. In summary, VNS may be a promising novel intervention to help mitigate arm impairment after chronic stroke.

Disclosures: I. Vora: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Microtransponder. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Microtransponder. **J. Dawson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Microtransponder. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Microtransponder. **C.Y. Liu:** B. Contracted

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Poster

P988. New Methods for Manipulating Neural Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P988.10

Topic: I.08. Methods to Modulate Neural Activity

Title: Fuzzing the connectome: sampling the input space for peripheral nerve stimulation

Authors: *C. CONNOLLY[1], J. CORNWELL[3], P. D. LINCOLN[2], N. TRIANTOS[3];
[2]Computer Sci. Lab., [1]SRI Intl., Menlo Park, CA; [3]Neurome, Inc., Menlo Park, CA

Abstract: Peripheral nerve stimulation is a potentially valuable therapeutic tool. Proper selection of stimulus parameters for optimal benefit must be balanced with the need to minimize off-target effects. This problem is compounded by the size of the stimulus signal space: infinite. An analogous problem is seen in software vulnerability research. In that domain, a surprisingly simple technique—fuzzing—has found critical vulnerabilities in many different software systems, despite the magnitude of the input space. By sampling the input space, either randomly or progressively, fuzzers have accelerated the discovery of "interesting" inputs to many different software systems. Here, we suggest that parameter sampling methods borrowed from computer science and engineering can be applied to help accelerate the experimental design process. Using an inexpensive experimental apparatus, parameter surveys that employ fuzzing—randomized search of the stimulus parameter space—or chirping of the parameter space can be collected in a relatively short time span using consumer off-the-shelf equipment. By averaging multiple time-aligned recordings using the same stimulus, we can identify stimulus parameter regimes as candidates for closer and more rigorous experimental scrutiny. As with fuzzing in the software setting, these surveys are not meant to be definitive experimental results, but rather indicators of interesting ("corner") cases: regimes of frequency, power, waveform shape, and waveform sequence that can shed light on effective parameters to optimize physiological effects.We present examples of parameter surveys performed with unilateral and bilateral acoustic stimuli, using high-quality headphones, a Polar H10 ECG chest strap, and a Macbook laptop. Certain acoustic parameter regimes appear to be effective at affecting heart rate, suppressing heart rate variability, and perhaps increasing or decreasing power in the gastric smooth muscle frequency band. We caution that, as is the case in computer science, physiological fuzzing is akin to assay development, and strong conclusions cannot be drawn from these surveys alone. However, data obtained from surveys provide a relatively fast, inexpensive approach to parameter discovery for rigorous experimental design.

Disclosures: C. Connolly: None. **J. Cornwell:** None. **P.D. Lincoln:** None. **N. Triantos:** None.

Poster

P988. New Methods for Manipulating Neural Activity

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:15 AM - 10:15 AM

Program #/Poster #: P988.11

Topic: I.08. Methods to Modulate Neural Activity

Title: Getting ahead in animal welfare practices: An analysis of the longevity of head restraint implants in rhesus macaques (Macaca mulatta)

Authors: *C. J. LONG, M. S. PUJARA, E. A. MURRAY;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Nonhuman primates, including rhesus macaques, contribute to biomedical research in a variety of fields, from cellular and molecular mechanisms of infectious disease to the neural underpinnings of cognition. Research employing neurophysiological recording, pupillometry, and eye-tracking typically requires the monkey's head to be in a stable, fixed position. This can be accomplished by using cranial implants—a post mounted on the skull that allows the head to be stabilized for short durations of experimental study. However, cranial implants, like other medical devices, can fail, affecting both study objectives and the well-being of the animal. In this study, we analyzed records from 124 macaques to identify which variables, if any, decreased the longevity of the implant in the 25% of subjects that had experienced an event (where an "event" involved either the repair or removal of an implant). We developed three main hypotheses: (1) Because infections of dental implants in humans can cause an implant to fail, we predicted that, as the number of infections increased in our sample, the likelihood of an event would also increase; (2) Titanium and fiberglass implants have been shown to produce similar results regarding stability; therefore, we predicted that material type would not contribute to the likelihood of an event; (3) Lastly, literature in humans suggests that males would be more likely to experience implant failure, whereas conflicting evidence suggests that females would have more failures; therefore, we predicted that there would be sex differences in implant failures but did not have a prediction with respect to directionality of the effect. We tested the effects of infection and implant type on the probability of an event using a multivariate binomial logistic regression. Both number of infections (OR = 2.77, p = 0.007) and fiberglass implants (OR = 0.279, p = 0.012) predicted the likelihood of an event. A chi-square test indicated no significant differences between males and females in experiencing an event (df = 1, $x;^2$=0.9877, p = 0.3203). To increase the longevity of implants, we propose implementing routine implant cleaning and incorporating head caps to decrease the chance of infection. Although systematic, longitudinal follow up studies are necessary to determine causality, we believe this study is the first step in identifying ways to improve the time available for data acquisition and the well-being of our animals.

Disclosures: C.J. Long: None. **M.S. Pujara:** None. **E.A. Murray:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: the Ministry of Health-Singapore National Medical Research Council MOH-000143 (MOH-OFIRG18may-0004)

Title: Acentrosomal microtubule assembly in the primary protrusion of quiescent neural stem cells

Authors: Q. DENG[1], Y. TAN[1], L. CHEW[2], ***H. WANG**[3];
[1]Duke-NUS Med. Sch., Singapore, Singapore; [2]Temasek Life Sci. Lab., Singapore, Singapore; [3]Duke-NUS Med. Sch., Singapore, Singapore

Abstract: The ability of stem cells to switch between quiescence and proliferation is crucial for tissue homeostasis and regeneration. *Drosophila* quiescent neural stem cells (NSCs) extend a primary cellular protrusion from the cell body prior to their reactivation. However, the structure and function of this protrusion are not well established. Here, we show that in quiescent NSCs, microtubules are predominantly acentrosomal and oriented plus-end-out toward the tip of the primary protrusion. We have identified Mini Spindles (Msps)/XMAP215 as a key microtubule regulator in quiescent NSCs that governs NSC reactivation via regulating acentrosomal microtubule growth and orientation. We show that quiescent NSCs form membrane contact with the neuropil and E-cadherin, a cell adhesion molecule, localizes to these NSC-neuropil junctions. Msps and a plus-end directed motor protein Kinesin-2 promote NSC cell cycle re-entry and target E-cadherin to NSC-neuropil contact during NSC reactivation. Together, this work establishes acentrosomal microtubule organization in the primary protrusion of quiescent NSCs and the Msps-Kinesin-2 pathway that governs NSC reactivation, in part, by targeting E-cad to NSC-neuropil contact sites.

Disclosures: Q. Deng: None. **Y. Tan:** None. **L. Chew:** None. **H. Wang:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: MEXT grant
Takeda Science Foundation
Uehara Foundation
Kanazawa Univ Sakigake Project
Kanazawa Univ Chozen Project

Title: Investigation of molecular mechanisms underlying the expansion and gyrification of the cerebral cortex using ferrets

Authors: N. MATSUMOTO, S. TANAKA, T. HAMABE-HORIIKE, Y. SHINMYO, ***H. KAWASAKI**; Sch. of Med, Kanazawa Univ., Ishikawa, Japan

Abstract: The cerebral cortex has changed during evolution, and there are many differences among the cerebral cortices of various mammals. The cerebral cortex has become larger, and gyri were formed on the surface of the cerebral cortex. Although these changes in the cerebral cortex are considered to be important for the development of the brain functions, the mechanisms underlying the expansion and folding of the cerebral cortex remain unclear. Therefore, we utilized ferrets, which have relatively large and gyrencephalic cerebral cortex and established in utero electroporation techniques for ferrets in order to manipulate gene expressions in the ferret cerebral cortex. Furthermore, we found that gene knockout in the ferret cerebral cortex can be achieved by combining in utero electroporation and the CRISPR/Cas9 system. Using our techniques, here we show the role of sonic hedgehog (Shh) signaling in the development of the ferret cerebral cortex. We found that activation of Shh signaling resulted in additional

folding in the ferret cerebral cortex. Consistently, suppression of Shh signaling by expressing Hhip-DeltaC22 inhibited cortical folding. Interestingly, we found that Shh signaling was more activated in the developing cerebral cortex of ferrets than that of mice, suggesting that Shh signaling is involved in the evolution of the cerebral cortex. Our techniques for the ferret cerebral cortex should be useful for investigating the mechanisms underlying the development and evolution of the cerebral cortex.

Disclosures: N. Matsumoto: None. **S. Tanaka:** None. **T. Hamabe-Horiike:** None. **Y. Shinmyo:** None. **H. Kawasaki:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH P20GM103620-08

Title: Transcriptional regulation of neural progenitor proliferation and cortical development by the macrocephaly related gene ZBTB7A

Authors: *N. K. TIWARI[1], P. KC[1], B. L. MEYERINK[1,3], C. EVANS[2], **L.-J. PILAZ**[1,3];
[1]Pediatrics and Rare Dis., [2]Histology Core, Sanford Res., Sioux Falls, SD; [3]Basic Biomed. Sci., Univ. of South Dakota, Vermillion, SD

Abstract: The cerebral cortex regulates complex cognitive tasks through intricate networks of neurons. The number of neurons is largely controlled through proliferation and differentiation of neural progenitor cells (NPCs) in a tightly regulated process. Deviation from these normal NPC divisions can give rise to lower or higher neuronal number and eventually lead to different neurodevelopment conditions such as microcephaly, macrocephaly, and autism. Many molecular pathways are known to control the balance between proliferation and differentiation in NPCs. Epigenetic regulation by chromatin accessibility factors is critical in NPCs, the constituents and timing of these signaling events remain to be fully discovered. Here, we investigate the role of one such chromatin accessibility factor *ZBTB7A* which when deleted in 19p13.3 deletion syndrome leads to macrocephaly, intellectual disability, sleep apnea and speech delay. While the role of ZBTB7A has been studied in many cell lineages, the molecular mechanisms through which it regulates cortical development are still not known. In mouse embryonic cortices, we discovered that ZBTB7A is specifically expressed in the nucleus of cells in the germinal zone which points to a role in NPCs. ZBTB7a's known dependence on other cis-acting factors suggests its impact may depend on the TF content of the cells, thus we expected that it may differentially influence proliferation and differentiation decisions in NPCs and thus play critical role in proper cortical development. We found that *in vivo* conditional deletion of *Zbtb7a* in cortex disrupts the proliferation of NPCs with lower progenitor numbers at E13.5 and higher progenitor numbers at E15.5. This ultimately leads to altered neuron numbers in different cortical layers and increased cortical thickness postnatally. RNA sequencing in cHet and cKO at 12.5, when the cortex is mostly composed of NPs, was performed to gain insight into the transcriptomic changes that could lead to altered proliferation. This experiment

revealed that *Zbtb7a* knockdown leads to misexpression of NPC proliferation and differentiation genes, including targets of Notch signaling: *Hes1* and *Hes5*., We tested if ZBTB7A binds to Hes genes promoters to mediate their expression, and thus impact NPC proliferation. Chip-PCR and luciferase assays confirmed that ZBTB7A binds to the *Hes5* promoter to repress its expression. This suggests that *Zbtb7a* regulates proliferation of NPCs in part by repressing *Hes5*. Altogether, this study will help us understand novel transcriptional mechanisms orchestrating cortical development and how their dysregulation leads to neurodevelopmental diseases.

Disclosures: N.K. Tiwari: None. **P. Kc:** None. **B.L. Meyerink:** None. **C. Evans:** None. **L. Pilaz:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: Maryland Stem Cell Research Fund Discovery Award
NIH/NIMH Grant R24 MH114815

Title: Setd1a hypofunction associated with poor cognition impacts neurodevelopment and cell cycle regulation

Authors: *R. LEASE, R. T. OSHONE, M. CORTES-GUTIERREZ, H. SAADI, S. A. AMENT;
Inst. for Genome Sci., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Exome sequencing in large case-control cohorts has revealed that loss-of-function or hypofunction of the gene SET Domain containing 1A (*SETD1A*) is associated with cognitive impairments and up to 20-fold increased risk for schizophrenia. In mice, *Setd1a* is first required in neural stem cells during prenatal development, but effects of *SETD1A* mutations on human neurodevelopment are unknown. Here, we characterized neurodevelopmental consequences of *SETD1A* hypofunction using induced pluripotent stem cells (iPSCs) derived from carriers of a hypofunctional SETD1A missense variant associated with clinical deficits in cognition. Our findings show *SETD1A* was expressed in pluripotent cells and throughout neural induction, with ~2-fold higher expression at the neural rosette stage, modeling early radial glia-like cells in the neural tube. During neural induction, SETD1A iPSCs displayed reduced cellular proliferation with G1 pileup, deficits in neural rosette formation, abnormal patterns of embryoid body expansion and spreading, and a 3-fold decrease in neurite extensions from iPSC-derived neural progenitor cells. Several assays suggest accelerated maturation of neural progenitors, including senescent cell morphology, strong expression of β-galactosidase, and accelerated induction of gene expression signatures for late-stage progenitor populations. These results suggest a critical role for *SETD1A* in regulating cell cycle progression and proliferation during early brain development, potentially relevant to clinical deficits in cognition and risk for schizophrenia.

Disclosures: R. Lease: None. **R.T. Oshone:** None. **M. Cortes-Gutierrez:** None. **H. Saadi:** None. **S.A. Ament:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: r15hd099023

Title: Linking mitochondria to experience-dependent cell proliferation in the developing brain

Authors: *J. E. BESTMAN[1], M. FENG[2], A. RAMAKRISHNAN[2];
[1]Dept of Biol. & Neurosci. Program, [2]Neurosci. Program, William & Mary, Williamsburg, VA

Abstract: Radial glial neural progenitor cells (NPCs) are the heterogeneous proliferating stem cell population that gives rise to all cells in the brain. Early on, NPCs are largely symmetrically dividing, progenitor pool-expanding cells, but as development continues the NPCs begin to asymmetrically divide to produce neurons. Intrinsic and extrinsic cues guide this irreversible and critical fate switch. If regulated inappropriately, a premature shift to neurogenesis limits brain development and contributes to the etiology of neurodevelopmental disorders. Although proliferating cells do not rely on mitochondria for ATP, mitochondria are abundant in these cells. The diverse cellular functions of the semi-autonomous, motile mitochondria place them at the intersection of the intrinsic and extrinsic cues that guide the fate of NPCs. We use time-lapse confocal imaging to image eGFP-labelled mitochondria in the NPCs and their cellular progeny in the intact optic tectum of albino *Xenopus laevis* tadpoles. This approach preserves the surrounding neural circuitry of the developing visual system and allows us to monitor and track the NPCs over days. Quantifying the labelled mitochondria throughout the slender radial process of the NPCs revealed that the mitochondria distribution is biased toward the site of cytokinesis before NPCs undergo a symmetric cell division, suggesting that the position of the mitochondria may forecast neurogenic cell divisions. Our data show that interfering with mitochondria through the delivery of the antisense morpholino against metabolic regulator peroxisome proliferator-activated receptor Gamma co-activator 1a (PGC-1a), a transcription factor that regulates mitochondrial biogenesis, limits neurogenesis. Together our data suggest that mitochondria within NPCs contribute to their fate.

Disclosures: J.E. Bestman: None. **M. Feng:** None. **A. Ramakrishnan:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant RO3HD10176701

Title: Nmda receptor-mediated transmission is required for brain-region-specific regulation of neurogenesis

Authors: *A. J. NAPOLI, J. D. ZOODSMA, B. BIJU, O. MUCOLLARI, S. SCHUBEL, A. SAYED, L. P. WOLLMUTH, H. I. SIROTKIN;
State Univ. of New York At Stony Brook, Stony Brook, NY

Abstract: Development of normal brain cytoarchitecture is dependent upon precise spatiotemporal regulation of neural stem cells (NSC) and neural progenitor cells (NPC) to ensure that the appropriate numbers of neurons populate each brain region. NMDA receptors (NMDAR) are glutamate-gated ion channels that mediate a calcium signal. They play essential yet complex roles in early neurodevelopmental events, not all of which are fully understood. The role of NMDARs in neurogenesis is controversial. Some studies indicate that suppression of NMDAR-mediated signaling promotes neurogenesis, while other studies support the opposite view. We have created a mutant zebrafish line that lacks NMDAR-mediated signaling (*grin1* double mutants). These fish survive to 10 days post fertilization, far beyond the comparable age of rodent models, thereby providing an opportunity to examine the role of NMDARs in early brain development, including neurogenesis. To address the role of NMDAR-mediated signaling in early neurogenesis, we quantified the number of cells within specific cell populations across the entire larval brain. We find that relative to wild type fish, *grin1* double mutant fish show dysregulation of neurogenesis but that the nature of the change depends on the specific brain region: In the forebrain and anterior hindbrain there is an overpopulation of cells whereas in the midbrain of the very same animals there is a reduced population. Both phenomena are observed without any gross morphological alterations to the brain. We next assessed changes in population size and proliferative activity of NSCs (radial glial cells and neuroepithelial cells) and NPCs (neuroblasts, type3 cells) to determine where the neurogenic process becomes dysregulated. Our preliminary forebrain evidence suggests that there are changes to the type3a progenitor cell population and proliferative rates, which could imply a maturational delay in these immature neuroblasts. Our results demonstrate that, within an individual organism, NMDAR perturbation causes diametrically opposed results in different brain regions. Furthermore, these disparate results may be due to changes in neuroblast maturation and the differential trajectory of this process in distinct regions of the developing zebrafish brain. This work helps resolve conflicting prior studies and establishes a framework to elucidate the mechanisms of NMDAR regulation of neurogenesis that unify these findings.

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Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1F31ES031855-01
NIH Grant R00ES022992

Title: "Lead (Pb) poisoning impairs thyroid hormone-dependent mechanisms of brain development"

Authors: *L. DAHORA[1], A. ROBINSON[2], C. K. THOMPSON[2];
[1]Dept. of Biol. Sci., [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Lead (Pb) poisoning during early development is associated with behavioral and cogntive deficits. The specific mechanisms by which Pb impairs brain development are still not fully understood, however. One potential mechanism is that Pb poisoning may impair thyroid hormone (TH)-mediated changes in brain development. To address this issue, we performed two experiments to assess the effects of Pb poisoning on (TH)-dependent changes in cellular and molecular mechanisms in the developing *Xenopus laevis* tadpole brain. We treated stage 47 tadpoles to combinations of 1000 ppb Pb bath for seven days and added one of three different concentrations of thyroxine (T_4) for the final two days of treatment. We found that lead exposure decreased body length, including in T_4-treated tadpoles. We also performed immuno-staining for proliferative marker pH3 and found that Pb disrupts T_4-induced increase in neuronal proliferation. Finally, we used syGlass VR data visualization software to measure volume of the forebrain, midbrain, and hindbrain in 3D. We found that Pb exposure impaired T_4- mediated changes in brain volume. Last, we found that Pb poisoning reduced T_4-mediated increases of some TH-sensitive genes. These results illustrate that Pb poisoning impairs TH-dependent changes in the developing brain. Second, we have performed a series of experiments to assess Pb poisoning impairs the degree to which TH is distributed throughout the developing brain. TH is carried throughout the body via TH distributor proteins (THDPs), and transthyretin (TTR) and lipocalin-like prostaglandin D_2 synthase (L-PTGDS) are critical THDPs, primarily passing through the choroid plexus. We found that Pb-poisoning decreased expression of TTR in the liver and L-PTGDS in the brain. These changes suggest Pb may diminish the degree to which TH is distributed throughout the brain via these THDPs. Ongoing experiments are assessing the effects of knocking down TTR and L-PTGDS via morpholinos to determine if they are necessary for TH-mediated changes in brain development. Additional experiments are assessing if overexpression of TTR and/or L-PTGDS in the choroid plexus can rescue the developing brain from the harmful effects of Pb poisoning.

Disclosures: L. Dahora: None. **A. Robinson:** None. **C.K. Thompson:** None.

Poster

P003. Neurogenesis and Gliogenesis: Proliferation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P003.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Research Foundation Grant
New Generation of Academics Programme (nGAP)

Title: Adult neurogenesis and protective effect of Combretum molle methanolic leaf extract on D-galactose induced aging rat model of Sprague Dawley

Authors: *T. M. D. FASEMORE[1,2], P. NKOMOZEPI[2], E. F. MBAJIORGU[1];
[1]Sch. of Anatom. Sci., Univ. of Wiwatersrand, Johannesburg, South Africa; [2]Human Anat. and Physiol., Univ. of Johannesburg, Johannesburg, South Africa

Abstract: INTRODUCTION During normal aging, the brain suffers both morphological and functional modifications affecting circulation, metabolism, and neurotransmission. These modifications such as decrease in dendritic trees and decrease sensitivity of catecholaminergic, dopaminergic and cholinergic systems alter sensory and motor systems, sleep, memory, and learning. Chronic subcutaneous injections of D-galactose (D-gal) with doses ranging from 50mg/kg to 200mg/kg in rodents induce cognitive dysfunction and lead to neurological impairments including increased apoptosis, decreased density of synapses and reduction in the migration of the neural progenitor cells in various areas of the mammalian brain. In this study, we sought for potential beneficial effects of *Combretum molle* (*C.molle*) methanolic extract against the D-gal induced aging in the brain of male SD rats. **MATERIALS AND METHODS** Fifty rats grouped into five groups were given daily subcutaneous injections of D-galactose (150mg/kg) and 500mg/kg of *C.molle* intragastrically for a period of 90 days. After treatment the animals underwent behavioural tests such as the Open Field, Novel Object recognition and Object location to investigate effects on memory retention. Five brains in each group were cut at 50 µm thick frozen sagittal sections (1 in 6 series) for immunohistochemistry using Doublecortin (DCX), Ki-67 and Caspase antibodies. **RESULTS** Strong DCX and Ki-67 expression was present in various established neurogenic sites and in the cerebellar white matter for animals that received *C.molle* only compared to the groups that received D-gal only which had high apoptotic cells. For the combination of Dgal and C.molle group DCX and Ki-67 expression was fair. **CONCLUSION** The *C.molle* has beneficial effect in reversing or protecting against the effects of D-gal induced aging in the brain.

Disclosures: T.M.D. Fasemore: None. **P. Nkomozepi:** None. **E.F. Mbajiorgu:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Grant BISC312167
Sigma Xi G2018031596227966

Title: Microrna-124 modulates neurogenesis and mesodermal specification

Authors: *K. KONRAD[1], J. L. SONG[1], S. SUAREZ[2];
[1]Univ. of Delaware, Newark, DE; [2]Regeneron, Albany, NY

Abstract: MicroRNA-124 (miR-124) plays a conserved role in regulating parts of neurogenesis; however, its additional function in various developmental processes is less defined. We aim to elucidate the function of miR-124 in early development, using the purple sea urchin (*Strongylocentrotus purpuratus*) as a model. The sea urchin has one of the most well-documented gene regulatory networks (GRN), making it an excellent model to integrate the function of miR-124 into its GRN. To identify the

function of miR-124, we microinjected miR-124 inhibitor into newly fertilized eggs and examined specific cell and tissue phenotypes. We observed that miR-124 inhibition resulted in decreased larval swimming and gut contractions, indicating potential neuronal defects. miR-124 inhibition also led to a decrease in mature neurons and a concurrent increase in neuronal progenitor cells. We find miR-124 to directly suppress *NeuroD1*. Blocking miR-124's suppression of *NeuroD1* with a target protector morpholino (*NeuroD1* TP) resulted in embryos exhibited similar swimming and gut contraction defects as in miR-124 inhibitor injected embryos. In addition, *NeuroD1* TP injected embryos had an increase in neural progenitor markers (*SoxC* and *Brn1/2/4*). These results suggest that NeuroD1 may function to sustain neural progenitor cells. Furthermore, we observed miR-124 has a novel role in regulating the differentiation of mesodermally-derived immune cells. The sea urchin immune cells consist of blastocoelar cells (BCs) and pigment cells (PCs), which are derived from the same progenitor cells that must make a binary fate decision to differentiate into BCs or PCs. We determined that miR-124 modulates mesodermal development by temporally regulating Nodal and then Notch signaling pathways to mediate proper immune cell development. We have systematically identified the function of miR-124 in the specification, differentiation, and maturation of neurons as well as miR-124's novel role in mesodermal development.

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Poster

P005. Mechanisms of Cell Fate

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY015290-15A1
Fight for Sight

Title: Defects in neurogenesis in the retinal ciliary margin alter binocular vision

Authors: *N. SLAVI[1], M. A. LEE[1], M. LIAPIN[1], C. MASON[2];
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Abstract: In animals with frontally positioned eyes, partial decussation of retinal ganglion cell (RGC) axons at the optic chiasm in specific proportions forms the basis of stereopsis. The albino visual system is characterized by a reduction in the number of RGCs expressing Zic2, the transcription factor necessary for ipsilateral specification, and a decrease in the ipsilateral RGC projection to the brain. To uncover the developmental processes important for the establishment of ipsi- and contralateral RGC properties, and ultimately stereo vision, we examined neurogenesis and its regulation by CyclinD2 in the ciliary margin zone (CMZ), a neurogenic niche at the embryonic retina periphery that may be a specialized source of ipsilateral RGCs. We combined genetic inducible fate mapping with birthdating to determine the number and production rate of CMZ-derived $Zic2^+$ RGCs. We performed dual pulse birthdating to monitor the cell cycle progression and exit of CMZ progenitors, and its regulation by CyclinD2 in pigmented, albino,

and CyclinD2-deficient mice. We find that in the albino fewer Zic2^{+} RGCs are generated from CMZ, where there is reduced CyclinD2 expression and delayed cell cycle progression. In addition, deletion of CyclinD2 from the pigmented CMZ leads to a reduced number of progenitors reaching mitotic exit in time to express Zic2 and acquire ipsilateral RGC identity. To examine whether these aberrations in the ipsi/contra RGC output lead to impaired depth perception, we compared the performance of pigmented, albino, and CyclinD2-deficient mice in a binocularly-driven visual cliff behavioral task. Both albino and CyclinD2-deficient mice failed to reliably recognize the "cliff", indicating reduced depth perception. Our study thus links proper RGC neurogenesis with the establishment of the circuit for binocular vision.

Disclosures: N. Slavi: None. **M.A. Lee:** None. **M. Liapin:** None. **C. Mason:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF IOS-1254060
NSF IOS-2019400

Title: Regulation of neural stem cell differentiation and brain development by MGAT5-mediated N-glycosylation

Authors: *A. YALE[1], E. KIM[2], J. L. NOURSE[2], M. SALVATUS[2], R. F. HUNT[2], E. S. MONUKI[3], L. A. FLANAGAN[1];
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Abstract: Neural stem and progenitor cells (NSPCs) have the potential to treat many neurological diseases and injuries due to their ability to secrete beneficial factors and form the major cell types of the central nervous system. In the brain, undifferentiated NSPCs encounter numerous extracellular signals that bind plasma membrane proteins and impact differentiation into neurons or glia. Plasma membrane proteins are regulated by N-linked glycosylation, making it possible that glycosylation has a significant impact on cell differentiation. However, links between specific glycosylation enzymes and NSPC differentiation have not been described. Our lab found that N-glycosylation patterns correlate with NSPC fate potential *in vitro*; specifically, NSPCs expressing more highly-branched N-glycans generate more astrocytes and fewer neurons. Furthermore, increasing expression of highly-branched N-glycans on NSPCs enhanced astrocyte formation at the expense of neurogenesis. We therefore tested whether enzymes in the N-glycan branching pathway directly affect NSPC differentiation. Disruption of mannosidase enzymes early in the branching pathway altered multiple cell surface N-glycan species and did not affect NSPC differentiation into neurons and astrocytes. However, loss of a later enzyme responsible for generating the most highly-branched N-glycans, N-acetylglucosaminyltransferase V (MGAT5), led to specific changes in NSPC differentiation *in vitro* and *in vivo*. *Mgat5* homozygous null NSPCs in culture formed more neurons and fewer astrocytes compared to wild-type controls. In the brain, loss of MGAT5 caused accelerated neuronal differentiation and expression of mature neuronal markers in

the cerebral cortex. Rapid neuronal differentiation led to a depletion of cells in the NSPC niche, resulting in a decrease in the numbers of neurons formed in *Mgat5* null mice. Thus MGAT5 plays a critical and previously unrecognized role in cell differentiation and early brain development.

Disclosures: A. Yale: None. **E. Kim:** None. **J.L. Nourse:** None. **M. Salvatus:** None. **R.F. Hunt:** None. **E.S. Monuki:** None. **L.A. Flanagan:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: K01 MH109747
DP2 GM137423

Title: Progenitor cell diversity in the developing mouse neocortex

Authors: *X. RUAN, B. KANG, C. QI, W. LIN, J. WANG, X. ZHANG;
Univ. of Chicago, CHICAGO, IL

Abstract: In the mammalian neocortex, projection neuron types are sequentially generated by the same pool of neural progenitors. How neuron type specification is related to developmental timing remains unclear. Our single-cell RNA sequencing (scRNA-Seq) analysis uncovered neuroepithelial cell-enriched genes when compared to radial glia cells (RGCs). RGCs display dynamic gene expression over time. Interestingly, intermediate progenitor cell marker gene *Eomes* coexpresses temporally with known neuronal identity genes at different developmental stages. Our results delineate neural progenitor cell diversity in the developing mouse neocortex and support that neuronal identity genes are transcriptionally evident in *Eomes*-positive cells.

Disclosures: X. Ruan: None. **B. Kang:** None. **C. Qi:** None. **W. Lin:** None. **J. Wang:** None. **X. Zhang:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R01NS111220

Title: A daily cell atlas of neural differentiation across embryonic and postnatal development by single-cell mass cytometry

Authors: *E. ZUNDER;
Univ. of Virgina, Charlottesville, VA

Abstract: Precisely controlled development of the central and peripheral nervous systems is essential for organismal function and survival. To produce a comprehensive day-by-day analysis of the diversification and maturation of neural cell types, we performed single-cell mass cytometry on brain and dorsal root ganglia from C57/B6 mice at daily time points from embryonic day E11.5 to postnatal day P4. Brain tissues were microdissected into cortex, diencephalon, midbrain, and hindbrain for separate analysis. Additionally, differences between in vivo and in vitro neural differentiation were assessed by monitoring E14TG2a mouse embryonic stem cells over a 12-day embryoid body culture with retinoic acid-induced differentiation. In each of these studies, daily biological replicates were analyzed with a 40+ antibody panel optimized for either brain (25 million cells), dorsal root ganglia (3 million cells), or E14TG2a (2 million cells). The resulting protein-level molecular profiles were used to identify specific progenitor, neuronal, and glial cell types, and track how these cell types changed over the course of development. By comparing these results to previous RNA-based studies, we observed substantial discrepancies between protein and RNA cognate pairs, highlighting the importance of protein-level measurements to identify functional cell states. We also observed dynamic changes in what appear to be cell engulfment events, indicating that this approach may be useful to monitor how phagocytosis regulates nervous system development. Overall, these studies demonstrate the utility of mass cytometry as a high-throughput platform to rapidly phenotype neural tissues by protein-level single-cell molecular profiling.

Disclosures: E. Zunder: None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: EY030861-01A1

Title: Essential role for Atoh7 in the proper establishment of the retinotectal topographic map in the visual system

Authors: *I. AL DIRI[1], M. DAGHSNI[2], T. KUWAJIMA[2];
[2]Ophthalmology, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: *Atoh7* is a bHLH transcriptional factor required for retinal ganglion cell (RGC) differentiation. *Atoh7* is transiently expressed in a subset of retinal precursor cells during retinogenesis, but mechanisms that control its own expression remain not well understood. Using single cell ATAC-Seq analysis, we defined cis-regulatory elements coupled with *Atoh7* expression during mouse retinogenesis. We show that activities of the *Atoh7* enhancer landscape is associated with a cluster of cells that demarcates the

transition from retinal proliferation to differentiation. We provide evidence that Atoh7 inhibits the activity of its own enhancer elements, underscoring a potential negative autoregulatory loop that controls Atoh7 expression. We further show that deletion of an *Atoh7* distal enhancer leads to a dramatic reduction in *Atoh7* expression in the developing retina but not in the cerebellum where *Atoh7* is also expressed. While genesis of RGCs proceeds normally upon loss of *Atoh7* enhancer, transcriptome analysis revealed a dysregulation of genes important for axonogenesis. Importantly, deletion of *Atoh7* enhancer disrupts eye-specific targeting of RGC axons in the dorsal lateral geniculate nucleus (dLGN). We propose that high levels of *Atoh7* expression is specifically required for proper circuit organization of the eye-specific targeting of visual system but is dispensable for RGC formation.

Disclosures: I. Al Diri: None. **M. Daghsni:** None. **T. Kuwajima:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01 MH094589
R01 NS089777

Title: Fezf2 specifies glutamatergic projection neuron identity by functioning as a selective repressor.

Authors: *J. TSYPORIN[1], D. TASTAD[2], T. FINN[3], X. MA[4], A. NEHME[5], L. HUEBNER[1], G. LIU[6], D. GALLARDO[1], A. MAKHAMREH[1], J. ROBERTS[1], S. KATZMAN[1], N. SESTAN[7], S. K. MCCONNELL[8], Z. YANG[9], S. QIU[5], S. QIU[5], B. CHEN[10];
[2]Dept. of Molecular, Cell, and Developmental Biol., [3]Molecular, Cell, and Developmental Biol., [1]Univ. of California, Santa Cruz, Santa Cruz, CA; [4]Univ. of Arizona Col. of Med., Phoenix, AZ; [5]Univ. of Arizona Col. of Med., Phoenix, CA; [6]Frontiers Ctr. for Brain Sci., Fudan, China; [7]Yale Sch. of Med., New Haven, CT; [8]Stanford Univ., Palo Alto, CA; [9]Fudan Univ., Fudan, China; [10]Univ. of California Santa Cruz, Santa Cruz, CA

Abstract: Excitatory projection neurons in the mammalian cerebral cortex are specified by genetic programs that confer a glutamatergic identity along with subtype-specific morphology, physiology, and axonal projections. Subtype-specific transcription factors have been identified as critical regulators of the specification and generation of distinct classes of projection neurons. Exactly how these genetic programs work is unclear. In neuroblasts of the Drosophila embryonic central nervous system, temporal transcription factors are sequentially expressed that confer temporal identity. In *C. elegans*, terminal selector genes initiate and maintain the expression of effector genes that define a particular neuronal phenotype. *Fezf2* was reported to be a terminal selector gene for layer 5 subcerebral neurons, yet its ability to directly activate effector gene transcription has not been rigorously tested. To determine how FEZF2 functions, we created a fusion protein consisting of the FEZF2 DNA binding domain and the Engrailed transcription repressor domain that we termed FEZF2-EnR. By utilizing BAC transgenics to express *Fezf2-EnR* in the context of a *Fezf2* knockout mouse, we observed that *Fezf2-EnR* fully rescued

the molecular and axonal projection defects. Therefore, in the context of cell fate specification, FEZF2 functions as a repressor. Furthermore, we conditionally knocked out *Fezf2* in newly born neurons, rather than at the progenitor level, and found that the defects seen when knocking out *Fezf2* in newly born neurons were comparable to the full *Fezf2* knockout. We found that *Fezf2* is also necessary for the proper development of layer 6 corticothalamic projection neurons. Without *Fezf2*, these neurons take on the molecular characteristics of layer 5 subcerebral projection neurons. We showed that *Tle4*, a gene highly specific to corticothalamic projection neurons and necessary for proper corticothalamic neuron physiology, encodes a co-repressor of FEZF2. Indeed, in *Tle4* knockout mice, layer 6 corticothalamic projection neurons take on molecular characteristics of layer 5 subcerebral projection neurons. These findings support a novel model of deep-layer projection neuron specification wherein FEZF2 promotes the acquisition of layer 5 subcerebral identity by directly repressing layer 6 corticothalamic genes; in the context of a newly born corticothalamic projection neuron, FEZF2 and TLE4, together, promote layer 6 identity by directly repressing layer 5 subcerebral genes. Therefore, FEZF2 functions as a selective repressor in a cell-type-specific context to inhibit the acquisition of alternate cell identities.

Disclosures: J. Tsyporin: None. **B. Chen:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: EU H2020 Thyrage (n°666869)
Fondation pour la Recherche Médicale
European Thyroid Association
NeurATRIS IONESCO

Title: Thyroid hormone regulates neural stem cell fate from development to ageing

Authors: *S. REMAUD;
CNRS MNHN 7221, PARIS, France

Abstract: <The subventricular zone (SVZ) of the adult mammalian brain harbors neural stem cells (NSCs) that generate neurons and oligodendrocytes throughout life. We have previously demonstrated that thyroid hormones (THs) regulate adult NSC fate in the SVZ: THs favour NSC commitment toward a neuronal fate whereas a transient lack of THs promotes the generation of new NSC-derived oligodendroglial precursors (OPCs), capable of restoring functional nerve conduction after a demyelinating insult. We also showed that intracellular TH availability in NSC and neuronal precursors is modulated by several TH regulators (i.e., TH distributors as TTR and TH-transporters as MCT8, OATP1C1), thus modulating the neuron/glia output: SVZ-oligodendrogenesis is favoured at the expense of SVZ-neurogenesis in *Ttr* KO or *Mct8/Oatp1c1* double-knock out mice. Our main goal is now to determine the action of TH at two other key developmental stages: the early postnatal life when a peak of

circulating THs occurs around postnatal day (P) 15 and later, as a function of ageing. First, re-analysis of single-cell data from the P2 and P20 SVZ data revealed increased expression of TH transporters and TH-(in)activating deiodinases in postnatal SVZ-NSCs, promoting local TH action. Immunostainings showed a concomitant burst in SVZ-neurogenesis between P4 and P21 whereas SVZ-oligodendrogenesis remained stable. Inducing neonatal hypothyroidism reduced NSC proliferation, disrupted expression of genes implicated in NSC determination and TH signaling, and altered neuro/glia outputs in newborns. Interestingly, three-month-old adult mice recovering from developmental hypothyroidism had fewer olfactory interneurons and underperformed on short-memory odor tests, dependent on SVZ-neurogenesis, showing long-term irreversible effects of a transient developmental lack of THs. Second, as a function of ageing, we showed by immunohistochemistry that the SVZ-OPC density in increased whereas neuronal cells derived from old NSC decreased as well as the olfactory memory. Molecular analysis demonstrated that ageing impacted the intrinsic properties of NSCs, favouring a gliogenic profile at the expense of a neurogenic profile. Together, our findings show that SVZ-oligodendrogenesis is maintained throughout life whereas the generation of new neuroblasts is strongly sensitive to any changes in TH levels, thus impacting the supply of newly-formed olfactory interneurons and olfactory behavior. The stable production of new oligodendroglial cells all along development till ageing could be promoted after a demyelination injury to participate to myelin repair and neuronal survival even in older animals.>

Disclosures:

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.09

Topic: A.01. Neurogenesis and Gliogenesis

Support: Welch Grant

Title: Investigating the celltype specific roles of foxp1 in the development of human neocortex using brain organoids

Authors: *S. E. PARK, G. KONOPKA;
Univ. of Texas southwestern medical center, Dallas, TX

Abstract: The molecular mechanisms underlying human cognition remain mostly unknown. Insights into the genes and pathways important for cognition will provide entry points into understanding cognitive disorders such as autism. De novo mutations in the gene encoding the transcription factor FOXP1 lead to a syndromic form of autism characterized by intellectual disability. Studies from our lab using Foxp1 cortical conditional knockout mouse models have shown that cortical lamination is altered and autism-relevant behaviors are affected. Recent findings in the human fetal brain show that FOXP1 expression is high in progenitor cells including the cell types (e.g. basal radial glia and basal intermediate progenitors) that are associated with human cortical expansion. Moreover, when overexpressed, human FOXP1 results in more progenitors than mouse Foxp1. Other genetic manipulation experiments have shown that knocking down Foxp1 at E13.5 affects results in cells unable to exit the intermediate progenitor stage.

Therefore, I hypothesize that FOXP1's role is important in the progenitors for proper generation of cortical projection neurons in the cortical plate. I am testing this hypothesis using stem cell-derived human cerebral organoids as model systems of early human neocortical development. My results indicate that proliferation of neural cells in the ventricular zone and sub-ventricular zone are affected with the loss of FOXP1. Excitatory neurons in the cortical plate also show signs of premature differentiation in the FOXP1 KOs. Overlap between snRNA-seq and Cut and Run chromatin profiling assay show changes in the regulation of genes involved in proliferation, differentiation and axonogenesis in a cell-type specific manner. Taken together, these data will inform our understanding of the role of FOXP1 in human brain development and how such mechanisms might be relevant to autism and human cognition.

Disclosures: S.E. Park: None. **G. Konopka:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01NS091027
OHSU Neuroscience Post-Baccalaureate Initiative

Title: Isl1 is Required for the Specification and Maturation of Starburst Amacrine Cells

Authors: *Y. C. SANTANA AGREDA[1], T. STACKHOUSE[1], P. C. KERSTEIN[2], B. SIVYER[3], K. M. WRIGHT[2];
[1]Oregon Hlth. & Sci. Univ. Neurosci. Grad. Program, Portland, OR; [2]Oregon Hlth. & Sci. Univ. Vollum Inst., Portland, OR; [3]Casey Eye Inst., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The mammalian nervous system is comprised of hundreds of distinct neuronal subtypes that wire together into functional circuits. During development, neuronal subtype differentiation is regulated by transcription factors (TF's) which control effector genes that define cell fate. TFs can regulate initial neuronal specification, the development of cell features (morphology, neurotransmitter expression, physiology) or both. The mammalian retina consists of 5 classes of retinal neurons with each type containing many subtypes. Specific transcriptional pathways that direct development for each subtype are unknown. The most diverse class of retinal neurons are amacrine cells (ACs), with ~63 distinct neuronal subtypes. Within the AC population, the TF *Isl1* is expressed in a single subtype: starburst amacrine cells (SACs). *Isl1* is also expressed in other retinal neuron classes, and pan-retinal deletion of *Isl1* results in a loss of these retinal neurons, thus confounding conclusions about *Isl1*'s role in SAC development. To examine *Isl1*'s role in SACs, we developed two approaches to selectively delete *Isl1* at distinct stages of development. The first deletes *Isl1* from AC precursors using a $Ptf1a^{Cre};Isl1^{cKO}$ mouse line, allowing us to examine its role in the initial specification of SACs. The second approach uses a $ChAT^{Cre};Isl1^{cKO}$ mouse line to delete *Isl1* after SACs are specified and migrate to their correct target area, but before the completion of dendritic growth. This approach allows us to examine how *Isl1* can regulate SAC-specific features. Preliminary data indicates that deleting *Isl1* in $Ptf1a^{Cre};Isl1^{cKO}$ results in an absence of SACs. If

deleted in *ChAT^{Cre};Isl1^{cKO}*, SACs adopt abnormal dendritic morphology and lamination. Together, these data suggests *Isl1* is required for the initial specification of SACs and the subsequent development of proper morphological maintenance. Detailing the specific roles TFs have in neuronal subtype development is crucial for understanding how morphological properties contribute to overall circuit function.

Disclosures: Y.C. Santana Agreda: None. **T. Stackhouse:** None. **P.C. Kerstein:** None. **B. Sivyer:** None. **K.M. Wright:** None.

Poster

P005. Mechanisms of Cell Fate

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH T32 GM113846
NIH T32 EY025187
NIH R21 NS117978
NIH R01 NS049357

Title: Thalamocortical axons regulate superficial layer neurogenesis and cell fate in the embryonic and neonatal sensory cortex

Authors: *T. MONKO[1], J. REBERTUS[1], J. STOLLEY[1], S. SALTON[2], Y. NAKAGAWA[1];
[1]Dept Neurosci, Univ. of Minnesota, Minneapolis, MN; [2]Fishberg Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The mammalian neocortex is composed of diverse types of neurons that are sequentially generated during embryonic development and are arranged in an orderly manner across layers. In the adult neocortex, the distribution and density of each neuronal type differ across the cortex. In primary sensory cortex—visual, somatosensory, and auditory—neurons that reside in layer 4 are targeted by axons from corresponding principal sensory nuclei of the thalamus. Synaptic activity of these thalamocortical axons are known to shape cellular organization, characteristic morphology, and patterns of gene expression of layer 4 neurons in postnatal sensory cortex. However, whether these axons influence earlier stages of development, including neurogenesis and neuronal fate specification is poorly understood. We first found that thalamocortical axons arrive in the cortex during the early period of superficial layer neurogenesis. Analysis of mutant mice lacking the majority of thalamocortical axons showed a decreased number of superficial layer neurons in primary visual and somatosensory areas, but not in motor areas, at early postnatal stages. During embryonic development, lack of thalamocortical axons decreased the number and division of radial glia and intermediate progenitor cells in a sensory area-specific manner. Cell fate analysis using pulse-labeling of progenitor cells with a thymidine analog revealed that thalamocortical axons are required for proper specification of superficial layer neurons towards layer 4. Further evidence revealed that this role of thalamocortical axons on cell fate is exerted as early as neonatal stages, demonstrating that these axons are required for the proper number of layer 4 neurons to

be generated and specified in primary sensory areas even before mature synaptic input. We found that these area-specific roles are in part played by the thalamus-derived molecule VGF. In summary, our study provides a mechanism by which afferent input to the neocortex from the thalamus complements the intrinsic program of early cortical development, allowing the sequential generation of diverse neuron types in an area-specific manner.

Disclosures: T. Monko: None. **J. Rebertus:** None. **J. Stolley:** None. **S. Salton:** None. **Y. Nakagawa:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.12

Topic: A.01. Neurogenesis and Gliogenesis

Support: Fondecyt 1191152

Title: Rcor2, from corepresor to tubulin interactor

Authors: *D. E. VERBEL-VERGARA[1], M. GONZÁLEZ[1], G. MERELLO[1], C. RIVERA[2], M. E. ANDRÉS[1];
[1]Dept. of Cell. and Mol. Biol., Pontificia Univ. Catolica de Chile, Santiago, Chile; [2]Dept. of Mol. Biol., Massachusetts Gen. Hosp., Boston, MA

Abstract: REST corepressor 2 (RCOR2) belongs to RCOR family proteins, which are mainly characterized as a repressor of neuronal gene expression in non-neuronal cells. RCOR2 is required for cell proliferation and division of embryonic stem cells, neural stem cells, and neural progenitor cells. Although RCOR2 is expressed mainly and to a great extent in neuronal tissues and has a relevant role in regulating the development of the cortex, it is unknown how it is distributed at the cellular level. The present study aimed to characterize the distribution of RCOR2 in neuronal cells and brain tissue. We identified cytoplasmic and nuclear subpopulations of RCOR2 in N2A, PC-12, HT22, and HEK293T cells using high-resolution microscopy. Neuronal cells show large granules within the nucleus and a smaller punctuated pattern in the cytoplasm, whereas kidney cells show a homogeneous small-punctuated pattern. Cells in the striatum show an RCOR2 pattern similar to that of neuronal cell lines. Recently, mass spectrometry studies have reported tubulin as an RCOR2 interactor. We performed an immunofluorescence analysis that confirmed that RCOR2 colocalizes with tubulin in N2A and HEK293 cells. Also, co-immunoprecipitation assays showed an interaction between RCOR2 and tubulin. There are two RCOR2 isoforms, but it is unknown their specific functions or cellular localization. To answer these questions, we expressed RCOR2-FLAG in different cell types. Recombinant RCOR2-FLAG isoform 1 shows a punctate pattern inside the nucleus while isoform 2 surrounds the nucleolus. Both are also localized in the cytoplasm and recapitulated the colocalization with tubulin. In conclusion, RCOR2 shows a conspicuous localization inside the nucleus, suggesting additional functional roles beyond the transcriptional corepression.

Disclosures: D.E. Verbel-Vergara: None. **M. González:** None. **G. Merello:** None. **C. Rivera:** None. **M.E. Andrés:** None.

Poster

P005. Mechanisms of Cell Fate

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Program #/Poster #: P005.13

Topic: A.01. Neurogenesis and Gliogenesis

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Brain Research Foundation Grant BRFSG-2016-04
March of Dimes Foundation Grant 5-FY15-33
Simons Foundation Autism Research Initiative Grant 402213
Simons Foundation Autism Research Initiative Grant 324586

Title: Chromatin regulation of subplate neuron identity and wiring of cortical connectivity

Authors: *D. Z. DOYLE[1,2,3], M. M. LAM[1,2], A. QALIEH[1,2], Y. QALIEH[1,2], A. SOREL[1,2], O. H. FUNK[1,2], K. Y. KWAN[1,2,3];
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Abstract: Subplate neurons orchestrate multiple developmental processes essential to cortical circuit assembly. Here, we uncover an unexpectedly selective role for chromatin remodeler *Arid1a* in subplate neurons and their circuit wiring functions. We find that pan-cortical deletion of *Arid1a*, but not sparse deletion, leads to non-cell autonomous mistargeting of callosal and thalamocortical axons reminiscent of subplate ablation. These miswiring phenotypes coincide with disruptions in subplate neuron transcriptional identity, and deficits in subplate organization, subplate-thalamocortical axon co-fasciculation ("handshake"), and extracellular matrix, revealing a necessity for *Arid1a* in distinct aspects of subplate circuit wiring functions. To empirically test *Arid1a* sufficiency in subplate, we generate a cortical plate deletion of *Arid1a* that spares subplate neurons. Subplate *Arid1a* is sufficient for subplate-thalamocortical axon co-fasciculation and extracellular matrix, and remarkably, non-cell autonomously supports callosal formation and thalamocortical axon targeting. Thus, in *Arid1a*, we identify a multifunctional regulator of subplate-dependent axon guidance mechanisms indispensable for cortical circuit wiring.

Disclosures: D.Z. Doyle: None. **M.M. Lam:** None. **A. Qalieh:** None. **Y. Qalieh:** None. **A. Sorel:** None. **O.H. Funk:** None. **K.Y. Kwan:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.14

Topic: A.05. Axon and Dendrite Development

Support: MH103339
MH109904
MH106934

Title: Neural Stem Cells Direct Axon Guidance via their Radial Fiber Scaffold

Authors: *N. KAUR, W. HAN, Z. LI, N. SESTAN;
Neurosci., Yale Univ. Sch. Med., New Haven, CT

Abstract: Neural stem cells are bipolar epithelial-like cells that reside in the ventricular and subventricular zones (VZ and SVZ) and transform into highly elongated radial glial progenitors as the central nervous system (CNS) grows. These cells are responsible for two key processes of the developing CNS. First, they directly or indirectly generate all neurons and macroglial cells. Second, they guide the migration of new-born neurons to their final destinations in the developing parenchyma using their long radial (basal) fibers, which traverse the entire wall of the CNS and form a physical palisade-like scaffold.Here, we describe a critical role for neural stem cells in axon guidance at a distance from their cell bodies. While investigating how corticospinal tract (CST) axons navigate the long distance from the cerebral cortex to the the spinal cord, we identified novel functions of the radial glia/ neural stem cells within the ventricular zone of the ventral forebrain's medial ganglionic eminence (MGE). We show that radial glial cells form an axon guidance scaffold to direct CST axons through a previously unknown choice point at the boundary between the embryonic striatum and globus pallidus (i.e., striatopallidal junction; SPJ). To our surprise, this role was dependent on a previously unknown function of RND3 (RHOE), an atypical member of the RHO GTPase superfamily that lacks GTPase activity but regulates actin cytoskeletal organization, and its binding partner, ARHGAP35 (P190A) a RHO GTPase-activating protein. RND3 and ARHGAP35 expression specifically in radial glia/ neural stem cells, but not in the growing CST axons, is essential for maintaining this radial glial scaffold. Thus, in addition to cell-autonomous roles in axonal and dendritic growth, RND3 and ARHGAP35 regulate axon pathfinding cell non-autonomously by promoting the hitherto unexplored role of the striatopallidal radial glial scaffold as a guidepost structure.

Disclosures: N. Kaur: None. **W. Han:** None. **Z. Li:** None. **N. Sestan:** None.

Poster

P005. Mechanisms of Cell Fate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P005.15

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS117978

Title: The zinc finger transcription factor SALL1 is required for normal developmental transition of microglia in mouse embryos

Authors: E. P. SCOTT, E. BREYAK, ***Y. NAKAGAWA**;
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Abstract: Microglia, resident immune cells in the CNS, play many critical roles in early neuraldevelopment ranging from neurogenesis, neuronal migration and axon growth, in addition tolater roles in synapse pruning and cell survival. Although recent single-cell RNA-sequencingstudies have found pronounced temporal and spatial diversity of developing microglia, howmicroglia diversity is generated during development is unknown. Knowledge of the underlyingmechanisms for this process is key to understanding how each subpopulation of microgliainfluences neural development. To address this question, we first characterized the expressionof CD206 as a potential marker of early-stage embryonic microglia in mouse brain sections. At E12.5, a majority of parenchymal Iba1-positive immune cells in most CNS regions that weanalyzed expressed CD206, which overlapped with a microglia-specific marker P2RY12.Between E12.5 and E13.5, there was a sudden reduction in CD206 expression, and thepercentage of CD206-positive parenchymal immune cells remained low throughoutdevelopment except in early postnatal microglia in the white matter. The period of this earlydevelopmental transition of microglia populations from CD206-positive to CD206-negativestatus coincides with the peak of many early neural developmental events in the CNS, and alsowith the onset of the zinc-finger transcription factor *Sall1*, a signature microglia gene in theadult CNS. Therefore, we tested if *Sall1* is required for this early transition of microglia status bydeleting the gene specifically in microglia. When *Sall1* was deleted in most microglia from theonset of its expression in early embryos, many *Sall1*-deficient microglia continued to expressCD206 when it is normally downregulated. In addition, the mutant microglia showed lessramified morphology compared with controls even at postnatal stages. Thus, SALL1 isintrinsically required for an early subpopulation of microglia to transition into a more maturestatus during embryonic development.

Disclosures: E.P. Scott: None. **E. Breyak:** None. **Y. Nakagawa:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.01

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Redox-dependent changes in trafficking of the neuronal glutamate transporter, EAAT3

Authors: *S. RADHAKRISHNAN, S. AMARA;
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Abstract: Glutamate transporters are essential for clearing glutamate from the extracellular space and thus limit the actions of glutamate within the brain. The neuronal glutamate transporter EAAT3 has also

been shown to transport cysteine, which serves as a rate-limiting substrate for the synthesis of neuronal glutathione, an essential regulator of oxidative stress in cells. Hence, EAAT3 can contribute to cellular redox by acting as the primary cysteine transporter in neurons. EAAT3 mutations are also involved in several neuropsychiatric disorders such as schizophrenia and obsessive-compulsive disorders. The activity of plasma membrane transporters can be altered by changes in trafficking, expression levels and recycling of the transporters. EAAT3 rapidly cycles to and from the cell surface and through intracellular compartments within a few minutes and this can be regulated through several different intracellular signaling pathways. Previous studies have demonstrated that activation of protein kinase C (PKC) can regulate EAAT3 trafficking and increase the localization of EAAT3 at the membrane surface which is potentially important for regulating neuronal cysteine intake. There is evidence of some redox-triggered mechanisms that can directly or indirectly influence signaling by altering the catalytic properties or influencing subcellular compartmentation of different PKC isoforms. This suggests a mechanism by which EAAT3 trafficking could be modulated by PKC as a response to cellular redox stress as cysteine is essential to the synthesis of the antioxidant glutathione. To study this, we monitored if oxidizing agents such as hydrogen peroxide can stimulate a redox response in the cell and lead to increased membrane localization of EAAT3. We found that application of hydrogen peroxide leads to an increase in EAAT3 membrane localization in Neuro2A cells expressing EAAT3. We used TIRF and biotinylation assays to confirm that EAAT3 localization can be altered by PKC activation and further examined whether this surface expression can be additionally modulated during redox stress. To further study the downstream effects of cysteine and N-acetyl cysteine on cytosolic and mitochondrial stress, we monitored the redox changes in the cytosol and mitochondria with live-cell imaging. This was done using genetically encoded fluorescent sensors that measure cellular redox status which were targeted to specific subcellular compartments. Using this approach, we were able to conduct live-cell imaging with spatio-temporal accuracy and delineate sub-cellular changes in redox dynamics caused by EAAT3 mediated transport of cysteine.

Disclosures: S. Radhakrishnan: None. **S. Amara:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.02

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: DGAPA-PAPIIT IA201420

Title: Stimulation of amygdalar-cortical projections induces release of glutamate and enhances synaptic communication

Authors: *A. HERNANDEZ-MATIAS, F. BERMUDEZ-RATTONI, D. OSORIO-GÓMEZ; Neurociencia Cognitiva, Inst. De Fisiologia Celular - UNAM, Mexico City, Mexico

Abstract: The basolateral nucleus of the amygdala (BLA) and the insular cortex (IC) are brain structures anatomically connected that are required for the formation and expression of conditioned aversive

responses. In this regard, the BLA and IC have a crucial role in tasks such as Conditioned Taste Aversion (CTA). However, there is also some evidence pointing at a possible modulation of the IC made by BLA. Nevertheless, more information on the functional role of the amygdalar projections that communicate to the insula in establishing aversive memories is needed. Previously, we obtained experimental evidence indicating that the induction of CTA is possible through activation and reactivation of the BLA-IC pathway at specific times; this behavioral outcome is similar to that observed in CTA protocols pairing a gustative stimulus with gastric malaise. Therefore, we aimed to investigate the neurochemical and plasticity changes by which the reactivation may generate an aversive memory. Male Wistar rats infected with channelrhodopsin-2 (ChR2) or only the EYFP reporter in BLA received a double photostimulation with blue light (473 nm) pulses at 20 Hz in the projections of amygdala that reach IC; we maintained the conditions of the behavioral experiments of reactivation, so that the stimulations lasted 10 minutes each and were separated by 30 minutes. Simultaneously, we carried out microdialysis experiments to identify changes in neurotransmitter release within IC, as well as recordings of excitatory postsynaptic potentials in independent groups of animals. The neurochemical activity monitoring in IC revealed an increase in extracellular levels of glutamate concurrent with both photostimulations and exclusively in the ChR2 group. Moreover, electrophysiological recordings of the BLA-IC projection showed that the double stimulation also leads to the induction of Long-Term Potentiation (LTP). Interestingly, LTP was not induced with two stimulations in the EYFP group nor with one stimulation in animals expressing the opsin; a similar pattern of results was previously observed in our taste avoidance experiments. Taken together, these findings suggest that stimulation of the BLA-IC pathway, a critical neural substrate for long-term aversive memory, is associated with release of glutamate and a sustained improvement in synaptic communication.

Disclosures: A. Hernandez-Matias: None. **F. Bermudez-Rattoni:** None. **D. Osorio-Gómez:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.03

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Colciencias-Código 210474455818
INS contract 672-2017

Title: Evaluation of the molecular interaction of viral E protein of ZIKA virus and the Alpha 1 and GluN2A subunits of GABA-A and NMDA receptors.

Authors: A. RENGIFO[1], O. TORRES FERNÁNDEZ[3], *Z. DUEÑAS[2], C. CASTRO[3], E. NINO[2]; [1]Doctorado en Ciencias Biomédicas, [2]Grupo de Neurofisiología Comportamental Dept. de Ciencias Fisiológicas, Facultad de Medici, Univ. Nacional de Colombia, Bogota DC, Colombia; [3]Morfología Celular, Inst. Nacional de Salud, Bogotá D.C, Colombia

Abstract: Zika virus (ZIKV) is a neurotropic flavivirus that produces malformations in the cortex and cerebellum with morphological changes associated with neuronal death or degeneration (1). It has been

reported that GABAergic neurons are vulnerable to neurotropic viruses (2) and that neuroinvasion by flavivirus requires the participation of calcium to mediate the entry and exit of the virion into the cell (3), for this reason, it is possible to consider that ionotropic NMDA-type glutamate receptors could also participate as viral targets. In this study, the molecular interaction of the Alpha 1 subunits of the GABA-A receptor and GluN2A of the NMDA receptor with the viral fusion E protein of ZIKV was evaluated using an in silico approach. Working files were obtained from the Protein Data Bank (PDB) or with structures generated from the Swiss model models of the UniProt database. Three-dimensional structures of GABA and glutamate ligands were obtained from the Pubchem database. Molecular docking between GABA-A and NMDA receptor subunits with ZIKV E protein was performed from the tertiary structures obtained from PDB using autodock vina, Haddock 2.2 and CPORT plugin software, using different models for residue interaction. In this study, high protein-protein molecular docking was found when GABA and glutamate binding sites for each evaluated subunit and asparagine residue 154 for ZIKV E protein were used as active residues. The ΔG-energy values found were -155.6±18.3 for the couplings with Alpha1 and -193±21.8 with GluN2A.The results suggest that ZIKV E-protein could be use GABA-A and NMDA receptor subunits as viral targets, with a more favorable value for NMDA subunits.This result could be attributed to the fact that flavivirus furins use calcium as a key signal for infection and perhaps their interaction with NMDA could have a significant contribution to the formation of calcifications observed in different models of ZIKV infection.

1. Tang H, Hammack C, Ogden SC, Wen Z, Qian X, Li Y, et al. Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth. Cell stem cell. 2016 Mar 4 **2. Rengifo AC, Torres-Fernández O.** Disminución del número de neuronas que expresan GABA en la corteza cerebral de ratones infectados con rabia. Biomédica. 2007;27:548-58.**3. Hoffmann HH, Schneider WM, Blomen VA, Scull MA, Hovnanian Noritaka N, Takeshi T, et al.** Diverse viruses require the calcium transporter SPCA1 for maturation and spread. Cell Host Microbe. 2017 Oct 11;22(4):460-470.e5. doi: 10.1016/j.chom.2017.09.002

Disclosures: A. Rengifo: None. **O. Torres Fernández:** None. **Z. Dueñas:** None. **C. Castro:** None. **E. Nino:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.04

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant R15DA038092
NIH Grant R15DA049260
BYU Mentoring Environment Grant

Title: Ventral tegmental area mRNA expression changes in delta-9-tetrahydrocannabinol exposed young mice

Authors: C. SMITH, I. CRESS, *J. EDWARDS;
Brigham Young Univ., Provo, UT

Abstract: The ventral tegmental area (VTA) is the reward center of the brain where synaptic plasticity is at the root of many learned behaviors, including maladaptive forms of drug dependence and addiction reinforcement. Used for recreation or for pain modulation purposes, delta-9-tetrahydrocannabinol (THC), the main psychoactive component in marijuana, alters synaptic plasticity in the VTA, and chronic use is associated with cannabis use disorder. The synaptic plasticity that we examined is long term depression (LTD) of glutamate inputs to VTA GABA cells. THC, an exogenous cannabinoid, induces LTD of these inputs via cannabinoid receptor 1 (CB1). While research shows that plasticity in the VTA changes in response to chronic THC exposure, there is little research on what happens to the transcription of genes in the VTA after exposure to THC. To understand the effects of THC in the VTA, we measured gene expression via mRNA levels in various groups of mice. We isolated mRNA from tissue punches of VTA taken from 400 μm thick brain slices. Samples then underwent reverse transcription to create a cDNA library of each. These samples were isolated from juvenile/adolescent mice (P15-32 days) that were either naive (n=8), mice chronically exposed to THC (n=8), THC seven-day withdrawal mice (n=7), or vehicle control mice (n=8). All groups included male and female subjects. We examined transcripts encoding for proteins involved in synaptic glutamate neurotransmission as well as the endocannabinoid system. These included AMPA receptor subunit 1 (GlutA1) and 2, NMDA receptor subunits 1, 2a and 2b, glutamate metabotropic receptor 5, diacylglycerol lipase-alpha (DAGLα), cannabinoid receptor 1 (CB1), Fatty Acid Amide Hydrolase and Tyrosine Hydroxylase.In mice exposed to chronic THC we identified significant increases in GlutA1 ($p<0.01$), DAGLα ($p<0.05$) and CB1 receptor transcripts ($p<0.05$). Surprisingly, after the withdrawal from THC the increase in CB1 receptors decreased to naïve levels, while the GlutA1 receptors did not ($p<0.05$). These results suggest GlutA1, CB1 and DAGLα as targets for further examination regarding the impact of THC on VTA synaptic transmission. Understanding the transcriptional changes in the VTA when exposed to THC helps further our understanding of the mechanisms behind marijuana impact at the molecular level, which may have relevance for cannabis use disorder or THC dependence development.

Disclosures: C. Smith: None. **I. Cress:** None. **J. Edwards:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.05

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: McKnight Foundation

Title: Application of a novel in silico / ex vivo pipeline to study the effects of glutamate kinetics on fast, excitatory neurotransmission

Authors: *C. CHEN, J. HENNESSEY, I. A. SAVTCHOUK;
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: <The excitatory neurotransmitter glutamate is a key signaling molecule in the brain whose dysregulation is a common feature in pathologies like dementia and drug addiction. Historically, studying

glutamate in the brain has been difficult. Because of glutamate's small diffusion radius and ultrashort timecourse in extracellular space, existing approaches to capture accurate glutamate kinetics have poor spatial and temporal resolution or use indirect measurements. Newer optical glutamate sensors (e.g. iGluSnFR) provide less biased readouts, yet still convolve the true glutamate waveform due to sensor kinetics and buffering properties. As such, computational (in silico) approaches that model molecular diffusion are attractive and have described key aspects of glutamate behavior. However, these have been limited due to lack of precise data on: 1) Extracellular membrane morphology; 2) Molecular expression profiles; and 3) Glutamate-specific kinetic interactions. Here, we exploited open-source reconstructions of 3D electron microscopy data, advances in computer hardware, and the growing body of accurate kinetic models for glutamate receptors and transporters to help resolve these limitations. To model glutamate diffusion and interaction, we used a Monte Carlo-based Mcell / Blender package that supports the use of membrane reconstructions while tracking individual molecules and their interactions. Our model consisted of EM reconstruction data of ~300 μm^3 of somatocortical space, while our glutamate interactions were modeled from previously-published kinetic schemes. The workflow consisted of using a Python-based environment to systematically set up simulations, vary parameters, launch simulations in a batch fashion, and analyze simulation readouts on glutamate's location, timecourse and interactions with transporters and receptors. Specifically, we built upon previous reports detailing the role of excitatory amino acid transporters (EAATs) in clearing glutamate from synaptic and extrasynaptic space. Our data suggests the existence of an EAAT-dependent submicron gradient with "near-field" regions closer to EAAT clusters establishing different concentrations of glutamate compared to "far-field" regions. We have also used the model to predict "true" glutamate activity in hippocampal slices based off SnFR-mediated glutamate transients recorded using two-photon imaging. Future questions include how LTP- and LTD-like stimulation patterns recruit different receptor subtypes and how patterned glutamate release from neurons (e.g., tetanic, theta-burst) and astrocytes (channel-mediated release) may skew plasticity.>

Disclosures: C. Chen: None. **J. Hennessey:** None. **I.A. Savtchouk:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.06

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: ICMR

Title: Inhibition of neuro-inflammation through glutamate signalling pathway in valproic acid induced autism spectrum disorder in rats: Neuroprotective role of Granulocyte colony-stimulating factor

Authors: *B. MEDHI, A. MISHRA, R. SINGLA, R. RAJPOOT, R. JOSHI, P. SARMA, A. SHARMA; Post Grad. Inst. of Med. Educ. and Res. (PGIMER), Chandigarh, India

Abstract: Background Granulocyte colony-stimulatingfactor(G-CSF) being a haemopoietic growth factor has been used in treatment of myelosuppression and also found to elicit anti-inflammatory and neuroprotective properties.Chronic neuro-inflammation induced anomalous glutamate receptor activation

has been identified as one of the important factor in pathogenesis of autism spectrum disorder (ASD).Thus, the current study was designed to elucidate the neuro-protective effect of G-CSF and to decipher the underlying mechanism(s) in valproic acid (VPA) induced experimental model of ASD. **Methods** Experimentally, ASDrat model was induced by single dose of VPA (600 mg/kg;i.p) on gestation day (GD) 12.5 to the pregnant female rats. After birth, pups were treated with vehicle i.e Normal saline 0.9% i.p), Risperidone (2.5 mg/kg; i.p) and G-CSF (10, 35, 70 μg/kg; i.p) from Post natal day (PND) 23 to 43. All the groups were subjected to various developmental, and behaviour tests from birth. The rats were sacrificed on PND 55 and their brain were excised and processed for biochemical (oxidative stress, inflammatory markers, BDNF), histological examination (H&E, Nissl staining), NMDA and AMPA receptor expression by immunohistochemistry and RT-PCR evaluation. **Results** In VPA-exposed rats, postnatal treatment of G-CSF rescued the social impairment and alleviated spatial memory and learning impairment in a dose dependent manner. There was increase in BDNF levels, IL-10 and reduction in IL-6,IL-1β and TNF-α levels with G-CSF treatment.The up-regulated expression of NMDA and AMPA both in the prefrontal cortex as well as hippocampus was alleviated by G-CSF thereby validating its anti-inflammatory and excito-protective properties. Additionally, G-CSF in a dose dependent manner improved oxidative stress (GSH, MDA, Catalase, SOD) and displayed neuropreservation of brain of ASD offsprings. **Conclusion** G-CSF demonstrated neuroprotection against the core symptoms of autism in the VPA induced rodent model, making it a potential candidate for treatment of ASD. The glutamate signalling (NMDA and AMPA) may be attributed as the underlying mechanism for its excitoprotective, anti-inflammatory and immunomodulatory effects.

Disclosures: B. Medhi: None. **A. Mishra:** None. **R. Singla:** None. **R. Rajpoot:** None. **R. Joshi:** None. **P. Sarma:** None. **A. Sharma:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.07

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: R15 DA044500

Title: The role of NMDA receptors subunits in the progression of inflammatory breast cancer (IBC).

Authors: *L. MENDEZ-SANTACRUZ, X. S. BITTMAN-SOTO, K. M. RODRIGUEZ-MARTIR, E. PETERSON, C. MALDONADO-VLAAR;
Univ. of Puerto Rico - Rio Piedras Campus, San Juan, Puerto Rico

Abstract: Inflammatory Breast Cancer (IBC) has a 73% incidence of metastasis to the brain as compared to other cancer types like breast, lung, and bone cancer. Previous research showed that tumor cells from different breast cancer subtypes (-HR / -HER2) and (-HR / + HER2) have a high incidence of crossing the blood-brain barrier and inducing increased expression of glutamate receptors NMDA subunits (NMDAR1 and NMDR2) in the brain. IBC is the most aggressive and rare type of breast cancer. The absence of a solid tumor is replaced by swelling, redness, and skin changes, resulting in many cases in misdiagnosis of

an infection in the invasion and migration phase; this type of cancer blocks blood and lymphatic vessels in the breast's skin, causing local inflammation and rapid metastasis. However, little is known of the role that these glutamatergic receptors have in the development and/or progression of IBC. The present work provides a new understanding of the cellular and molecular effects NMDA receptors (NMDAR) have on oncogenic phenotypes in IBC. The detection and quantification of the NMDAR were evaluated by RT-qPCR, Western blot, and immunofluorescence (IF) techniques in deferments breast cancer cell lines (MCF7, MDA-MB-231) and IBC cell lines (SUM149, and SUM190). Also, NMDAR antagonists (memantine and dizocilpine "MK-801") were used in 2D cell cultures to see the pro-oncogenic effects of migration and proliferation in cell models. Results showed a significant increase in the expression of NMDARs in IBC cell lines. In the functional cell culture assays with NMDAR antagonists, a decrease in migration and proliferation in IBC cell lines was found. These findings may be related to the high aggressiveness and the high rate of metastasis by IBC within the brain. Our results have high clinical relevance since having extensive knowledge of the role of NMDARs in IBC progression could complement therapeutic approaches for patients with IBC.

Disclosures: L. Mendez-Santacruz: None. **X.S. Bittman-Soto:** None. **K.M. Rodriguez-Martir:** None. **E. Peterson:** None. **C. Maldonado-Vlaar:** None.

Poster

P080. Glutamate

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P080.08

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Hope College Biology, Chemistry and Neuroscience Program
A. Paul and Carol Schaap

Title: Exposure to H_2O_2 leads to a change in ubiquitination status of the glutamate/cystine exchanger, System x_c-

Authors: C. BUCK[1], A. GIBSON[2], S. MACKENZIE[2], *L. CHASE[2];
[1]Hope Col., Holand, MI; [2]Hope Col., Holland, MI

Abstract: System x_c^- exchanges intracellular glutamate for extracellular cystine across the membrane of many cell types, including astrocytes. Its activity directly regulates the synthesis of the antioxidant glutathione and the extracellular concentration of glutamate in some areas of the brain. We recently demonstrated that oxidants acutely upregulate System x_c^- activity by triggering the rapid redistribution of the transporter from intracellular compartments to the cell surface. However, little is known about the mechanism by which oxidants regulate the cell surface expression of the transporter. Given that the trafficking of many transporters and ion channels are regulated by alterations in their ubiquitination status, we sought to determine if a similar mechanism may be responsible for the oxidant-induced upregulation of System xc-. Specifically, we hypothesized that H_2O_2 exposure may lead to a decrease in ubiquitination of the transporter, thus leading to an increased residence time in the cell membrane. To test this hypothesis, we used site-directed mutagenesis to determine if alteration of lysine residues with xCT

would alter cell surface expression. There are seven highly conserved lysine residues within xCT that are located on the cytoplasmic side of the membrane. These residues are located at positions 4, 37, 41, 43, 422, 472, and 473. Using a radioisotope uptake assay and cell surface biotinylation assay, we found that mutation of three of the N-terminal lysine residues to arginine (K4, K41 and K43) increased transport activity and cell surface expression, while mutation of K37 led to a significant decrease in activity and cell surface expression. Similarly, a triple mutation of the C-terminal lysine residues (KKK422,472,473RRR) also decreased activity or cell surface expression. Collectively, these results suggest that post-translational modification of lysine residues do appear to alter trafficking of System x_c^-, but the regulation is complex. In a follow up experiment, we performed an immunoprecipitation of xCT in the presence and absence of H_2O_2. Surprisingly, we observed that the H_2O_2 led to an increase in transporter mono-ubiquitination with no observable changes in poly-ubiquitination. Therefore, we are currently assessing which lysine residue is likely the site of mono-ubiquitination. Given that the K37R and the C-terminal triple mutant exhibited decreased activity, we are focusing specifically on those residues. However, our initial results suggest that xCT monoubiquitination is associated with an increase in cell surface expression following oxidant exposure.

Disclosures: C. Buck: None. **A. Gibson:** None. **S. Mackenzie:** None. **L. Chase:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.01

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant 1F30MH126548
NIH Grant 1R01MH123748

Title: Sub-sedative allopregnanolone effects on cortical EEG in mice

Authors: *P. M. LAMBERT[1], N. RENSING[2], R. NI[1], S. SALVATORE[1], A. BENZ[1], M. WONG[2], C. ZORUMSKI[1], S. MENNERICK[1];
[1]Psychiatry, [2]Neurol., Washington Univ. In St Louis, Saint Louis, MO

Abstract: Depression is one of the most common mental health disorders. Pharmacologic treatment for depression has relied on monoamine reuptake inhibitors, which have significant drawbacks. Recently the FDA approved Brexanolone, a formulation of the endogenous neurosteroid allopregnanolone (AlloP), as a novel rapid-acting treatment for postpartum depression. The antidepressant effects of AlloP occur at relatively low sub-sedative doses, but the sedative effects of AlloP are an important safety concern for its use as an antidepressant therapy. Unlike monoamine treatments, AlloP is a positive allosteric modulator (PAM) of $GABA_A$ receptors. While there is a rich literature on how AlloP affects neural physiology at the level of $GABA_A$Rs and single neurons, our understanding of how these cellular changes converge to affect network activity such as neural oscillations is lagging. This information can aid in the continued development of safer, more effective therapies. We characterized the acute effects of sub-sedative doses of AlloP in mice on network-wide neural activity recorded with cortical EEG, including comparisons to

pentobarbital and diazepam, $GABA_AR$ PAMs that lack antidepressant effects clinically, and to ketamine, another rapid-acting antidepressant. Five adult mice of both sexes were assigned to each drug treatment, and a control vehicle injection was delivered prior to administration of a sub-sedative dose of the assigned drug. Sub-sedative doses of drugs were selected based on pilot experiments. Acute network effects of AlloP (5 mg/kg) were evident with rapid onset and persisted for thirty minutes. These effects included a decrease in the peak frequency of the theta rhythm in the parietal electrodes and a broad increase in power spectral density between 15-60 Hz in all cortical electrodes. EEG responses in animals treated with pentobarbital (15 mg/kg) or diazepam (1 mg/kg) shared many similarities to the effects of AlloP, including a slowing of theta rhythms, and a mid-frequency power increase. Ketamine (10 mg/kg) mainly showed a reduction in mid-frequency spectral power and an increase in power in faster gamma range frequencies (>40 Hz). Additionally, the three $GABA_AR$ PAMs shift theta-gamma phase-amplitude coupling in the parietal EEG to the slower theta rhythm peak and lower gamma frequencies, and the strength of the modulation decreases significantly, whereas ketamine led to a strengthening of modulatory coupling between the same frequencies observed prior to drug treatment. Overall, the results suggest that in the baseline state, little differentiates allopregnanolone from other $GABA_A$ PAMs to mark its selective antidepressant effects.

Disclosures: P.M. Lambert: None. **N. Rensing:** None. **R. Ni:** None. **S. Salvatore:** None. **A. Benz:** None. **M. Wong:** None. **C. Zorumski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. F. Consulting Fees (e.g., advisory boards); Sage Therapeutics. **S. Mennerick:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.02

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH RO1-MH115900

Title: Preventing adolescent synaptic pruning in female mouse prelimbic cortex via local knockdown of $\alpha_4\beta\delta$ $GABA_A$ receptors generates anxiety in adulthood.

Authors: *M. R. EVRARD, M. E. LI, S. SMITH;
Physiol. and Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: Anxiety is increasingly reported, especially in adolescent females. The etiology is largely unknown, which limits effective treatment. Layer 5 prelimbic cortex (L5PL) generates anxiety but undergoes extensive adolescent synaptic pruning, raising the question of the impact of pruning on anxiety. Here we show that preventing pubertal L5PL pruning increases anxiety in response to an aversive event in adolescent and adult female mice. Spine density of Golgi-stained neurons decreased ~63% from puberty (~PND35, vaginal opening) to post-puberty (PND56, $P<0.0001$). Expression of $\alpha4\beta\delta$ $GABA_A$ receptors (GABARs) transiently increased 10-fold in L5PL at puberty (<0.00001), but decreased post-pubertally. Both global and local knockdown of these receptors during puberty prevented pruning, increasing spine

density post-pubertally (P<0.0001), an effect reversed by blocking NMDA receptors (NMDARs). Pubertal expression of the NMDAR-dependent spine protein kalirin7 decreased (50%, P<0.0001), an effect prevented by α4 knock-out, suggesting that α4βδ-induced reductions in kalirin7 underlie pruning. Increased spine density due to local α4 knockdown at puberty decreased open arm time on the elevated plus maze post-pubertally (62%, P<0.0001) in response to an aversive stimulus, suggesting that increases in L5PL synapses trigger anxiety. These findings suggest that prelimbic synaptic pruning is necessary to limit anxiety in adulthood and may suggest novel therapies.

Disclosures: M.R. Evrard: None. **M.E. Li:** None. **S. Smith:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.03

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH-R01-MH100561

Title: Sex differences in α4βδ $GABA_A$receptor mediated motor behavior flexibility correlated with selective pruning of mushroom spines in adolescent mice

Authors: *M. TEKIN[1], S. S. SMITH[2];
[1]Dept Physiol Pharmacol MS31, S.U.N.Y. Downstate Med. Ctr., BROOKLYN, NY; [2]Dept Physiol Pharmacol MS31, SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: Adolescent synaptic pruning is critical for proper neurodevelopment and we have shown this is mediated by α4βδ $GABA_A$ receptors (GABAAR) in the motor cortex. These receptors have high expression in the ventrolateral (VL) thalamic relay nuclei which projects to the primary motor cortex, but synaptic pruning has not been assessed in this area. Thus, for this study, we assessed synaptic pruning in adolescence in the thalamic relay nuclei. To this end, spine density/types were assessed in Golgi-stained brain slices from z-stack projection (0.3 μm) photomicrographs taken with a Nikon DS-U3 camera mounted on a Nikon Eclipse Ci-L microscope using a 100x oil objective. Spine density across the dendrites of multi-polar excitatory neurons in the VL relay nucleus of the thalamus (proximal and distal segments) was compared using pubertal and post-pubertal female mice (~P35, vs. P56). In the multi-polar excitatory neurons of the VL relay nucleus of the thalamus, no general synaptic pruning was observed (P35=0.348 ±0.022 spines per 10 μm, P56=0.404±0.022, P>0.05), but there was selective mushroom spine pruning in the distal region (P35=0.098±0.012 spines per 10 μm, P56=0.064 ±0.0091, P<0.05). We additionally explored whether there were sex differences in motor behavioral flexibility since we have previously shown that hippocampal adolescent mushroom spine pruning is needed for spatial learning flexibility. To this end, we performed a rotarod test with four groups of post-pubertal mice: male wildtype, female wildtype, female α4 knockouts, and male α4 knockouts. During this test, the mice were first trained at 4 RPM for 4 trials. Then to test behavior flexibility we trained them the next day at an accelerated speed of 4 to 40 RPM over 5 minutes for 4 trials. Only female wildtype mice showed improvement (T1 = 87±12 seconds, T4=138±9 seconds, P<0.05). These results suggest that sex

differences in the pruning of mushroom spines in VL thalamus are associated with improved behavioral flexibility on a motor task post-pubertally, an effect prevented by knock-out of α4βδ GABAARs.

Disclosures: M. Tekin: None. **S.S. Smith:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.04

Topic: B.02. Ligand-Gated Ion Channels

Title: Distinct functional alterations and therapeutic options of two pathological de novo variants of the T292 residue of GABRA1 identified in children with epileptic encephalopathy and neurodevelopmental disorders

Authors: *W. CHEN[1], Y. GE[1], J. LV[1], J. MELO[2], R. JUNEJA[2], L. LIU[1], Y. WANG[1];
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Abstract: The $GABA_A$ receptor ($GABA_AR$) is a chloride (Cl^-) channel receptor and the primary mediator of neuronal inhibition, and thereby plays critical roles in controlling excitation-inhibition balance in the mammalian brain. Mutations of $GABA_AR$ have reportedly led to epileptic encephalopathy and neurodevelopmental disorders. In our experiments, we first identified a novel *de novo* T292S (C875G) missense variant from a pediatric patient with developmental delay. This mutation coincidentally occurs at the same residue as that of the previously reported variant T292I (C875T) identified from a pediatric patient with epilepsy. The distinct phenotypes associated with these two patients promoted us to compare the functional alterations of the two mutant receptors and search for suitable therapeutics. To achieve our objectives, we used biochemical techniques, whole-cell patch-clamp recordings, and pharmacological characterizations in HEK293 cells overexpressing the wild-type and mutated human recombinant $GABA_ARs$ containing α1/β2/γ2 subunits. We found that the $\alpha1_{T292S}$ variant significantly increased GABA-evoked whole-cell currents, shifting the dose-responsive curve to the left with an unchanged maximal response. In marked contrast, the $\alpha1_{T292I}$ variant significantly reduced GABA-evoked currents, shifting the dose-responsive curve to the right with a severely diminished maximal response. Neither mutation affected $GABA_AR$ expression in the cell and on the plasma membrane, suggesting the functional alterations are resulted from the changes in channel gating properties. Indeed, $\alpha1_{T292S}$ variant increased and $\alpha1_{T292I}$ variant decreased single-channel open time and open probability. After screening several $GABA_AR$-targeted therapeutics, we found that $GABA_AR$ allosteric inhibitor thiocolchicoside removed the gain of function due to T292S mutation by restoring the mutant receptor's GABA agonist sensitivity. On the other hand, a combination of $GABA_AR$ positive allosteric modulator diazepam and a calcium channel blocker verapamil, which was recently shown to rescue the functional loss caused by several other *de novo* GABRA1 mutations, rescued the loss of function due to T292I mutation. In conclusion, the bidirectional change in receptor function caused by these two *de novo* mutations suggests that $\alpha1_{T292}$ is a critical residue for controlling $GABA_AR$ channel gating. Moreover, we provided differential therapeutic suggestions for managing these two patients, highlighting the importance of precision medicine for pediatric channelopathies.

Disclosures: W. Chen: None. **Y. Ge:** None. **J. Lv:** None. **J. Melo:** None. **R. Juneja:** None. **L. Liu:** None. **Y. Wang:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.05

Topic: B.02. Ligand-Gated Ion Channels

Support: NINDS Grant NS108378

Title: Lmtk3 deficiency alters steady-state $gaba_a$ receptor-mediated cl^- currents via kcc2 in dentate granule cells

Authors: *N. CHO[1], G. KONTOU[2], J. L. SMALLEY[2], G. GIAMAS[3], P. A. DAVIES[2], S. J. MOSS[2]; [1]Neurosci. Program, Tufts Univ. Grad. Sch. of Biomed. Sci., Boston, MA; [2]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [3]Univ. of Sussex, Falmer, Brighton, United Kingdom

Abstract: In the adult mammalian CNS, fast hyperpolarizing postsynaptic inhibition is mediated by $GABA_A$ receptors. Deficits in GABAergic inhibitory transmission is implicated in the pathophysiology of epilepsy, anxiety, mood disorders, schizophrenia, and autism spectrum disorders. The establishment and maintenance of proper hyperpolarizing GABA signaling is dependent on the expression and activity of KCC2, a neuron-specific K^+/Cl^- cotransporter. KCC2 membrane transport and activity can be modulated via the phosphorylation of individual serine and threonine residues within the intracellular C-terminus. Using affinity purification coupled to LC-MS/MS, our lab has previously identified numerous proteins that comprise the KCC2 proteome on the mouse plasma membrane. Lemur tyrosine kinase 3 (LMTK3), a brain specific transmembrane serine/threonine-protein kinase, was highly enriched within KCC2-containing complexes (Smalley et al., 2020). Given the consequences of KCC2 dysfunction, it is of great interest to identify targets that can modulate KCC2 levels and transporter activity. Our current study focuses on evaluating the role of LMTK3 in regulating KCC2-mediated GABA signaling. Using biochemical experiments, immunocytochemistry, and immunohistochemistry, we have characterized the interaction between KCC2 and LMTK3 in the brain. To investigate the functional impact of LMTK3 and KCC2 in dentate granule neurons, we have utilized a whole-cell patch-clamp Cl^- loading electrophysiological assay to measure the reversal potential of $GABA_AR$-mediated currents (E_{GABA}) that reports KCC2 activity and Cl^- extrusion capacity under specific chloride loads. Our observations show a significant hyperpolarizing shift of E_{GABA} in dentate granule cells of 8-week-old $LMTK3^{-/-}$ mice. Our findings suggest that LMTK3 is a novel kinase regulator of inhibitory neurotransmission and we hope further investigation of the phosphorylation balance among key players that mediate GABAergic inhibition will provide a better understanding of how these are able to be modulated and used for novel therapies.

Disclosures: N. Cho: None. **G. Kontou:** None. **J.L. Smalley:** None. **G. Giamas:** None. **P.A. Davies:** None. **S.J. Moss:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

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Program #/Poster #: P104.06

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01MH114908
T32 GM133332

Title: Benzodiazepine tolerance induced by prolonged treatment is characterized by GABAergic synaptic plasticity

Authors: *C. CHAPMAN[1], J. M. LORENZ-GUERTIN[1], S. DAS[1], N. POVYESHEVA[2], A. COYNE[3], J. LOMBARDI[3], J. PABLO[3], T. JACOB[1];
[1]Pharmacol. and Chem. Biol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Dept. of Neurosci., [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Benzodiazepines (BZDs), such as Valium or Xanax, are commonly prescribed drugs for seizure, anxiety and pain control. They act as positive allosteric modulators at GABA type A receptors ($GABA_AR$s), which mediate the majority of fast inhibitory neurotransmission in the central nervous system. This results in the sedative, anxiolytic, anticonvulsant, and myorelaxant effects of BZDs. Despite the therapeutic efficacy of BZDs, their clinical use is limited by tolerance, dependence, and cognitive impairment. Our lab is studying the BZD-induced GABAergic neuroadaptations involved in tolerance. $GABA_AR$ inhibitory synaptic strength is determined by the abundance and type of $GABA_AR$s, which is regulated through dynamic trafficking mechanisms, regulatory proteins, and post-translational modifications. We previously showed 24-hour treatment with the BZD diazepam (DZP) increases phosphorylation and destabilization of the inhibitory postsynaptic scaffolding protein gephyrin, decreasing synaptic retention of receptors and enhancing lysosomal-mediated degradation of the $GABA_AR$ γ2 subunit, which is required for BZD binding. We are further investigating GABAergic synaptic plasticity *in vitro* and *in vivo* under conditions of prolonged DZP treatment. Prior data from our 7-day DZP tolerance model found that mice treated with DZP vs vehicle have synaptic alterations in $GABA_AR$ subunit composition and significantly reduced sensitivity to DZP. Ongoing *in vivo* co-immunoprecipitation and *in vitro* FRET experiments are further evaluating $GABA_AR$ subtype changes during BZD treatment. Phosphorylation of the $GABA_AR$ γ2 subunit at serine 327 has been implicated in reduced BZD sensitivity, while an additional phosphorylation site serine 343 remains largely uncharacterized. We have developed single and double $\gamma2^{S327A}$ and $\gamma2^{S343A}$ mutants to elucidate the role of each site in BZD tolerance through surface biotinylation, immunofluorescence, and electrophysiological experiments in primary neurons subjected to 7-day vehicle or DZP treatment. Finally, we are investigating the mechanisms by which Shisa7, a novel $GABA_AR$ auxiliary subunit that increases DZP potentiation, regulates $GABA_AR$ trafficking and how this is modified with DZP treatment. By uncovering DZP-induced GABAergic neuroadaptations that define tolerance we will provide a foundation for approaches to promote the development of safer prescription drugs without long-term risks to patients.

Disclosures: C. Chapman: None. **J.M. Lorenz-Guertin:** None. **S. Das:** None. **N. Povyesheva:** None. **A. Coyne:** None. **J. Lombardi:** None. **J. Pablo:** None. **T. Jacob:** None.

Poster

P104. Ionotropic GABA Receptors and Glycine Receptors II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P104.07

Topic: B.02. Ligand-Gated Ion Channels

Support: Crozer Health Department of Psychiatry

Title: Physiologically-based pharmacokinetic and pharmacodynamic modeling of lorazepam: predicted brain concentrations with implications for neuronal excitability

Authors: *P. BURKAT;
Psychiatry, Crozer Hlth., Upland, PA

Abstract: **Introduction:** Lorazepam belongs to the benzodiazepine class of pharmacological compounds that have amnestic, anticonvulsant, anxiolytic, hypnotic, myorelaxant, and sedative properties. Benzodiazepines modulate gamma-aminobutyric acid type A ($GABA_A$) receptors in the brain, leading to enhanced inhibition and reduced neuronal excitability. The aims of this study were to i) develop a physiologically-based pharmacokinetic (PBPK) model of lorazepam, ii) predict interstitial unbound brain concentrations of lorazepam over a range of intravenous doses, iii) determine the concentration effects on GABAergic function and neuronal excitability, and iv) correlate the findings to sedation and impaired recall in individuals. **Methods:** The PBPK model was developed with PK-Sim® modeling software (version 9.0, www.open-systems-pharmacology.org). Data from the scientific literature was digitized with WebPlotDigitizer (version 2.0, https://automeris.io/WebPlotDigitizer) for analysis and model development. Sensitivity analysis was performed on all input parameters prior to parameter identification for optimization. Model parameters were optimized using a Monte Carlo algorithm while simultaneously fitting average parent-metabolite plasma concentration-time profiles from a subset of clinical studies. Interstitial unbound brain concentrations were determined after model validation. Graphing, data fitting, and calculations were accomplished with Origin 2021 (www.originlab.com) and Microsoft Excel (2013). **Results:** After single intravenous doses of lorazepam, plasma levels rise within minutes, and decline over 40-60 hours. Peak plasma levels increase linearly with dose. The PBPK model for lorazepam and the metabolite lorazepam glucuronide successfully predicts lorazepam plasma levels not used in model development. Following a 4 mg intravenous dose, peak interstitial unbound brain concentration is 172 nM and declines to 15 nM by 30 minutes. Maximum potentiation of 10 microM GABA-triggered responses from hippocampal cells in culture is 26% at 36 seconds and 13% at 30 minutes. The percentage of spinal cord neurons in culture with sustained repetitive firing at high frequency of action potentials declines to 7% at 36 seconds with 94% recovery by 30 minutes. The time-course of lorazepam brain concentrations parallels the clinical endpoints of sedation and impaired recall seen in individuals who received a 4 mg intravenous dose of lorazepam. **Conclusions:** PBPK modeling can be applied to compounds that target the central nervous system to determine pharmacodynamic effects at clinically relevant levels.

Disclosures: P. Burkat: None.

Poster

P112. Long-Term Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P112.01

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R15DA038092
NIH Grant R15DA049260
BYU

Title: The modulation of inhibitory inputs onto vta gaba neurons

Authors: *B. WU[1], T. M. NUFER[2], J. G. EDWARDS[1];
[1]Brigham Young Univ., Provo, UT; [2]Univ. of Utah, Salt lake city, UT

Abstract: The ventral tegmental area (VTA) is an essential component of the mesolimbic dopamine circuit, processing reward and motivated behaviors. VTA dopamine (DA) cells are crucial in this process as well as GAD67-expressing GABAergic inhibitory cells that regulate DA cell activity. In response to drug exposure, synaptic connections in this circuit can be altered via synaptic plasticity, a phenomenon thought to be responsible for some of the pathological development of addiction. Currently, much less is known regarding VTA GABA cell plasticity. Expanding on the work of Bocklisch et al. (2013; Science), we investigated the plasticity of inhibitory inputs to VTA GABA neurons. Using whole cell physiology in male and female GAD67/GFP mice (14 -30 PND), we observed that these VTA GABA cells not only exhibit significant long-term potentiation (LTP; n=7, $P<0.001$) as demonstrated previously, but also significant long-term depression (LTD; n=8, $P<0.001$) in response to a 5 Hz stimulus. Therefore, we focused on characterizing this novel form of plasticity. Paired pulse ratios suggest a presynaptic mechanism for both LTP and LTD. VTA DA cells also exhibit presynaptic LTP that is mediated by the nitric oxide synthase (NOS) pathway (Nugent & Kauer, 2007; Journal of Physiology), therefore we examined the involvement of the NOS pathway in the plasticity of inhibitory inputs to VTA GABA neurons and noted that neither the NO analog SNAP nor the antagonist L-NAME altered plasticity. Interestingly, the observed LTP was blocked by APV, an NMDA receptor antagonist, demonstrating its dependence on nearby glutamatergic synapses. As many forms of LTD are dependent on cannabinoid-1 receptor (CB1), we tested its potential involvement at this synapse, but determined that neither CB1 antagonism with AM251, physiologic absence in CB1 knockout mice, nor direct antagonism with WIN55 demonstrated robust modulation of the inhibitory inputs to GABA neurons. We also tested the involvement of $GABA_B$, an important presynaptic modulator, and found that application of $GABA_B$ antagonist CGP 54626 blocked LTD. As alcohol is known to modulate the GABAergic circuit and alter plasticity in the dorsal striatum, we also examined alcohol impact on inhibitory inputs to VTA GABA neurons. We determined that chronic exposure to alcohol occluded the observed LTD while leaving LTP intact. In summary, the LTD at the inhibitory synapse onto VTA GABA cells have not been reported previously. We believe such findings will help us better explain not only VTA neural circuitry, but also the neurological and molecular basis on how dependency is developed in the CNS upon alcohol administration.

Disclosures: B. Wu: None. **T.M. Nufer:** None. **J.G. Edwards:** None.

Poster

P112. Long-Term Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P112.02

Topic: B.07. Synaptic Plasticity

Support: NINDS/NIH NS075136
Klingenstein Foundation
HHMI Gilliam Fellowship
NSF GRFP
Stanford DARE Fellowship

Title: Postsynaptic synucleins regulate the release of endocannabinoids

Authors: *E. ALBARRAN[1], Y. SUN[2], Y. LIU[2], K. RAJU[3], L. CUI[5], S. WANG[4], J. SHEN[5], T. C. SUDHOF[3], J. B. DING[2];
[1]Stanford Univ. Neurosci. Phd Program, Stanford, CA; [2]Neurosurg., [3]Mol. and Cell. Physiol., [4]Ophthalmology, Stanford Univ., Stanford, CA; [5]Neurol., Harvard Med. Sch., Boston, MA

Abstract: α-Synuclein (α-Syn), whose mutations contribute to Parkinson's Disease (PD), is thought to function presynaptically as a regulator of neurotransmitter vesicular release. Here we utilized mice lacking all three isoforms of synuclein: alpha, beta, and gamma (Synuclein triple-KO, Syn-tKO) and measured basal synaptic transmission and both short and long-term plasticity in the striatum. We found that Syn-tKO results in a loss of both forms of endocannabinoid (eCB)-dependent plasticity - long-term depression (eCB-LTD) and depolarization-induced suppression of inhibition (DSI) - at synapses onto striatal spiny projection neurons (SPNs). Direct presynaptic weakening via pharmacological activation of cannabinoid CB1 receptors (CB1Rs) in Syn-tKO mice is intact, suggesting normal presynaptic CB1R function. Instead, the expression of α-Syn in postsynaptic striatal SPNs was able to fully restore eCB-dependent synaptic plasticity in Syn-tKO mice. Furthermore, we identified α-Syn membrane-interacting domains that are required for normal eCB plasticity. Finally, postsynaptic expression of A30P mutation, one of the mutations that were linked to familial PD, could not rescue eCB-dependent plasticity. Together, our study demonstrates a role for synucleins, traditionally thought to be solely presynaptic proteins, in regulating postsynaptic eCB release and synaptic plasticity in health and PD.

Disclosures: E. Albarran: None. **Y. Sun:** None. **Y. Liu:** None. **K. Raju:** None. **L. Cui:** None. **S. Wang:** None. **J. Shen:** None. **T.C. Sudhof:** None. **J.B. Ding:** None.

Poster

P112. Long-Term Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P112.03

Topic: B.07. Synaptic Plasticity

Title: Subcellular segregation of synaptic long-term depression in hippocampus CA1

Authors: *K. M. KEARY, III[1], Z. LI[2];
[1]Brown Univ. NIH Grad. Partnership Program, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Synaptic plasticity is a cellular substrate for learning and memory in the brain, with abnormalities in plasticity associated with many neurological and psychiatric disorders. Synaptic plasticity can vary in duration from seconds (short-term plasticity) to hours or days (long-term plasticity). Long-term plasticity is divided into long-term potentiation, strengthening synapses, and long-term depression (LTD), weakening synapses. The Schaffer Collateral synapse, Hippocampus CA3 to CA1, is a widely studied model long-term plasticity, including NMDAR dependent LTD. NMDAR dependent LTD is required for spatial navigation, behavioral flexibility, and social recognition in mice. Interestingly, this form of LTD is only readily inducible at the Schaffer Collateral synapse in pre-adolescent mice. This developmental shift coincides with an increased number of autophagosomes at the proximal dendrites in CA1, the termination site for the Schaffer Collaterals. Previous work from our lab has shown that inhibiting autophagy is both necessary and sufficient for long-term synaptic depression at the Schaffer Collateral synapse. Knocking out ATG5, autophagy related protein 5, can even rescue LTD inducibility in adult mouse slices. Compared to the proximal dendrites, there are fewer autophagosomes at the CA1 distal dendrites, the termination site for the direct cortical input (DCI) from medial entorhinal cortex. We hypothesized that this existing subcellular difference may allow for the persistence of NMDAR dependent LTD inducibility at the DCI synapse in adult slices. To test this, we utilized field recordings from the distal dendrites of CA1 in adult slices. Here we show that LTD is in fact inducible at the DCI synapse in adult hippocampal slices. This LTD is dependent on NMDA receptor activation, and independent of mGluR activation. Knocking out caspase-3, a protein upstream of autophagy inhibition, abolished LTD. Furthermore, pharmacologically increasing autophagy via rapamycin was able to block LTD as well. This effect was autophagy specific, as rapamycin administration in ATG5 knockout slices had no effect on LTD. Further investigations will revolve on the behavioral relevance of this form of LTD in adult animals, as well as how the existing differences between autophagy and LTD at proximal and distal dendrites affect dendritic spine refinement throughout development.

Disclosures: K.M. Keary: None. **Z. Li:** None.

Poster

P112. Long-Term Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P112.04

Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH117130
NIH Grant MH116315
NIH Grant GM099608

Title: Glycine-site Occupancy as a Determinant of Synaptic Plasticity Directionality

Authors: *E. V. BARRAGAN[1,2], J. A. GRAY[2,3];
[1]Neurosci. Grad. Group, [2]Ctr. for Neurosci., [3]Dept. of Neurol., Univ. of California, Davis, Davis, CA

Abstract: NMDA receptors (NMDARs) are arguably the most complex subfamily of ionotropic glutamate receptors and master regulators of synaptic plasticity. NMDARs are unique among receptors in that, in addition to glutamate binding, they also require binding of a co-agonist - either glycine or D-serine - to the glycine-site on the GluN1 subunit. However, the fundamental role of this co-agonist requirement remains poorly understood. Recent evidence has shown that NMDAR-mediated LTD may occur during the competitive antagonism of the co-agonist binding site, a phenomenon that has been termed non-ionotropic LTD. Interestingly, blocking the co-agonist site also results in a typically LTP-inducing stimulus to instead lead to LTD. Based on these results, we hypothesized a role for glycine-site occupancy in determining the directionality of synaptic plasticity, specifically that low glycine-site occupancy biases synaptic plasticity towards LTD. To investigate this hypothesis, we manipulated glycine-site occupancy during the induction of synaptic plasticity using pharmacological approaches and enzymatic scavenging. We show that in the third postnatal week, decreasing glycine-site occupancy results in an overall bias towards synaptic depression regardless of the synaptic plasticity induction protocol. In addition, increasing extracellular co-agonist concentration during induction results in synaptic potentiation, supporting an overall shift of the plasticity curve. These results support our hypothesis that a primary role of the NMDAR glycine-site is to influence the direction of synaptic plasticity, highlighting the glycine-site as an attractive target for treatment of the vast range of psychiatric and neurologic disorders that arise due to NMDAR dysfunction.

Disclosures: E.V. Barragan: None. **J.A. Gray:** None.

Poster

P112. Long-Term Depression

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Topic: B.07. Synaptic Plasticity

Support: NIDA Grant R15DA038092
NIDA Grant R15DA049260
BYU Mentoring Environment Grant

Title: Differential activation of CB1-dependent long-term depression in ventral tegmental area GABA neurons in adult versus adolescent mice

Authors: *I. OSTLUND, M. VON GUNTEN, J. G. EDWARDS;
Brigham Young Univ., Provo, UT

Abstract: Within the ventral tegmental area (VTA) dopamine (DA) signaling mediates reward prediction, pleasure, and motivation. DA cells are regulated by neighboring inhibitory GABA cells, which express glutamic acid decarboxylase 67 (GAD67). Using whole-cell electrophysiology in juvenile/adolescent and

adult GAD67-GFP knock-in mice we examined glutamatergic plasticity in fluorescent VTA GABA neurons. We previously determined that cannabinoid type 1 receptor (CB1) mediated a novel form of long-term depression (LTD) of GABA neurons in the VTA. This LTD could be evoked via high-frequency stimulus (HFS), was dependent on both metabotropic glutamate receptor 5 (mGluR5) and CB1, and was occluded by injections of chronic Δ9 -tetrahydrocannabinol (THC). We sought to examine the mechanism of THC-induced LTD occlusion and whether THC impact or CB1-dependent plasticity was different between adult (PD70-130) and adolescent (PD15-32) male and female rodents. First, we noted that chronic (7-10 days) THC injections occluded CB1 agonist WIN55-212,2-mediated depression, illustrating chronic THC desensitizes or removes CB1 from this synapse. Many drug-induced plasticity changes are reversible, thus we examined and noted that seven days of THC withdrawal restored LTD and WIN55-212,2-induced depression. Next, as adult animals tend to exhibit reduced drug affect when compared to adolescents we examined if LTD of VTA GABA neurons was present in adults. Surprisingly, adult mice no longer undergo HFS-induced LTD. We then examined what changed in adults to eliminate this LTD by investigating direct mGluR5 and CB1 agonist activation and discovered both still elicit depression. These data illustrate mGluR5/CB1 are still functional in adults. As adults seemed to retain the key components necessary for LTD, but resist HFS-induced LTD, we examined the quantitative nature of this plasticity by doubling the HFS protocol. We determined that HFS doubling was sufficient to induce LTD in adults which suggests the mGluR5/CB1 pathway of LTD is present but requires a greater electrical stimulus to activate. To determine if this was due to changes in AMPA and NMDA receptors, key factors in many forms of plasticity, we examined AMPA/NMDA ratios. We noted that AMPA/NMDA ratios were decreased in adults compared to adolescents, potentially due to a decrease in NMDA receptor levels which would reduce calcium influx and require greater activation to induced LTD in adults. Collectively, our data demonstrate differences in adult and adolescent CB1-mediated plasticity, which illustrates a potential rationale for the increased severity of long-term THC impact in adolescents versus adults.

Disclosures: I. Ostlund: None. **M. Von Gunten:** None. **J.G. Edwards:** None.

Poster

P112. Long-Term Depression

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Program #/Poster #: P112.06

Topic: B.07. Synaptic Plasticity

Support: NIAAA K99/R00 AA022651
NIAAA T32 AA007577

Title: Investigation of adolescent alcohol exposure interactions with stress on BNST CRF signaling across sex

Authors: *E. B. HOLMGREN, J. M. LACEY, T. A. WILLS;
Cell Biol. and Anat., LSU Hlth. Sci. Ctr. Cell Biol. & Anat., New Orleans, LA

Abstract: Adolescent alcohol exposure and stress are strong predictors of future development of alcohol use disorders. Understanding how adolescent alcohol exposure impacts plasticity in the bed nucleus of the stria terminalis (BNST) is critical as this region mediates negative affect and stress-induced drug relapse. Previous research from our lab finds that adolescent intermittent ethanol vapor exposure (AIE) mediates BNST synaptic plasticity through two distinct mechanisms depending on sex. Adolescent alcohol exposure enhances spontaneous EPSCs (sEPSCs) frequency in both sexes, in conjunction with an increase in NMDA receptor-mediated plasticity in male mice and mGluR1/5-mediated plasticity in female mice. As stress is a strong trigger for relapse, we then explored if AIE-mediated changes persist into adulthood and if stress modulates these changes. When mice with an AIE history receive one hour of restraint stress in adulthood, the adolescent phenotype of sEPSC frequency is uncovered in male but not female mice. Female mice instead have increased sEPSC amplitude, an effect not seen in male mice. Restraint stress also recapitulates sex-dependent AIE-induced changes in BNST plasticity. Corticotropin releasing factor (CRF) signaling through corticotropin-releasing factor type 1 receptors (CRFR1) is known to be critical in alcohol withdrawal, stress-induced relapse, and withdrawal-associated negative affect. Our current work investigates the influence of CRF-CRFR1 signaling on sex dependent plasticity and glutamate release in the BNST. C57Bl/6J male and female mice were exposed to two, 4-day cycles of alcohol vapor exposure (16 hr/day) with a 3-day period of rest between cycles from PND30-41. Whole-cell voltage clamp experiments were performed during acute withdrawal or in adulthood (PND 70+) following one-hour of restraint stress. Preliminary data suggests that antagonism of CRFR1 with 1μM NBI27914 can blunt enhanced frequency sEPSCs in high frequency responding cells in adolescent male but not female mice during acute withdrawal. In adulthood following restraint stress, we find CRFR1 antagonism in adult female mice specifically ameliorates enhanced DHPG-induced LTD in AIE treated mice, potentially suggesting a novel interaction of CRFR1 signaling on mGluR1/5-mediated plasticity in female mice following adolescent alcohol exposure. Future studies will further investigate the role of CRFR1 antagonism on AIE and adulthood stress-induced changes in BNST plasticity.

Disclosures: E.B. Holmgren: None. **J.M. Lacey:** None. **T.A. Wills:** None.

Poster

P112. Long-Term Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P112.07

Topic: B.07. Synaptic Plasticity

Support: Kavli NDI Postdoctoral Fellowship
NIH Grant R21-EY031265
NIH Grant R01-EY025922

Title: Mechanisms gating of a rapid disconnection of fast-spiking cell circuits in visual cortex

Authors: *D. SEVERIN, C. MORENO, L. MESIK, S. MENHTA, C. KNIGHT, H.-K. LEE, A. KIRKWOOD;
Johns Hopkins Univ., Baltimore, MD

Abstract: Disinhibition is an obligatory initial step in the remodeling of cortical circuits by sensory experience. Previous investigations on disinhibitory mechanisms in the classical model of ocular dominance plasticity uncovered an unexpected novel form of experience-dependent circuit plasticity. In layer 2/3 of the mouse visual cortex, monocular deprivation (MD) triggers a complete, “all-or-none”, elimination of connections from pyramidal cells onto nearby parvalbumin-positive interneurons (Pyr→PV). This binary form of circuit plasticity is unique as the remaining connections are not affected in strength. We aimed to examine the mechanism underlying the “all-or-none” Pyr→PV disconnection, testing some of the elements described for spike timing LTD induction in PV cells. In PV cells, α1-adrenergic receptors enable spike timing LTD independently of the induction mechanism and depending on mGluR5 receptors. Using a combination of standard slices electrophysiology method, along with optogenetics and whole-cell recordings from PV and pyramidal cells, we evaluated the modifiability of local excitatory inputs originating from layer 2/3. We found that mGluR5 is necessary for the MD-evoked Pyr→PV disconnection. Also, α1-adrenergic receptor activation, in-vivo and in slices, in conjunction with presynaptic activation, enable “all-or-none” elimination of excitatory input onto PV cells. We propose that the α1-adrenergic dependent Pyr→PV disconnection resembles the MD-evoked synapse elimination and mechanistically works according to the pull-push rule.

Disclosures: D. Severin: None. **C. Moreno:** None. **L. Mesik:** None. **S. Menhta:** None. **C. Knight:** None. **H. Lee:** None. **A. Kirkwood:** None.

Poster

P112. Long-Term Depression

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Program #/Poster #: P112.08

Topic: B.07. Synaptic Plasticity

Support: National Science Foundation CAREER Award to AMM (2047700)
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Whitehall Foundation to AMM (Grant 2017-05-35)
GSU 2CI Neurogenomics Fellowship to MAG
Kenneth W. and Georganne F. Honeycutt Fellowship to MAG
GSU Brains and Behavior Fellowship to MAG

Title: Disruption of Arc ubiquitination alters calcium-dependent intracellular signaling pathways and protein localization.

Authors: *M. A. GHANE[1], Z. D. ALLEN[1], B. DONG[2], J. YANG[2], N. FANG[2], A. M. MABB[1];
[1]Neurosci. Inst., [2]Chem., Georgia State Univ., Atlanta, GA

Abstract: Arc is an immediate-early gene that is rapidly expressed in response to learning and memory-related behaviors. Arc is rapidly degraded partly through the ubiquitin-proteosome pathway. Disruption of Arc ubiquitination by mutation of the relevant ubiquitinated lysine residues (K268/269R; ArcKR) leads to enhanced metabotropic glutamate receptor (mGluR)-mediated long-term depression (LTD), a process dependent on endoplasmic reticulum-mediated calcium release. Here, we show that aspects of

intracellular calcium signaling are disrupted in ArcKR neurons. This change is coupled to altered activity states as well as changes in co-localization of calcium-dependent molecular regulators of plasticity. Our findings contribute to our understanding of how Arc regulates a key form of plasticity and provides a potential link in how disrupting Arc ubiquitination can lead to changes in learning behaviors.

Disclosures: M.A. Ghane: None. **Z.D. Allen:** None. **B. Dong:** None. **J. Yang:** None. **N. Fang:** None. **A.M. Mabb:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P139.01

Topic: B.09. Network interactions

Support: NIH Grant K99MH121355
NIH Grant R01MH090067

Title: Characterizing distinct pyramidal cell populations in the ventral hippocampus

Authors: D. J. LODGE[1], H. B. ELAM[1], A. M. BOLEY[1], ***J. J. DONEGAN**[2];
[1]The Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX; [2]Dell Med. Sch. at UT Austin, Austin, TX

Abstract: The ventral hippocampus (vHipp) regulates a diverse set of behaviors associated with motivation and emotion. Hyperactivity in this region has been observed in schizophrenia and we have previously shown that normalizing the activity of specific vHipp projections can alleviate behavioral and physiological deficits in a neurodevelopmental disruption model. Specifically, reducing activity in the vHipp-medial prefrontal cortex (mPFC) pathway improves correlates of negative and cognitive symptoms while inhibition of the vHipp-nucleus accumbens (NAc) pathway improves correlates of positive symptoms. In the current experiments, we aimed to further characterize these distinct projection pathways. We first used retrograde viral tracing to show that vHipp-mPFC and vHipp-NAc projections are distinct and anatomically segregated cell populations. NAc projections made up approximately 43% of labeled cells while mPFC-projections accounted for ~56%. Only ~1% of cells projected to both regions. Next, RNASeq was used to characterize the transcriptional profile of these two cell populations. We identified 99 differentially regulated genes, including Nedd and Grn, involved in synaptic plasticity. RNAScope confirmed the differential expression of these two genes. We have shown previously that unique interneuron subtypes (parvalbumin (PV) or somatostatin (SST)) within the vHipp also differentially regulate behavior. Therefore, the next set of experiments aimed to determine the anatomical connectivity and functional regulation of vHipp projections by local interneuron populations. First, eGRASP was used to map the synaptic connections between pyramidal cell projections and PV or SST interneurons. We found that PV interneurons form a similar number of synaptic connections on pyramidal cells that project to both mPFC and NAc while SST-positive interneurons form far fewer synapses on mPFC projections. Electron microscopy confirmed these results. To determine if these anatomical differences result in functional changes, we used fiber photometry, *in vivo* electrophysiology, and optogenetics to show that inhibiting PV cells increased pyramidal cell acitivty regardless of projection

target while SST cell inhibition has a much smaller effect on the activity of mPFC-projecting cells. Together, these results suggest that vHipp projections are made up of discrete cell populations with unique gene expression and patterns of connectivity. Characterization of these cell populations may lead to the identification of new molecular targets for the treatment of specific symptoms of schizophrenia and other psychiatric disorders associated with vHipp dysfunction.

Disclosures: D.J. Lodge: None. **H.B. Elam:** None. **A.M. Boley:** None. **J.J. Donegan:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P139.02

Topic: B.09. Network interactions

Support: NINDS U19-NS112953

Title: Investigating cortical readout of temporal codes

Authors: *R. BLAZING[1], K. M. FRANKS[2];
[2]Neurobio., [1]Duke Univ., Durham, NC

Abstract: Many neural circuits exhibit reproducible sequences of activity that correlate with perception, action, or distinct internal states. Neural sequences lasting on the order of tens to hundreds of milliseconds have been proposed to mediate essential cognitive processes including navigation, memory encoding and retrieval, and sensory discrimination. Temporal features of sequence activity, such as the precise response timing and order of activated cells, are thought to encode perceptually or behaviorally relevant information. However, the sensitivity of downstream brain regions to the temporal structure of input sequences is not known. Moreover, while many possible mechanisms for the cortical readout of millisecond-timescale temporal codes have been identified, few have been explicitly tested in-vivo. To address these questions, we implemented a system to perform patterned optogenetic activation of olfactory bulb glomeruli while recording extracellularly from large populations of neurons in mouse piriform cortex (PCx). Odors evoke activity from spatiotemporally-specific sequences of glomeruli, and this information is propagated to downstream PCx where sparse ensembles of neurons encode odor identity. To assess how glomerular sequence timing impacts PCx output, we optogenetically activated sequences of glomeruli and varied the relative onset timing of each glomerulus in the sequence. We found that neurons in PCx exhibit tuning to specific temporal patterns that depend on the identity of activated glomeruli. We hypothesized that the dense recurrent network in PCx coordinates these temporally specific responses. We therefore eliminated recurrent circuits within PCx using tetanus toxin light chain, which blocks synaptic transmission in infected cells, but does not affect responses to feedforward input. Our preliminary experiments suggest that eliminating recurrent circuitry sharply attenuates the temporal specificity of PCx responses. Thus, operations carried out by recurrent circuits may be essential for precise sequence readout in cortical networks.

Disclosures: R. Blazing: None. **K.M. Franks:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

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Program #/Poster #: P139.03

Topic: B.09. Network interactions

Support: NIH/NNDS R01 Grant NS107599
Whitehall Foundation Grant 2017-05-71

Title: Proactive and context-dependent motor to sensory cortical feedback regulation of network excitability

Authors: *Z. ZHANG, E. ZAGHA;
UC Riverside, Riverside, CA

Abstract: Cortical feedback, the anatomical pathways from higher-order to lower-order brain regions, are believed to modulate sensory processing according to internal and behavioral context. Current studies on cortical feedback focus primarily on resolving how it shapes post-stimulus activity of lower-order regions, with the assumption that cortical feedback regulation requires a stimulus-triggered bottom-up signal. In this study, we recorded single unit activity in the mouse whisker primary somatosensory cortex (lower-order), while conducting interleaved inhibition in the whisker motor cortex (higher-order) to assess the impacts of cortical feedback under different conditions. We found that cortical feedback strongly influences spontaneous (pre-stimulus) activity. We found that cortical feedback modulates spontaneous network excitability differently under different behavioral contexts, and that these modulations of excitability can, at least in part, account for changes in post-stimulus responses. Overall, our study emphasizes the importance of cortical feedback as proactive regulators of feedforward signal processing.

Disclosures: Z. Zhang: None. **E. Zagha:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

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Program #/Poster #: P139.04

Topic: B.09. Network interactions

Support: NIH OT2-OD-023867

Title: Transcutaneous auricular vagal nerve stimulation (taVNS) parameters differentially influence neuronal activity in the nucleus of the solitary tract and spinal trigeminal nucleus

Authors: *M. OWENS[1], L. DUGAN[1], C. COOPER[1], *E. HARRIS[1], V. NAPADOW[2,3], E. BEAUMONT[1];
[1]Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [2]Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA; [3]Radiology, Logan Univ., Chesterfield, MO

Abstract: Transcutaneous auricular vagal nerve stimulation (taVNS) activates axons located in the auricular branch of the vagus nerve, which terminates at the concha of the ear. Currently, taVNS is under investigation to treat a wide range of disorders including gastric motility, cardiac, and migraine disorders. Human fMRI studies have localized taVNS response to the nucleus of the solitary tract (NTS) and spinal trigeminal nucleus (Sp5c), which also receives input from the meningeal layer of the brain, making this pathway relevant for migraines. It is hypothesized that the ability of taVNS to increase or decrease neuronal firing rates in these brain regions can act to counterbalance abnormal function that occurs in these disorders. To identify the optimal taVNS parameters for modulating neuronal activity within NTS and Sp5c, six different taVNS paradigms were administered to chloralose-anesthetized rats (n = 24). The activity of 60 to 70 neurons from rostral NTS (rNTS) and caudal NTS (cNTS) were recorded individually using a high-impedance tungsten electrode. Neuronal firing rates were analyzed for changes in activity during and immediately following stimulation as compared to their individual baseline level. Neurons were then classified as non-responders, negative responders, positive responders, or super responders. We found that the optimal stimulation parameters were dependent on NTS sub-region. Specifically, cNTS showed greater positive activation using low-frequency standard parameters regardless of intensity and bursting parameters at higher intensities. Alternatively, rNTS showed greater levels of positive activation with standard low-frequency stimulation at high intensities. The only parameters producing negative activation in NTS were high-frequency standard patterns regardless of NTS sub-region. Interestingly, NTS is also differentially activated by cervical vagal nerve stimulation (cVNS), potentially allowing for future identification of taVNS parameters that better mimic cVNS effects in chronic disease. Furthermore, it is not known if positive or negative NTS neural activation is beneficial for disease outcomes, particularly for disorders characterized by aberrant NTS activity. Studies are ongoing to contrast Sp5c activation with NTS, using these same taVNS parameters to determine optimal activation for this important trigeminal processing brainstem region. Identification of ideal stimulation parameters will be important for broader applicability of both taVNS and implanted cVNS therapy across a range of disorders.

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Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P139.05

Topic: B.09. Network interactions

Support: NSF DGE 1633516

Title: Concentration-dependent effects of volatile anesthetics on network dynamics in layer 2/3 somatosensory cortex

Authors: *J. NOUEIHED, F. R. FERNANDEZ, J. A. WHITE;
Biomed. Engin., Boston Univ., Boston, MA

Abstract: The effects of volatile anesthetics are generally well understood at the behavioral and molecular levels. However, these effects and how they result in different anesthetized states have not been well-characterized at the mesoscale level (i.e. networks of neurons). We address this gap in the field by simultaneously recording through calcium imaging, the dose-dependent changes in spontaneous activity of excitatory and inhibitory neurons in temperature-controlled animals under isoflurane-induced anesthesia.
Dual color two-photon calcium imaging was used to capture the activity of excitatory neurons and inhibitory interneurons in layer 2/3 of the mouse somatosensory cortex during the induction and emergence from different states of anesthesia (awake, partially anesthetized, and deeply anesthetized). For animal comfort and to control for any confounding effects of changes in body temperature, head-fixed mice were placed on a heated treadmill. The calcium indicator jGCaMP7f was used to track neuronal activity, along with a static fluorophore (tdTomato) to identify specific sub-populations of inhibitory neurons (glutamate decarboxylase (GAD2+), parvalbumin (PV+), or somatostatin (SST+)) in adult mice. In post-hoc analysis, hundreds of cells in layer 2/3 were identified and tracked in multiple sessions by extending the approach used in existing calcium image analysis pipelines to account for long, discontinuous recording sessions with computational efficiency.
Consistent with previous studies, we observed a suppression of activity across all neuron types during the induction into deep states of anesthesia, with activity gradually restored during emergence. We also established the correlation between neurons as a function of anesthesia depth, distance between neurons, and type of neurons. We observed an increase in the pairwise cross-correlation between excitatory neurons as depth of anesthesia increases, and a corresponding decorrelation during the emergence out of anesthesia. Preliminary evidence indicates that inhibitory neurons are more sensitive to isoflurane than excitatory neurons.

Disclosures: J. Noueihed: None. **F.R. Fernandez:** None. **J.A. White:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

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Program #/Poster #: P139.06

Topic: B.09. Network interactions

Support: NIH T32 EB006359
NSF DGE-1633516

Title: Principal Component Analysis for Neuronal Network Analysis Under Isoflurane Sedation in Mice

Authors: *D. CARBONERO, J. NOUEIHED, J. A. WHITE;
Biomed. Engin., Boston Univ., Boston, MA

Abstract: Anesthetics are essential to modern medicine, allowing painless performance of medical procedures that would otherwise be unbearable. Characterization of the mechanisms of anesthesia has focused principally on either receptor-level biophysics or gross, cortical (e.g. field potential) activity levels. The impact on regional network activity at the cellular level remains poorly understood, for two reasons. First, it has until recently been very challenging to collect local-network data with cellular resolution. This has been largely solved by the development of in vivo imaging of calcium transients from identified call types. Second, data sets from such experiments are immense and challenging to interpret. Here, we explore using principal component analysis (PCA) to make such data sets manageable and understandable. PCA and related techniques produce a low-dimensional representation of high-dimensional data while maintaining innate variation necessary for feature extraction. Harnessing PCA to extract, highlight, and analyze latent features of anesthetized neuronal networks can give insight regarding how populations of neuron work as an ensemble to determine an animal's behavioral state. To measure behaviorally salient activity in local cortical networks, we used 2-photon microscopy to image calcium activity of identified neocortical neurons from mice expressing the calcium indicator jGCaMP7f. Layer 2/3 somatosensory cortex was imaged under varying concentrations of anesthesia (0%, 0.7%, and 1.4% isoflurane by volume). Recorded activity was processed to extract neuronal spatial footprints and traces of calcium activity from individual neurons. Recordings from the three states of anesthesia were then stitched together to create one cohesive time series. A PCA model was fit using this extended stitched recording, and the data were reduced to a lower number of dimensions. The PCA model was then used to detect hidden structures of activity in the network under the different levels of anesthesia. Analyzing the activity in the lower dimensional space, activity progressively collapses, becoming more consistent, and distinctly different network behaviors arise as a function of progressively deeper anesthesia. PCA of the data, therefore, suggests a complex structure of activity, with several highly active subnetworks competing to drive the majority of activity during awake conditions. However, while under increasing sedation, the data suggest a shift to a network that is driven by a set of formerly dormant, more cohesive networks.

Disclosures: D. Carbonero: None. **J. Noueihed:** None. **J.A. White:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P139.07

Topic: B.09. Network interactions

Support: DBT BT/PR12255/MED/122/8/2016
NCBS-TIFR
DBT-NaMoR, INDIA

Title: Circuit and synaptic mechanisms of E-I balance and cell firing as a function of repeated pulses of spatially patterned input

Authors: *A. ASOPA, U. S. BHALLA;
Natl. Ctr. for Biol. Sci., Bengaluru, India

Abstract: Hippocampal CA3-CA1 circuit represents multiple modalities including time, space, and orientation. One feature of this network is its tight and precise balance of inputs between excitation and inhibition (E-I) at CA1 (Bhatia et al 2019). When excitation at CA1 is increased by activating more CA3 cells, the inhibitory inputs also increase proportionately, thus balancing the depolarization. But for CA1 cells to represent information, they must cross the threshold and fire. We study how the precise and tight E-I balance in CA1 pyramidal neurons evolves with changing firing rates in CA3 layer cells, resulting in action potentials.
We performed in vitro whole cell patch clamp recordings from CA1 cells in acute mouse hippocampal sections (male and female, 2-3 months of age). We simultaneously stimulated Channelrhodopsin (ChR2) expressing CA3 pyramidal cells with 13um x 8um spots using a sub-cellular-resolution patterned projection (Mightex Polygon 400). We created 5-spot and 15-spot patterns from a set of 45 spots. These patterns were used to stimulate CA3 cells at multiple frequencies (8 pulses at 20, 30, 40, 50, and 100Hz). Current clamp recordings were made to record suprathreshold responses and voltage clamp recordings were made to record E and I synaptic conductances resulting from these stimuli. Responses to single spots that form the patterns were also recorded to determine the expected subthreshold responses. Gabazine was used for no-inhibition control.
We measured the responses of CA1 cells to these stimuli in CA3 to find which conditions induce spiking and corresponding E-I dynamics. We find that spiking in CA1 is modulated by tight E-I balance, degree of convergence of inputs at interneurons and CA1 cells, and short-term plasticity of E and I synaptic inputs. The combined effect of these factors can allow repeating CA3 activity at certain frequencies to stimulate CA1 cells out of E-I balance, resulting in spikes. We found that the subthreshold responses build up over successive repetitions till about the fourth pulse, and then fall. Spikes occur in earlier pulses for stronger stimuli (15 spots vs 5). Moreover, lower frequency stimuli (20-30 Hz) are more likely to induce spiking in CA1 neurons.
To further understand the role of these parameters we developed a model of CA1 cell activity from the E-I currents obtained from voltage clamp recordings along different stimulation dimensions: stimulating frequency, and pattern size.
We propose that these E-I dynamics resulting in activity gating may be relevant to understand the formation and representation of place and time cell sequences and have implications for understanding diseases that arise from E-I imbalance.

Disclosures: A. Asopa: None. **U.S. Bhalla:** None.

Poster

P139. Network Interactions: In Vivo and In Vitro

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P139.08

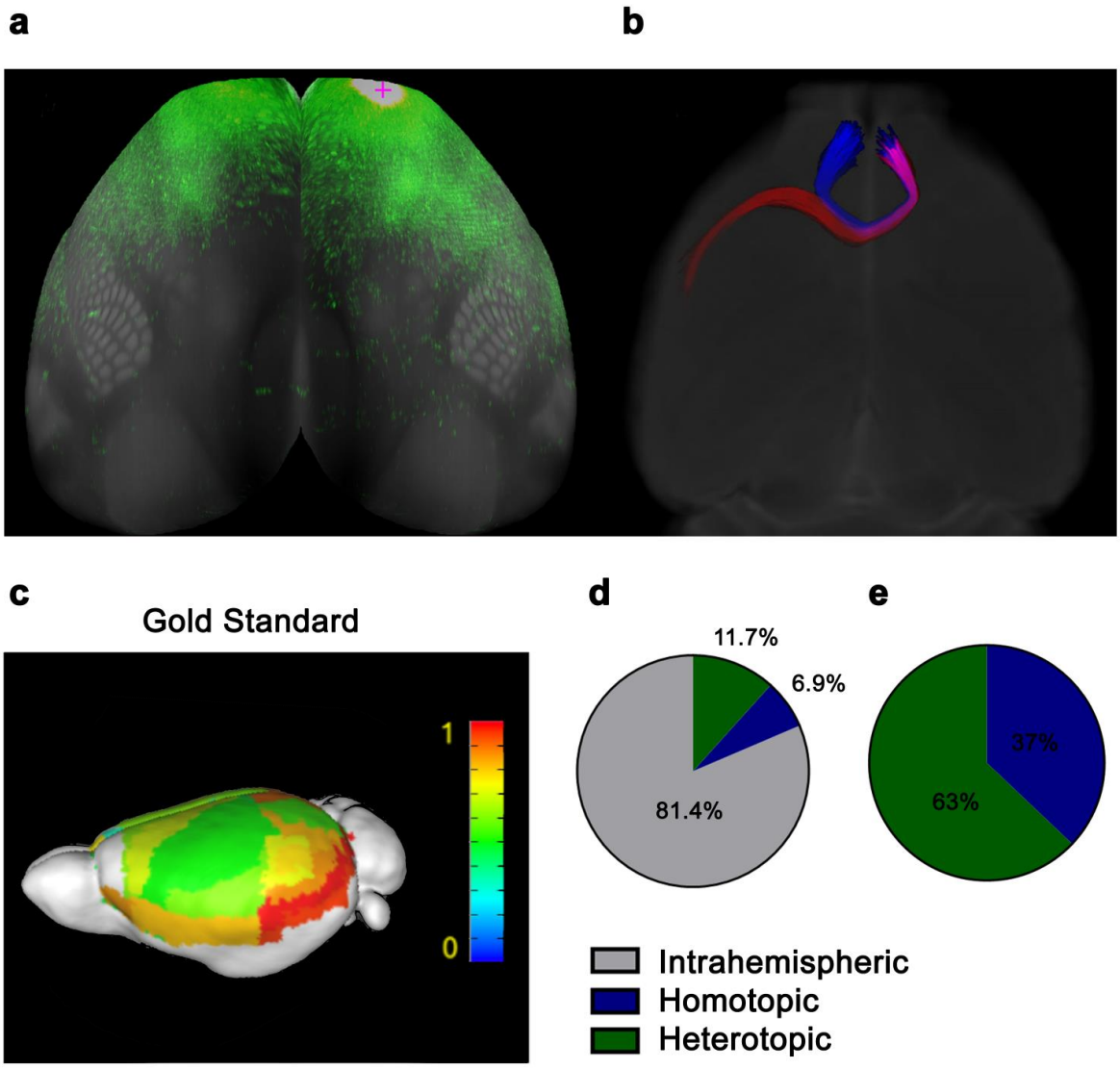
Topic: B.09. Network interactions

Support: PA Department of Health SAP #4100083102 to ACS

Title: The Corpus Callosum is heterotopic and its heterotopicity directly impacts cortical networks

Authors: *D. SZCZUPAK[1], P. M. IACK[2], D. RAYEE[3], R. LENT[2], F. TOVAR-MOLL[4], A. C. SILVA[1]; [1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [3]Albert Einstein Col. of Med., New York, NY; [4]D Or Inst. For Res. and Educ. / UFRJ, Rio de Janeiro, Brazil

Abstract: The corpus callosum is the most extensive white matter structure of the brain. Previous studies have associated and characterized it as a structure that connects homotopic cortical areas with a small number of heterotopic connections possibly related to plastic adaptations in corpus callosum dysgenesis and sprout/pruning mechanisms in normal callosal development. We hypothesized that callosal heterotopic connections are underestimated given its complex and plastic structure. Using the Allen Brain Institute histology connectivity atlas, we show that heterotopic connections are roughly two thirds of the overall interhemispheric connections in the C57BL6/J wild-type mice (Figure1). Furthermore, based on diffusion-weighted imaging, we show that these heterotopic connections are the major constituents of the corpus callosum in mice, monkeys, and humans and present in distinct topographies. These connections have a significant impact on the cortical network across species and their network properties. This set of results reshape the view of the corpus callosum and its connectivity, directly impacting on multiple neuroscience fields that investigate cortical connectivity and brain development.



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Poster

P139. Network Interactions: In Vivo and In Vitro

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Program #/Poster #: P139.09

Topic: B.09. Network interactions

Support: NIH Grant T32EY07001
NIH Grant P50HD103555

Title: Cellular Organization of the Locus Coeruleus in Adult Mice

Authors: *A. MCKINNEY[1,2], X. JIANG[1,2];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Texas Children's Hosp., Houston, TX

Abstract: The Locus Coeruleus (LC) is the source of ~90% of the brain's noradrenergic connections and coordinates behavioral responses that are crucial to survival, yet our understanding of its physiology is largely restricted to its long-range projections and diverse effects on postsynaptic targets. Utilizing an *ex vivo* brain slice preparation that allows simultaneous recording of up to 8 adult LC neurons (targeted by expression of dopamine β-hydroxylase, DBH+), we performed parallel recordings of the connections between LC DBH+ neurons. From these paired recordings, we have evidence that synaptic connectivity between LC neurons is absent in the adult murine locus coeruleus, that gap junctions are the primary means by which LC neurons pool information and coordinate their responses, and that blocking these Cx36-mediated gap junctions decreases synchrony between simultaneously recorded LC neurons. Leveraging our high-throughput patch clamp technique, we have also constructed a systematic survey of the electrophysiological and morphological properties of LC neurons that validates existing morphological classifications and compares the intrinsic properties between LC neuronal classes for the first time. We find that the probability of gap junction connectivity is a function of intersoma distance and morphological class. More experiments are currently underway to uncover how molecular and genetic variation underlies the unique organization of LC microcircuits and what roles these properties play in the construction of putative ensembles in the LC.

Disclosures: A. McKinney: None. **X. Jiang:** None.

Poster

P162. Glia Mechanisms: Microglia and Oligodendrocytes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P162.01

Topic: B.11. Glial Mechanisms

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NIH Grant P50 MH096889
NIH Grant R01 MH73136
NIH Grant R01 NS14609
NIH Grant R01 AI121945
NARSAD Young Investigator Grant
Hewitt Foundation for Biomedical Research

Title: Impaired developmental microglial pruning of excitatory synapses on CRH-expressing hypothalamic neurons exacerbates stress responses throughout life.

Authors: Z. NGOZI[1], A. K. SHORT[2], S. OTHY[3], C. L. KOOIKER[4], M. SHAO[2], B. G. GUNN[5], J. BECK[4], X. BAI[4], S. M. LAW[2], J. C. SAVAGE[6], J. J. LAMBERT[5], D. BELELLI[5], M.-E. TREMBLAY[6], M. D. CAHALAN[3], T. Z. BARAM[2], ***J. L. BOLTON**[1];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Pediatrics; Anatomy/Neurobiology, [3]Physiol. & Biophysics, [4]Anatomy/Neurobiology, Univ. of California- Irvine, Irvine, CA; [5]Neurosci., Dundee Univ., Dundee, United Kingdom; [6]Axe Neurosciences, Ctr. De Recherche Du CHU De Quebec, Quebec, QC, Canada

Abstract: The developmental origins of stress-related mental illnesses are well-established, and early-life stress/adversity (ELA) is an important risk factor. However, it is unclear how ELA impacts the maturation of salient brain circuits, provoking enduring vulnerability to stress and stress-related disorders. Here we find that ELA increases the number and function of excitatory synapses onto stress-sensitive hypothalamic corticotropin-releasing hormone (CRH)-expressing neurons, and implicate disrupted synapse pruning by microglia as a key mechanism. Microglial process dynamics on live imaging, and engulfment of synaptic elements by microglia, were both attenuated in ELA mice, associated with deficient signaling of the microglial phagocytic receptor Mer. Accordingly, selective chemogenetic activation of ELA microglia increased microglial process dynamics and reduced excitatory synapse density to control levels. Selective early-life microglial activation also mitigated the adrenal hypertrophy and prolonged stress responses in adult ELA mice, establishing microglial actions during development as powerful contributors to experience-dependent sculpting of stress-related brain circuits.

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Poster

P162. Glia Mechanisms: Microglia and Oligodendrocytes

Location: Virtual Only

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Program #/Poster #: P162.02

Topic: B.11. Glial Mechanisms

Support: GW4 BioMed DTP funding
ARUK South West small grant

Title: Microglia morphology is altered by gamma oscillations within the hippocampus

Authors: *M. ELLEY, J. WITTON, J. BROWN;
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Abstract: Microglia are the immune cells of the central nervous system, which are responsible for mediating neuroinflammation in both health and disease. Their activity has been implicated in several neurological diseases such as dementia, and it is currently debated as to whether the inflammatory response observed in neurodegenerative disease is causative or compensatory. A recent series of studies has demonstrated that inducing neuronal network oscillations at the gamma frequency of 40 Hz is capable

of reducing the neuropathology and cognitive deficits associated with dementia, which appears to occur as a result of microglia activation. To investigate this novel neuron-microglia interaction, we have developed an *ex vivo* assay, using hippocampal brain slices prepared from two mouse models (C57BL/6J and CX3CR1-GFP$^{+/-}$, which express GFP exclusively in microglia). This assay involves pharmacologically inducing gamma oscillations in the CA3 region of the hippocampus, fixing the brain tissue and then assessing microglia morphology following staining and mounting using two-photon microscopy. We have demonstrated that microglia morphology is altered in response to gamma oscillations, as microglia that have been exposed to these network oscillations have a significantly more amoeboid morphology than those in a control condition, where no oscillations were induced. These data suggest that sustained gamma oscillations result in the activation of microglia. Therefore, we have developed a new reduced model of gamma oscillation-microglia signalling that can be used to gain mechanistic understanding of this novel neuroimmune interaction.

Disclosures: M. Elley: None. **J. Witton:** None. **J. Brown:** None.

Poster

P162. Glia Mechanisms: Microglia and Oligodendrocytes

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P162.03

Topic: B.11. Glial Mechanisms

Support: NINDS F32 NS114040
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The Mayo Foundation

Title: Microglial Calcium Signaling and It's Role in Phagocytosis

Authors: *A. UMPIERRE[1], L.-J. WU[2];
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Abstract: Microglial calcium signaling underlies a number of key physiological and pathological processes in vivo in awake mice. Here, we investigate the role of microglial calcium signaling during epilepsy development, modeled by the systemic administration of kainate. In WT microglia, calcium signaling is exceptionally elevated in the days following status epilepticus (up to 10 days). During this time, calcium transient frequency is greatly heightened, transients are prolonged, and spreading calcium waves can emerge. Mechanistically, we have identified a key contribution of the UDP-sensitive purine receptor, P2Y6, in mediating this calcium rise. In P2Y6 general KO mice, microglial calcium signaling during epileptogenesis is largely attenuated. P2Y6 is identified as a receptor that promotes recognition of stressed neurons in a key first step underlying phagocytosis. We are actively developing a new in vivo assay to promote neuronal cell death through excitotoxicity in order to study P2Y6 and phagocytosis in an isolated, experimental system.

Disclosures: A. Umpierre: None. **L. Wu:** None.

Poster

P162. Glia Mechanisms: Microglia and Oligodendrocytes

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Program #/Poster #: P162.04

Topic: B.11. Glial Mechanisms

Support: American Federation for Aging Research Scholarship for Research in the Biology of Aging
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Title: Spinal cord microglia age in a caudal to rostral fashion and preferentially target motor neurons

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Abstract: The impact of aging on spinal cord microglia remains largely unknown, despite the critical role these cells play in innate immunity, tissue homeostasis, and neuronal modulation. In the brain, previous work has revealed that microglia present with regional diversity in their adoption of an immunogenic, pro-inflammatory state during aging. Thus, it is possible that spinal cord microglia also exhibit unique spatiotemporal responses to age-related damages. Using light microscopy, we found spinal cord microglia with a phagocytic and pro-inflammatory phenotype. Our data strongly indicate that microglia age in a caudal to rostral progression within the spinal cord and between the spinal cord and motor cortex. Additional analysis revealed that microglia preferentially aggregate around the somata of motor neurons compared to other neurons in the spinal cord. Using RNA sequencing, we uncovered pathways dysregulated and potentially responsible for the accelerated aging of spinal cord microglia and their preferential association with motor neurons. These comprehensive analyses provide insights critical to reducing the deleterious actions of aging microglia in the spinal cord, and particularly on motor neurons.

Disclosures: R. Castro: None. **L.M. De Biase:** None. **G. Valdez:** None.

Poster

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Title: Astrocyte Ensheathment of Calyceal Axons Precedes Myelination in the Ventral Brainstem

Authors: *D. HELLER[1], E. AMICK[1], D. KOLSON[3], A. BRANDEBURA[4], J. RAMADAN[3], T. DEERINCK[5], M. H. ELLISMAN[6], P. MATHERS[3], G. A. SPIROU[2];
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Abstract: During neurodevelopment, axons are encompassed by growing myelin sheaths to provide an electrically insulating layer, thereby allowing for rapid and temporally precise propagation of action potentials. Myelination is a complex process involving the coordinated orchestration of several myelin-associated proteins, resulting in axonal ensheathment and compaction of the myelin sheath. This process has long been attributed to Schwann cells in the periphery and oligodendrocytes in the central nervous system, but recently the functional role of astrocytes in regulating myelination has come to light. Astrocytes regulate oligodendrocyte proliferation and differentiation and provide lipids for myelin synthesis. Additionally, several studies have shown that astrocytes promote myelination, but the extent of astrocyte-axonal interactions has not been described. The medial nucleus of the trapezoid body (MNTB) has become an attractive model system for studying neuronal-glial cell interactions during neural circuit formation. During the short time-period of nerve terminal competition and growth from postnatal day (P)2-6, astrocyte and oligodendrocyte populations increase in number and begin to exhibit mature morphological features, thus allowing for a detailed study of the synergistic roles of glial cells during myelination. To achieve high structural resolution, a series of serial block-face scanning electron microscopy (SBEM) data sets from the mouse MNTB at P2, P4, P6, P9, and P30 were employed for this study. This allowed for a detailed investigation of individual calyceal axons at various timepoints, which elucidated ultrastructural characteristics of the onset and progression of axonal wrapping and myelin compaction. Glial cells from our electron microscopy volumes were classified using multiple correspondence analysis for discrete data, followed by hierarchical clustering based on ultrastructural criteria from classic EM literature. At P4, a majority of calyceal axons exhibited single glial wraps, with compaction of the myelin sheath beginning at P6, after most MNTB principal neurons are mono-innervated, and becoming widespread by P9. From the analysis of our SBEM volumes, we find early axonal wrapping at P4 by astrocytes, while oligodendrocytes do not begin wrapping until P6. Quantification of the spatial distribution of glial wrapping across calyceal axons, MNTB principal cell axons, and fiber fascicles reveal that astrocytes predominately ensheathe the CH. This study highlights a novel role for astrocytes during developmental myelination.

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Poster

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Title: TDP-43 maximizes nerve conduction velocity by repressing a cryptic exon for paranodal junction assembly and maintenance in Schwann cells

Authors: *K.-J. CHANG[1], *K.-J. CHANG[1], I. AGRAWAL[2], A. VAINSHTEIN[3], W. HO[2], W. XIN[1], G. TUCKER-KELLOGG[2], K. SUSUKI[4], E. PELES[3], S.-C. LING[2], J. R. CHAN[1];
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Abstract: TDP-43 is extensively studied in neurons in physiological and pathological contexts. However, emerging evidence indicates that glial cells are also reliant on TDP-43 function. We demonstrate that deletion of TDP-43 in Schwann cells results in a dramatic delay in peripheral nerve conduction causing significant motor deficits in mice, which is directly attributed to the absence of paranodal axoglial junctions. By contrast, paranodes in the central nervous system are unaltered in oligodendrocytes lacking TDP-43. Mechanistically, TDP-43 binds directly to *neurofascin* mRNA, encoding the cell adhesion molecule essential for paranode assembly and maintenance. Loss of TDP-43 triggers the retention of a previously unidentified cryptic exon, which targets *neurofascin* mRNA for nonsense-mediated decay. Thus, TDP-43 is required for neurofascin expression, proper assembly and maintenance of paranodal junctions, and rapid saltatory conduction. Our findings provide a framework and mechanism for how Schwann cell-autonomous dysfunction in nerve conduction is directly caused by TDP-43 loss-of-function.

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Poster

P162. Glia Mechanisms: Microglia and Oligodendrocytes

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Topic: B.11. Glial Mechanisms

Support: NIH R21 AG066059

Title: Investigating the mechanism underlying pyridazine-derivatives enhanced functional and structural plasticity of tripartite glutamatergic synapse

Authors: *Z. XU[1], X. WANG[2], J. B. FOSTER[2], C.-L. G. LIN[3];
[2]Neurosci., [1]The Ohio State Univ., Columbus, OH; [3]Dept Neurosci, Ohio State Univ., Columbus, OH

Abstract: Tripartite synapse is formed by a pre-synapse, a post-synapse, and a peri-synaptic astrocytic process (PAP). Exosomes, a type of extracellular vesicles (EVs) carrying molecules such as microRNAs, proteins and lipids, can be released from the PAP to regulate synaptic activity. Changes in the function and structure of tripartite synapses have been found in Alzheimer's disease (AD). We discovered that pyridazine-derivatives can enhance functional and structural plasticity of tripartite glutamatergic synapse. Efficacy studies of one of the pyridazine-derivatives in AD mouse models demonstrated therapeutic potential for clinical use. However, the underlying mechanism of the compound action has not been fully understood. In a previous study, we found that the compound action site is located at the PAP. A set of PAP proteins is rapidly upregulated following compound treatment, and a subset of these PAP proteins is locally synthesized. Recently, we found that a set of proteins immediately localizes to the plasma membrane of the PAP following compound treatment. These proteins include membrane trafficking proteins, endocytic proteins, adhesion proteins, cytoskeletal proteins, signaling proteins, receptors and transporters. Rab35, a small GTPase that regulates exosome secretion, was found to be increased on the plasma membrane. In light of these observations, we hypothesize that the compound activates a signaling pathway which results in localization of a set of proteins to the plasma membrane, and subsequently, a subset of these proteins is released from the PAP via exosomes to regulate synaptic activity. To test this hypothesis, we isolated EVs from mouse brains followed by size fractionation to obtain exosomes. Isolated exosomes were then assessed for concentration and size distribution by nanoparticle tracking analysis. Results showed increased secretion of exosome following compound treatment. Furthermore, exosomes were subjected to proteomic analysis. Ingenuity pathway analysis (IPA) suggested the activation of synaptic signaling pathway, PKA signaling pathway following compound treatment. These results suggest that exosomal release folowing compound treatment may regulate synaptic function. We are investigating the underlying mechanism of immediate compound action at the PAP and the effects of released proteins on the functional and structural plasticity of the synapses.

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Poster

P221. Cellular and Molecular Mechanisms III

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Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

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NIH Grant K08AG065463

Title: Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes

Authors: A. KAWLES[1], R. KESZYCKI[1,2], G. MINOGUE[1], C. SPENCER[1], I. AYALA[1], R. SHEPARD[1], N. GILL[1,3], J. LILEK[1,4], K. AJROUD[1,4], C. COVENTRY[1], E. ROGALSKI[1,2], S. WEINTRAUB[1,2], A. FELDMAN[1,4], Q. MAO[1,4], M. E. FLANAGAN[1,4], H. ZHANG[1,3], M.-. M. MESULAM[1,5], C. GEULA[1,6], ***T. GEFEN**[1,2];
[1]Mesulam Ctr. for Cognitive Neurol. & Alzheimer's Dis., [2]Dept. of Psychiatry and Behavioral Sci., [3]Dept. of Preventative Med., [4]Dept. of Pathology, [5]Dept. of Neurol., [6]Dept. of Cell and Developmental Biol., Feinberg Sch. of Med. at Northwestern Univ., Chicago, IL

Abstract: Background: Frontotemporal lobar degeneration of the tau form (FTLD-tau) is a neurodegenerative disease that leads to different dementia syndromes. For example, primary progressive aphasia (PPA) is characterized by an isolated and progressive impairment of language, and focal atrophy of left-hemispheric regions. In contrast, behavioral variant of frontotemporal dementia (bvFTD) is characterized by progressive dysfunction in personality, and atrophy in bilateral frontal regions. Interestingly, both PPA and bvFTD can be causeed by th common 3R FTLD-tauopathy of Pick's disease (PiD). This stereological study investigated the cortical distribution of Pick bodies in bvFTD and PPA to establish clinicopathologic concordance between Pick's disease and the salience of the aphasic versus behavioral phenotype.
Methods: 12 right-handed cases with PiD as the sole pathologic diagnosis were identified from the Northwestern University Alzheimer's Disease Center brain bank (bvFTD, N=6; PPA, N=6). Paraffin-embedded sections were stained immunohistochemically with AT-8 to visualize Pick bodies. Unbiased stereological analysis (MicroBrightField, MBF Bioscience) was performed on all 12 cases in 3 regions bilaterally [middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior temporal gyrus (STG)] and unilaterally in occipital cortex (OCC). Bilateral anterior temporal lobe (ATL) was analyzed in PPA cases only. Paired t-tests and one-way nonparametric ANOVAs were used to compare regional and hemispheric distribution within and between groups.
Results: Highest densities of Pick bodies were found in ATL (M=31,634; SD=10,502) in PPA, whereas peak densities were evident in the MFG (M=26,036; SD=8,719) in bvFTD. In PPA cases, there was leftward asymmetry of Pick bodies in MFG, IPL, and STG, the latter of which reached statistical significance ($p<0.05$; L>R). Interestingly, the ATL showed slight rightward predominance. Cortical distributions of Pick bodies in bvFTD were generally symmetric. As expected, the occipital cortex showed extremely sparse to no pathology in both groups.
Conclusions: Stereological quantitation confirms that the distribution of Pick body pathology is concordant with salient clinical features unique to PPA vs bvFTD. In bvFTD, Pick bodies were symmetric and highest in MFG, a region implicated in behavior/comportment, while in PPA, Pick bodies showed leftward asymmetry consistent with the aphasic phenotype. The vulnerability of the ATL to Pick's disease is remarkable, raising future questions about its functional significance within the human language network and the relationship of tau pathology to neuronal degeneration.

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Poster

P221. Cellular and Molecular Mechanisms III

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Program #/Poster #: P221.02

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

Support: NIH grant R01AG061188

Title: Caspase-dependent tau cleavage as a pathogenic mechanism in Alzheimer's disease

Authors: *C. K. OPLAND[1], S. SINGH[2], Y. CHEN[3], X. TIAN[3], J.-H. TSENG[1], R. MEEKER[3], T. J. COHEN[3];
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Abstract: With an estimated 5.8 million Americans affected and the sixth leading cause of death in the United States, Alzheimer’s disease (AD) is a neurodegenerative disease associated with extracellular amyloid beta plaques and intracellular accumulation of tau protein leading to pathological neurofibrillary tangles. Normally, in a healthy individual, tau is a microtubule-associated protein that stabilizes axonal microtubules in neurons. However, in an AD diseased neuron, tau collapses into twisted strands to form tangles correlated with neuronal degeneration. Tau undergoes many different post-translational modifications (PTMs), however, these modifications are still poorly understood on how they contribute to tau pathogenesis in AD. Tau cleavage by caspases, is believed to be an early toxic modification that precedes other later pathological modifications and drive neuronal degeneration found in human AD brain. Although the mechanism of tau cleavage and its role in Alzheimer’s disease is unclear, a current model suggests that tau is cleaved by caspase-3 at the C-terminus where it then changes tau’s conformation to generate a disease-associated species. With few reliable model systems with which to study this process, our lab has discovered that proteasome defects result in caspase-3 activation resulting in robust tau cleavage. In the absence of caspase-3 in neurons, tau cleavage is no longer produced suggesting that caspase-3 is the main component driving tau cleavage. As it is still unclear where and how tau is cleaved in the neuron, I observed both cleaved tau and caspase-3 enrichment at the post-synaptic density (PSD) where toxic tau species may be causing further damage resulting in neuronal network dysfunction. Forced expression of a cleaved tau species in neurons allowed us to further characterize the extent to which cleaved tau results in neuronal toxicity. Our study suggests that proteasome deficiency and subsequent accumulation of cleaved tau is a pathogenic mechanism that incites neurodegeneration in AD and likely other tauopathies as well.

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Poster

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Title: Locus coeruleus degeneration is related to pathologic stages of progressive supranuclear palsy and predicts laminar distributions of tau pathology

Authors: *D. T. OHM[1], C. PETERSON[1], S. AREZOUMANDAN[1], W. TROTMAN[1], E. XIE[1], C. MCMILLAN[1], D. WOLK[1], J. Q. TROJANOWSKI[2], E. B. LEE[2], M. GROSSMAN[1], D. IRWIN[1];
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Abstract: The locus coeruleus (LC) sends widespread projections to the isocortex that result in a high density of noradrenergic fibers across cortical layers, especially infragranular layers in select regions. We recently demonstrated that LC degeneration is prominent among all tauopathies, including progressive supranuclear palsy (PSP). However, it is not clear whether LC degeneration increases with PSP stages and contributes to laminar distributions of pathology across heterogeneous isocortex. Here, we tested the hypothesis that LC degeneration worsens with increasing pathologic stages of PSP and is related to unique laminar distributions of tau pathology measured in up to ten isocortical regions. We digitally quantified neuromelanin content to measure the severity of LC degeneration in 19 cognitively unimpaired healthy controls (HC) and 44 PSP patients pathologically staged according to Kovacs et al. published criteria. In a subgroup of staged PSP patients (n=21) with available cortical tissue for laminar analyses, we measured the percent area occupied by AT8-immunoreactive tau pathology in supragranular (I-III) and infragranular (IV-VI) layers and calculated a ratio of supragranular-to-infragranular tau burden per region. Mann-Whitney U analyses compared LC degeneration between PSP stages and HC. Linear regressions adjusted for age and disease duration determined the association between LC degeneration and layer ratios of tau burden. We found severe LC degeneration in advanced stages of PSP that was greater than LC degeneration measured in HC ($Z=-4$, $p<0.001$) and early PSP stages ($Z=-2$, $p=0.04$). Less severe LC degeneration (found in early PSP stages) was associated with an infragranular-dominant profile of tau pathology, while more severe LC degeneration (found in later PSP stages) was associated with a more bilaminar to supragranular-dominant profile of tau pathology ($\beta=0.33$; $p<0.02$). Regional analyses showed that these relationships were evident among association regions ($\beta=0.53$; $p=0.004$) and temporo-occipital regions with mild pathology involved later in PSP progression ($\beta=0.54$; $p=0.007$). However, these relationships were not found in earlier-involved paralimbic and primary motor regions with severe pathology ($\beta=-0.07$; $p=0.76$). These findings suggest that the LC progressively degenerates with advancing pathologic stages of PSP. Furthermore, increasing LC degeneration was associated with more tau pathology accumulation in both infra- and supragranular layers. Therefore, LC degeneration may play a central role in trans-synaptic propagation of tau pathology into cortical regions and potentially between cortical layers in PSP.

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Poster

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NACC New Investigator Award U01 AG016976

Title: Characterization of distinct neuropsychiatric trajectories in FTLD-tauopathies

Authors: *R. KESZYCKI[1,2], A. KAWLES[1], G. MINOGUE[1], N. GILL[1,3], S. JUTHAPAN[1], C. NASSIF[1,2], M. RILEY[1], C. COVENTRY[1], H. ZHANG[1,3], E. ROGALSKI[1], S. WEINTRAUB[1,2], M. M. MESULAM[1], C. GEULA[1], T. GEFEN[1,2];
[1]Mesulam Ctr. for Cognitive Neurol. & Alzheimer's Dis., [2]Dept. of Psychiatry and Behavioral Sci., [3]Dept. of Preventative Med., Northwestern Univ., Chicago, IL

Abstract: Introduction: Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease commonly caused by 3R (Pick's disease, "PiD") or 4R tauopathies (corticobasal degeneration, "CBD" and progressive supranuclear palsy, "PSP"). FTLD-tauopathies can lead to language decline in primary progressive aphasia (PPA) or comportmental changes in behavioral variant frontotemporal dementia (bvFTD). Patients diagnosed with these distinct dementias often develop debilitating neuropsychiatric symptoms (NPS) over time. This study examined NPS in PiD, PSP, and CBD early and late in the disease course, as well as their change over time, in participants with PPA or bvFTD.
Methods: Fifty-one participants with clinical diagnoses of PPA (N=26) or bvFTD (N=25) and autopsy-confirmed PiD (N=17), PSP (N=14), or CBD (N=20) were identified from the Mesulam Center for Cognitive Neurology and Alzheimer's Disease research programs. NPS (total=12) were examined at initial and final visit (M=0.76 years before death; SD=0.72) with the Neuropsychiatric Inventory—Questionnaire (NPI-Q) and placed into 3 domains based on co-occurrence: 1) *Frontal/Comportmental* (apathy, disinhibition, motor disturbance, and appetite change), 2) *Affective* (depression, anxiety, elation, and irritability), and 3) *Disruptive/Psychotic* (delusions, hallucinations, agitation, and nighttime behaviors). Linear and logistic regressions controlling for disease duration and dementia severity (CDR global score) were used to compare group differences in average percentage of *total* and *domain-specific* symptoms endorsed at initial and final evaluation between PiD, PSP, and CBD with PPA or bvFTD.
Results: Across all participants with FTLD-tau, the most common symptom at initial presentation was irritability (47%) whereas apathy (67%) predominantly emerged at final evaluation. Psychosis (e.g., hallucinations) was nearly absent at both timepoints, ranging from 0-5%. Total NPS increased in CBD and PiD over time (by ~11%) and was driven by high endorsement of *Frontal/Comportmental* symptoms; compared to CBD and PiD, total symptom endorsement in PSP remained relatively stable ($p<0.01$). Regardless of pathology, *Frontal/Comportmental* symptoms increased in both bvFTD and PPA over time, but the magnitude of this was significantly higher in PPA (by ~25%; $p<0.05$).

Conclusions: FTLD-tauopathies can present with distinct neuropsychiatric phenotypes. PPA and bvFTD, though clinically distinct at onset, appear to converge in their neuropsychiatric presentations close to death. Findings highlight the prognostic value of identifying and monitoring NPS in non-amnestic neurodegenerative dementias.

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Poster

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Title: Differential Vulnerability of the Dentate Gyrus to Tauopathies in Aphasic Dementia

Authors: *A. KAWLES[1], G. MINOGUE[1], C. NASSIF[1], R. KESZYCKI[1,2], C. COVENTRY[1], E. ROGALSKI[1,2], M. E. FLANAGAN[1,3], M.-. M. MESULAM[1,4], C. GEULA[1,5], T. GEFEN[1,2]; [1]Mesulam Ctr. for Cognitive Neurol. & Alzheimer's Dis., [2]Dept. of Psychiatry and Behavioral Sci., [3]Dept. of Pathology, [4]Dept. of Neurol., [5]Dept. of Cell and Developmental Biol., Feinberg Sch. of Med. at Northwestern Univ., Chicago, IL

Abstract: Background. The dentate gyrus (DG) is a region of the hippocampal formation characterized by a single layer of densely packed granule cells, followed by an underlying polymorphic layer of the long-projecting hilus neurons. The granule cells receive input from the entorhinal cortex and send excitatory output to the hippocampal CA3 subfield via its mossy fibers. Prior work in Alzheimer's disease (AD) has shown that the dentate gyrus generally resists the development of tau tangles in the typical amnestic clinical syndrome. The susceptibility of the DG in non-AD tauopathies has not yet been investigated and can offer key insights into hippocampal function and selective vulnerability of the region to disease. Here, we report stereologic densities of tau inclusions in the DG across three conformationally distinct tauopathies, namely the FTLD 3R-tauopathy of Pick's disease (PiD); the FTLD 4R-tauopathy of corticobasal degeneration (CBD); and the 3/4R-tauopathy of Alzheimer's disease (AD), all of which manifested an aphasic dementia syndrome known as Primary Progressive Aphasia (PPA), in which language abilities are compromised and memory functions are spared.
Methods. Fifteen right-handed cases with clinical diagnoses of PPA and autopsy-confirmed tauopathy

diagnoses were obtained from the Northwestern Alzheimer Disease Center (PiD, N=5; CBD, N=5; AD, N=5). Specimens were stained immunohistochemically with AT-8 to visualize tau pathology of both the 3R and 4R type. Unbiased stereological analysis (MicroBrightField Bioscience) was performed on the left dentate gyrus to quantitate densities of tau-positive neurons. One-way nonparametric ANOVA was used to compare distributions.
Results. Highest densities of dentate gyrus tau pathology were found in PiD (~74,000 per mm^3), followed by CBD (~20,000 per mm^3), and then AD (~4,000 per mm^3); PiD showed significantly higher densities ($p<0.005$) compared to AD by an order of nearly 20-fold. While some tau pathology was found in PPA-AD cases in the hilus neurons, very few inclusions were present in the granule cells of the dentate gyrus. In contrast, the granule cells of the dentate gyrus contained a relatively dense collection of inclusions in CBD and particularly in PiD.
Conclusion. The dentate gyrus of the hippocampal complex is differentially vulnerable to tauopathies, with high selectivity to FTLD-tauopathies but not to Alzheimer-type neurofibrillary tau. These patterns of susceptibility in the non-amnestic, language-based clinical dementia syndrome known as PPA raise intriguing questions about the functional and structural integrity of hippocampal circuits in neurodegenerative dementias.

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Poster

P221. Cellular and Molecular Mechanisms III

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Program #/Poster #: P221.06

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

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Title: Clinicopathologic correlates of psychiatric symptoms in chronic traumatic encephalopathy across brain regions

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Abstract: BACKGROUND
Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease with cognitive, behavioral, and

psychiatric symptoms, with depression and suicidality present in a large proportion of CTE cases. Pathologically CTE is defined by a distinctive accumulation of hyperphophorylated tau (pTau) predominately involving the frontal and temporal cortices, medial temporal lobe, and brainstem. However, the association between pathology in particular brain regions and psychiatric CTE symptoms is unknown.
METHODS AND RESULTS
Human postmortem brains from CTE cases and controls were obtained from the VA-BU-CLF Brain Bank. Trained neuropathologists examined each brain for gross and microscopic pathology, and provided semi-quantitative assessments. Regions of interest (including frontal, temporal, limbic, and brainstem structures) were sectioned and stained for pathological markers of interest (e.g. pTau, β-amyloid, α-synuclein, pTDP43, etc). Stained slides were scanned and traced digitally, with staining quantified using a Leica Aperio system. Preliminary analyses suggest alterations in specific cortical, limbic, midbrain, and white matter structures may associate with depressive and suicidal features in CTE. In particular, cortical white matter loss as well as hippocampal and midbrain pathology were associated with psychiatric features. We have also found myelination and inflammation-associated changes in the anterior cingulate cortex of depressed CTE cases. Cytotoxic t-cells may be involved in depressed mood and disease progression in CTE.
CONCLUSIONS
This investigation is the first to explore associations between neuropathology in particular brain regions and psychiatric features in CTE. Preliminary results suggest increased neurodegenerative pathology, loss of white matter, neuroinflammation, and gliosis could underlie psychiatric phenotypes in CTE.

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Poster

P221. Cellular and Molecular Mechanisms III

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Program #/Poster #: P221.07

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

Support: NIH R56 NS110384-01
NIH R21 NS093440

Title: Pathological tau species promotes maladaptive RNA translation

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Abstract: A fundamental gap in the field is the incomplete identification of the mechanisms by which tau promotes cellular dysfunction. Several labs, including our own, established that pathological tau shifts the translatome yielding a maladaptive response. However, the molecular mechanisms driving this effect remain unknown. The overall objective of this study is to establish these mechanisms by defining 1) the impact of pathological tau on translation, 2) the components of RNA translation machinery that interact

with tau, 3) whether improving translation rescues brain function in models of tauopathy, and whether pathological tau impacts mRNA availability. We adapted surface-sensing of translation (SUnSET) for identification of newly-synthesized proteins in the brain. To this end, we used puromycin, a structural tRNA analog, and detected overall reduced levels of newly-synthesized (pumocyinylated) proteins in both in vitro and in vivo models of tauoapthy. We then coupled the puromycin assay with LC-MS/MS proteomics in the brains of TET-regulatable rTg4510 tau transgenic mice (+/- doxycycline) to identify proteins translationally altered by tauopathy. With microarrays, we confirmed that changes in the synthesis of translational machinery were not attributed to transcription. These results were further validated in Alzheimer's brains. Then, treating mice with a kinase inhibitor that inhibits the PERK pathway thereby restoring translation, we observed marked functional rescue in rTg4510 tau transgenic mice as evidenced by manganese-enhanced MRI and behavioral assays. Finally, to assess the extent to which tau impacts RNA availability for translation, we used enhanced-CLIP to determine tau-associated RNA sequences in human Alzheimer's brains, and we identified a discrete number of sequences that associate differentially with tau as a consequence of disease progression. These results suggest that pathological tau promotes a maladaptive response. A central group of proteins that are translationally reduced are those necessary for production of ribosome machinery. Overcoming deficits in their translation offers functional benefits. In addition, tau exerts unanticipated and potentially devastating effects on availability of RNAs for translation. Therefore, tau-mediated maladaptive translation may be a pathogenic event in tauopathies, and efforts to rescue these effects are currently underway.

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Poster

P221. Cellular and Molecular Mechanisms III

Location: Virtual Only

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Program #/Poster #: P221.08

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

Support: Indiana University Grand Challenge Precision Health Initiative

Title: Trem2 modulates tau spreading in vivo

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Abstract: Triggering Receptor Expressed on Myeloid Cells-2 (TREM2) variants increase the risk of late-onset Alzheimer's Disease (AD). Recently, the interaction of TREM2 on tau pathology and inflammation has been investigated, but mainly in tau overexpression models. Here, we used an *in vivo* model of tau propagation using wild-type (WT) and TREM2$^{-/-}$ female and male mice. In this study, we aim to determine the role of TREM2 in tau propagation, and its cellular and molecular mechanisms. At 3 months of age, twelve mice per group were injected intracranially with PBS or tau isolated from an AD patient. Six months later, brain tissues were harvested for histological analysis and gene expression using NanoString. Histological analysis revealed a decrease on tau propagation in TREM2$^{-/-}$ mice observed by a reduction in tau AT8 immunoreactivity in different brain regions such as the mammillary area and the retrosplenial cortex contralateral. We also showed that in those brain areas, the number of microglia/macrophages by Iba1 staining in TREM2$^{-/-}$ mice does not increase compared to PBS injected animals, as it does in WT mice. We observed no change in the morphology of the microglia/macrophages in all groups. Furthermore, we determined that there are no changes in reactive astrocytes by GFAP immunofluorescence. Next, in order to identify a TREM2-related pathway or mechanism involved on tau propagation, we used the mouse neuroinflammation panel by NanoString and found that multiple pathway annotations were downregulated in the TREM2$^{-/-}$ mice injected with AD-tau compared to the WT, namely the microglia function score and the inflammatory signaling score. Our findings suggest that TREM2 modulates tau spreading *in vivo* by changing microglia/macrophages functionality. These findings provide more insight on the role of TREM2 in tauopathy models.

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Poster

P221. Cellular and Molecular Mechanisms III

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Program #/Poster #: P221.09

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

Support: The Ressler Family Foundation

Title: Molecular activation of gliovascular signaling precedes blood-brain barrier disruption and neuronal loss in a mouse model of tauopathy

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Abstract: Increasing evidence points to disruption of the blood-brain barrier (BBB) as an inciting event in the pathogenesis of Alzheimer's disease. The contribution of tau-mediated pathways driving blood-brain dysfunction are comparatively understudied. Using the P301S mouse model of tauopathy, we employed dynamic contrast enhanced MRI (DCE-MRI) to demonstrate widespread BBB dysfunction in late stage tauopathy. Quantitative spatial analysis of BBB breakdown in the frontal cortex and

hippocampus of P301S transgenic mice was confirmed post-mortem using Gadolinium high-resolution metallomic imaging mass spectrometry (Gd-MIMS) to detect residual gadolinium in cerebral tissue. To identify molecular pathways regulating intercellular signaling between neurons and gliovascular support cells that are dysregulated in advance of BBB disruption, we developed a cell-specific viral approach for transcriptional profiling of novel pathways within the multicellular environment of the neurovascular unit (NVU) in tauopathy. Viral constructs using cell-type specific promoters (hSynapsin, GFAP, or PDGFRβ) to drive expression of antigen-tagged ribosomes (TRAP) were used to study variance in spatial and temporal gene expression patterns in NVU cell types in P301S transgenic mice prior to widespread BBB disruption. Coupling vTRAP with endothelial MACS-seq in P301S transgenic mice, we generated multiple cell-type specific transcriptomic databases of the neurovascular unit across several pathologically-relevant time points that precede BBB disruption seen by DCE-MRI. Gene ontology analysis indicates that multiple molecular programs driving neuronal differentiation, neurite outgrowth, and synaptogenesis are expressed in gliovascular cells in the prodromal stage. This specific and temporally regulated coordination of pathways in pericytes and astrocytes to support injured neurons may lessen with age and increased stress, leading to a failure in maintaining homeostasis and further neuronal injury. This suggests a paradigm for gliovascular rescue of neurodegeneration and implicates numerous novel perivascular molecular pathways in the pathogenesis of tauopathy and Alzheimer's disease.

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Poster

P221. Cellular and Molecular Mechanisms III

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Program #/Poster #: P221.10

Topic: C.05. Tauopathies, Tau-dementias, and Prion Diseases

Support: NIH/NINDS 1R01NS119280
AARGD-591887

Title: Phosphorylation at serine 214 correlates with tau seeding activity in disease progression and promotes synaptic tau accumulation.

Authors: *H. PATEL[1,2], P. MARTINEZ[1,2], A. PERKINS[1,2], Y. YOU[1,2], A. LEE-GOSSELIN[1,2], N. JURY[1,2], R. VIDAL[1,3], C. A. LASAGNA-REEVES[1,2];
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Abstract: Hyperphosphorylation of the microtubule-associated protein tau under pathological conditions causes abnormal aggregation of tau, leading to the formation of neurofibrillary tangles (NFTs), an important hallmark of Alzheimer's Disease (AD) and other tauopathies. Increasing evidence supports the idea that the intermediate soluble tau aggregates propagate between synaptically connected neurons and induce "seeding" of non-pathogenic monomeric tau, thereby spreading tau pathology. Despite the knowledge acquired, the nature of the tau species involved in the propagation and seeding remains

unclear. In this study, we aim to identify the nature of the tau species responsible for seeding activity in order to use this species as a target or biomarker for disease progression. We profiled the temporal evolution of tau seeding activity in the brains of two mouse models of human tauopathies, hTau P301S (0N4R) and hTau P301S (1N4R), using a FRET-based biosensor cell line. Tau seeding was observed to be an early pathological indication and increased with age in both models. We then correlated seeding activity with the tau protein levels using a diverse set of antibodies against phospho- and conformational tau species in the same brain samples. Our results demonstrated that phosphorylation of tau at Serine 214 (pTauS214) was the only tau specie that correlates with seeding activity during disease progression in both tauopathy models. Interestingly, the deposition of pTauS214 was observed from an early stage and had a distinct histopathological pattern than the AT8-positive tau species, which is a common specie used to measure tau pathology. Furthermore, the pTauS214 species was enriched in synaptic fractions while AT8-positive tau species was absent in the synaptic fractions. Synaptic fractions displayed tau seeding activity at levels comparable to the cytosolic fractions, suggesting that the pTauS214 species is associated with the observed seeding activity at the synapse. Using AAV-based tauopathy mouse models we have also observed how the inhibition of tau phosphorylation at Ser214 decreases the overall tau levels at the synapse. Our results suggest that inhibition of phosphorylation at Serine 214 reduces the ability of the tau seed to migrate to the synapses and propagate trans-synaptically. Together, these results also set the stage for demonstrating the diversity of tau species present in the brain during the disease course and identify pTauS214 as an early target of therapeutic intervention for tauopathies.

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Poster

P221. Cellular and Molecular Mechanisms III

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P221.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Super-resolution live cell microscopy of lysosomal organelle dynamics in health and neurodegeneration

Authors: E. LEISTEN, T. BELTON, ***Y. C. WONG**;
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Abstract: Lysosomes are critical organelles for regulating cellular degradation, metabolism, and crosstalk with other organelles. Interestingly, endolysosomal dysfunction has been implicated in many neurological disorders, highlighting their importance for maintaining neuronal homeostasis. Using advanced super-resolution imaging and live cell microscopy, we have investigated novel aspects of lysosomal network dynamics and function which are key for regulating cellular homeostasis. Moreover, lysosomal dynamics may be directly disrupted by specific disease mutations linked to neurodegenerative diseases, including various lysosomal storage disorders and Alzheimer's disease. Our findings further support a key role for properly regulated lysosomal dynamics in neuronal health, and the importance of investigating their

regulation using advanced imaging techniques and microscopy to elucidate new pathways contributing to neurodegeneration.

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Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Predicting conversion to Alzheimer's Disease from longitudinal changes in Hippocampal and Entorhinal Volume in Mild Cognitive Impairment

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Abstract: Many patients with Mild Cognitive Impairment (MCI) progress to Alzheimer's disease (AD), but others do not, and understanding the factors that distinguish the two groups is a central challenge in the field. Here we applied multilevel growth curve modeling to data from 813 MCI subjects in the Alzheimer Disease Neuroimaging Initiative (ADNI) Database to examine whether longitudinal changes in hippocampal volume and/or entorhinal cortex (EC) volume were related to conversion. For both the Hippocampus and EC models, a two-level model (level 1 = timepoints nested within level 2 = subjects), which allowed for individual variation in both baseline volumes and slope (trajectories of change), fit better than one where slopes were fixed across subjects or in which both baseline volumes and slopes were fixed. Including a third level of nesting by grouping MCI individuals by their conversion to AD (age and sex matched groups, n(converters) = 329) yielded the best predictions of structural volumes with age. In particular, slopes of change in both Hippocampus and EC were more negative in converters than in non-converters. Model fits were compared using AIC measures, and both outcome volumes were divided by the whole brain volume to control for individual differences in brain size. We also tested whether the difference in rates of volume change before conversion would predict subsequent conversion. Specifically, we fit regression slopes to Hippocampus and EC volumes for each subject individually after excluding information from post-conversion visits. We saw that both the Hippocampus ($t(349.42) = 3.59$, $p<0.001$) and EC slopes ($t(395.54)=2.29$, $p=0.02$) significantly differed across cohorts with the slopes being significantly more negative in the converters than in the non-converters. A logistic regression model with cohort as outcome and ventricle volume as a nuisance covariate also revealed that both Hippocampus ($b_{Hippocampus}$ = -0.34(0.1), p = <0.001) and EC slopes (b_{EC} = -0.24(0.09), p = 0.012) were significant predictors of conversion. These results indicate that the rates of change in both hippocampal and entorhinal cortex volume in MCI patients are significant predictors of subsequent conversion to AD. They also demonstrate the promise of growth curve modeling in understanding the precursors of Alzheimer's disease.

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Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Program #/Poster #: P244.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSF SBIR #2033921

Title: Varied ligand spacing as an approach for label-free phenotype-based screening of astrocytes in a mouse model of Alzheimer's disease

Authors: E. G. THOMPSON[1], ***P. J. CALHOUN**[2], M. C. ROBITAILLE[3], J. A. CHRISTODOULIDES[3], J. M. BYERS[3], M. P. RAPHAEL[3], J. D. ROTHSTEIN[1];
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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disease affecting more than 6 million Americans currently, expected to affect 12 million Americans by 2050. While there have been significant scientific advances in AD research, the causative agent of AD is still unknown. To date animal models of AD have primarily relied on aggregate protein mechanisms, namely tau and amyloid β, but have led to limited advancements therapeutically. To better understand AD disease pathology in a manner independent of identified key molecular players, we employed lithography and self-assembled monolayer surface chemistry to vary ligand spacing thereby challenging astrocytes during cellular attachment. In combination we utilized a novel self-supervised machine learning (SSL) algorithm to parameterize phenotypes of healthy- and AD model-derived astrocytes from mice. Importantly, the difference in phenotype parameters are not observable on completely coated or commercially available cultureware. Surfaces were characterized by surface plasmon resonance and high (not challenging) and low (challenging) density ligand spacing were identified for astrocyte adhesion. Key morphological biomarkers were identified including altered cell area, cell perimeter, and feret ratio allowing for quantification of "reactive" and healthy astrocyte populations *in vitro*. Utilizing Streptolysin O-mediated delivery of antibodies against amyloid oligomers, we demonstrate that this device could not only function as a drug-screening platform in AD, but also in various other neurodegenerative diseases. This approach represents a new tool for the cell biologist's toolkit that relies on the intimate relationship between cellular structure and function and is independent of prior knowledge of aberrant protein mechanisms or gene regulation.

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Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Program #/Poster #: P244.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01AG031581
NIA P30AG19610

Title: Plasma NfL is Associated with APOE e4 Allelic Dose, Hippocampal Atrophy and Alzheimer's-related Cerebral Hypometabolism in Cognitively Unimpaired Late-Middle-Aged and Older Adults

Authors: *M. MALEK-AHMADI[1], Y. SU[1], V. GHISAYS[1], V. DEVADAS[1], J. LUO[1], Y. CHEN[1], H. PROTAS[1], K. CHEN[1], K. BLENNOW[2], H. ZETTERBERG[2], R. J. CASELLI[3], E. M. REIMAN[1]; [1]Banner Alzheimer's Inst., Phoenix, AZ; [2]Univ. of Gothenburg, Gothenburg, Sweden; [3]Mayo Clin. Arizona, Scottsdale, AZ

Abstract: Background
Plasma neurofilament light (NfL) measurements appear to provide an indicator of neuronal neurodegeneration in persons with Alzheimer's disease (AD) and a wide range of other neurological disorders. Here, we used an ultra-sensitive assay to characterize plasma NfL measurements in cognitively unimpaired (CU) late-middle-aged and older adults to test our hypotheses that plasma NfL concentrations are associated with APOE e4 allelic dose, MRI measurements of hippocampal atrophy, and cerebral glucose hypometabolism. We also explored associations with PET measurements of cerebral amyloid plaque and tau tangle burden and MRI measurements of white matter hyperintensity (WMH) volume.
Methods
Plasma NfL concentration was measured using a Single molecule array (Simoa) assay on an HD-X Analyzer in 194 CU 69±9 year-old participants from the Arizona APOE Cohort Study, including 43 APOE4 homozygotes (HM), 51 heterozygotes (HT), and 100 non-carriers (NC). Generalized linear models were used to characterize associations with APOE4 allelic dose before and after adjustment for age, sex, and education to characterize associations with hippocampal volume, HCI, mean cortical PiB PET measurements of amyloid plaque burden, meta-region-of-interest (meta-ROI) flortaucipir PET measurements of tau tangle burden, and VMH volume before and after adjustment for age and APOE4 allelic dose. The association between NfL and the Delayed Recall portion of the Rey auditory verbal learning test (AVLT) was also explored.
Results
Plasma NfL levels were associated with APOE4 allelic dose after adjustment for age, sex and education ($p=0.006$, HM>HT>NC), and they were also associated with our brain imaging measurements of neurodegeneration after adjustment for age, sex, education, and APOE4 allelic dose ($p<0.001$ for hippocampal volume and $p = 0.003$ for HCI). A non-significant trend suggested a possible association between plasma NfL levels and tau tangle burden ($p=0.07$), which may be moderated through

measurements of neurodegeneration ($p = 0.008$). There were no significant associations with amyloid plaque burden or WMH volume. A weak, but statistically significant, correlation was noted for NfL and AVLT Total Learning ($r = -0.27$, $p<0.001$).

Conclusions

Plasma NfL measurement, a promising blood-based biomarker of neuronal degeneration, is associated with APOE4 allelic dose and brain imaging measurements of neuronal degeneration in CU adults, adding further support for its value as an indicator of neuronal degeneration in the preclinical study of AD.

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Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Program #/Poster #: P244.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG060148
AARFD-20-677771

Title: C5ar1 receptor antagonist pmx205 attenuates neuropathology-associated biomarkers in arctic mice

Authors: *A. MENDOZA ARVILLA, N. D. SCHARTZ, S.-H. CHU, A. J. TENNER;
Univ. of California, Irvine, Irvine, CA

Abstract: In the healthy brain, complement promotes synaptic pruning, clearance of neuronal blebs, recruitment of phagocytes, and protection from pathogens. However, in Alzheimer's disease (AD), aberrant complement activation may contribute to inflammatory pathways, neuronal dysfunction, and cognitive decline. Engagement of C5aR1 by the downstream complement activation fragment, C5a, can instigate a feed-forward loop of inflammation, injury, and neuronal death, thus providing a potential target for modulation in AD therapeutics. Therefore, we assessed the effects of C5aR1 antagonist PMX205 on plasma neurofilament light (NfL) as a biomarker for neurodegeneration in the Arctic mouse model of AD.PMX205 (20 µg/mL) was provided via drinking water. A group of WT and Arctic mice received milliQ water without drug. Treatment began at ages 4.5, 5.5, or 6.5 months and ended at 7 months of age. Blood was collected for plasma before treatment via submandibular face bleed. At 7 months, blood was collected and processed for assay of NfL with the MSD Neurofilament Light kit (MesoScale Diagnostics). We measured volume of PMX205/water consumed and body weight throughout our study. Mice consumed 4.5-5.5 mL of PMX205 or water per day with no effect of treatment. Similarly, PMX205 treatment did not alter body weight over treatment duration. Plasma NfL significantly increased in the Arctic mice between 4.5 and 7 months ($p<0.01$). However, after 12 or 2 weeks of PMX205, increase in NfL was suppressed, suggesting an attenuation of the neurodegeneration in the brain. Interestingly, after treating for 6 weeks, there was a strong trend for a reduction in plasma NfL ($p=0.06$). Finally, when we compared NfL levels between groups at 7 months, there was a significant

increase in plasma NfL in untreated Arctic compared to WT ($p<0.0001$). However, treatment with PMX205 for any duration resulted in lower NfL levels compared to untreated Arctic at 7 months ($p<0.05$). In summary, treatment with PMX205 can prevent increase of the blood biomarker NfL. This is consistent with our previous report in which genetic ablation of C5aR1 rescued loss of neuronal complexity in the Arctic mouse and provides support for the use of plasma NfL as a proxy for measuring neurodegeneration and treatment efficacy.

Disclosures: A. Mendoza Arvilla: None. **N.D. Schartz:** None. **S. Chu:** None. **A.J. Tenner:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Histone deacetylase expression in pre-clinical Alzheimer's disease: an ADNI study

Authors: *J. SHRIRAM[1], M. H. MALEK AHMADI[2], L. MAHADY[3];
[1]Col. of Med., Univ. of Arizona, Phoenix, AZ; [2]Banner Hlth., Phoenix, AZ; [3]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: ***Background*** Identifying serum biomarkers of prodromal Alzheimer's disease (AD) may have great clinical utility in facilitating early intervention against significant cognitive decline. Histone deacetylase (HDAC) proteins are major epigenetic modulators that represent a potential early-stage biomarker target with three human isoforms that have been previously implicated in AD pathogenesis. ***Objective*** We sought to determine whether HDAC 1, 2, and 6 expression differed based on APOE ε4 allele carrier status and AV-45 amyloid positivity status. ***Methods*** We extracted data for 114 cognitively unimpaired subjects from the Alzheimer's Disease Neuroimaging (ADNI) database. HDAC 1, 2, and 6 expression levels were compared between APOE ε4 carriers vs. non-carriers and AV-45 amyloid positive vs. negative subjects. ***Results*** We found that serum expression of HDAC6 was significantly higher in amyloid positive compared to amyloid negative subjects at two probes (11754957-A-AT, $p = 0.04$, Cohen's $d = 0.49$; 11756962-X-AT, $p = 0.03$, Cohen's $d = 0.56$). The remaining HDAC6 probes and all HDAC 1 and 2 probes did not significantly differ in expression levels across APOE ε4 carrier and amyloid status groups. ***Discussion*** We found that amyloid positive subjects had significantly higher HDAC6 expression relative to amyloid-negative subjects. Given the increasing interest in the use of blood-based biomarkers in AD, HDAC6 expression may be a potential biomarker of early AD. In particular, it may also serve as a potential treatment target for future AD therapies.

Disclosures: J. Shriram: None. **M.H. Malek Ahmadi:** None. **L. Mahady:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P30 AG028383
R35 GM124977
R21AG066865

Title: The Influence of Age on Microglia Degeneration in the Human Brain

Authors: *R. SHAHIDEHPOUR[1], P. T. NELSON[2,3], A. D. BACHSTETTER[4];
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Abstract: Microglia activation—typically described in terms of hypertrophic appearance—is a well-established feature of aging. However, recent studies have suggested that microglia dystrophy, not activation, that may lead to increased propagation of progressive neurodegenerative diseases such as Alzheimer's disease. Yet, a clear understanding of causes and consequences of dystrophic microglia is lacking. Although frequently observed in diseased brains, the appearance of dystrophic microglia in the hippocampus of individuals free of cognitive impairment suggests that microglia may be undergoing senescence with age, leading to dystrophy. Therefore, we hypothesized age could be a significant contributor to senescence and the presence of dystrophic microglia. To investigate this relationship, we employed stereological counts of total microglia, hypertrophic, and dystrophic microglia across the decades of the human lifespan. The microglia counts were completed in the CA1 subregion of the hippocampus in individuals without known neuropathology or neurodegenerative disease. We then compared these cases to previously generated data of individuals with confirmed neurodegenerative disease. We found a significant increase in the number of total microglia in the CA1 region related to age in disease-free individuals. However, further investigation showed that the bulk of this increased number of microglia was predominantly due to an increased population of hypertrophic cells but not dystrophic. In the presence of disease pathology, the percentage of microglia observed to be dystrophic was significantly greater than in normal aging individuals, while quantity of hypertrophic microglia did not change. These results challenge the current belief that microglial activation and hypertrophy are drivers of disease progression. Our findings provide evidence that normal aging is not associated with an increase in dystrophic microglia and suggest that dystrophic microglia may be a disease-associated microglia phenotype. Future work is required to understand the link between the increase in dystrophic microglia and neurodegenerative disorders.

Disclosures: R. Shahidehpour: None. **P.T. Nelson:** None. **A.D. Bachstetter:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R21 AG070595

Title: Unique Molecular Signatures associated with Alzheimer's Disease in the Retina

Authors: *J. NGOLAB[1], A. MARK[3], J. BUCHANAN[4], S. KOROURI[2], A. WANG[4], S. PRIESSL[4], K. FISCH[3], R. A. RISSMAN[2];
[1]Neurosciences, [2]Neurosci., UCSD Sch. of Med., La Jolla, CA; [3]Ctr. for Computat. Biol. & Bioinformatics, [4]Ctr. for Epigenomics, UCSD, La Jolla, CA

Abstract: Background: Clinical studies of the retina in Alzheimer's Disease (AD) patients have reported alterations to the retinal structure and amyloid deposition. However, detection of amyloid-beta (Aβ) inclusions and retinal thinning have been inconsistent due to various protocols. Retinal Aβ deposition and phosphorylated tau also coincide in retinal diseases such as age-related macular degeneration and glaucoma, indicating that traditional pathological hallmarks of AD in the retina do not exclusively signify AD diagnosis. Microlevel assessment is needed to validate the retinal changes observed in AD. Next-generation sequencing technologies have revealed unique insights into the mechanisms involved in other retinal diseases such as age-related macular degeneration.
Methods: To gain molecular insight into the pathophysiology of retinal AD changes, we propose to conduct single-nuclei RNA-seq (snRNA-seq) analysis on retinal tissues extracted from severe AD cases indicated by clinical and pathological diagnosis. Postmortem tissues from the left eye of two autopsy-confirmed AD cases and two non-demented age-matched controls were processed for snRNA-seq analysis. Raw reads are to be processed to identify retinal cell types and differential gene expression within samples and between groups. Additionally, we will histologically process the right eye of each case to conduct morphological retinal assessments.
Results: We hypothesize that the molecular changes will localize to cells with thinning retinal layers. Both retinal measurements and snRNA-seq analysis are currently underway. By determining the transcriptional profile of the retinal cells and the corresponding architecture, we will potentially pinpoint the key players involved in AD-mediated retinal changes.
Conclusion: Structural changes to the retinal architecture may not be sufficient to signify AD, nor is the presence of retinal Aβ and phosphorylated tau restricted to AD retinopathy. Studying the transcriptional profile of the AD retina will provide biological context to retinal changes observed in AD.

Disclosures: J. Ngolab: None. **A. Mark:** None. **J. Buchanan:** None. **S. Korouri:** None. **A. Wang:** None. **S. Priessl:** None. **K. Fisch:** None. **R.A. Rissman:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.08

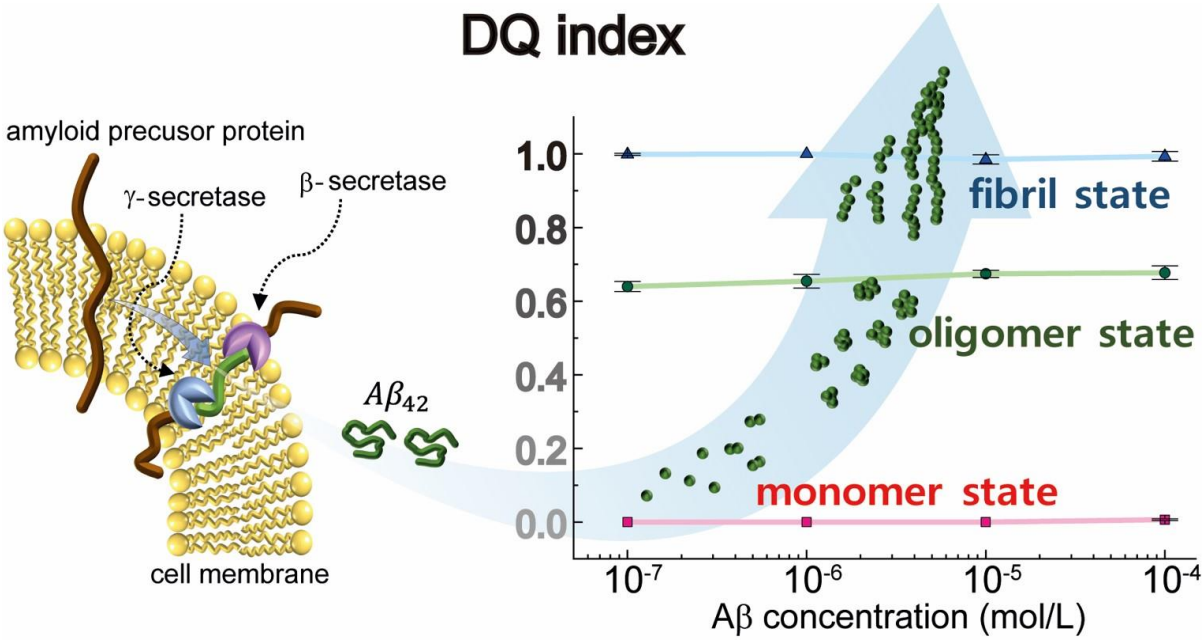
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the Institute for Basic Science (IBS-R011-D1)

Title: A biophysical marker for Aβ oligomerization and fibrillization in Alzheimer's disease

Authors: *C. HEO[1,4], T. HA[2], H.-J. KWAK[3], Y. LEE[2];
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Abstract: <META NAME="author" CONTENT="허채정">**A biophysical marker for Aβ oligomerization and fibrillization in Alzheimer's diseaseChaejeong Heo**[1,2]*, Taewoo Ha[1], Hee-Jin Kwak[1], and Young Hee Lee[11] Center for Integrated Nanostructure Physics (CINAP), Institute for Basic Science (IBS), Suwon 16419, Republic of Korea.[2] Institute for Quantum Biophysics (IQB), Department of Biophysics, Sungkyunkwan University, Suwon 16419, Republic of Korea.*Corresponding to, C.Heo (cjheo@skku.edu) and Y.H. Lee (leeyoung@skku.edu)
Identification of evolution of Aβ proteins from monomer to misfolding fibril and its pathophysiology associated with Aβ structural conformation are not clearly understood until now. The early diagnostic method to monitor the progressive Alzheimer's disease (AD) is a key for therapeutics. Here, we identified the Aβ aggregation states by a biophysical marker (dementia quotient, DQ) depending on light absorption with terahertz (THz) spectroscopy without any label. We developed the solution-based THz measurement system with specially designed solution chamber plate and identified the monomer, oligomer and, fibril states by DQ based on optical conductance change of Aβ structural conformation in real-time. The DQ is extracted the molecular localization constant by modified Drude-Smith model and DQ values are approximately 1 in fibrils, 0.64 in oligomers, and nearly zero in monomers, which is the limit of detection at nanomolar Aβ concentration. In addition, DQ index can measured in various Aβ polymerization medium during and long-term period up to 5 days. This suggests the new biophysical diagnostic method for AD since the DQ index is clearly identified the progressive stage of different Aβ protein structural states, which from monomer evolves to oligomer and reaches to fibrils, by using the label-free THz optical measurement.



Disclosures: C. Heo: None. **T. Ha:** None. **H. Kwak:** None. **Y. Lee:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 DC014296

Title: The role of brain networks in predicting time of progression to dementia in Primary Progressive Aphasia

Authors: M. QUIMBY[1,2], Y. KATSUMI[1,2], D. HOCHBERG[1,2], N. CARVALHO[1,2], M. BRICKHOUSE[1,2], B. DICKERSON[1,2], ***A. TOUROUTOGLOU**[1,2];
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Abstract: BACKGROUND. Patients with Primary Progressive Aphasia (PPA) have a prominent, isolated language deficit during the initial phase of the illness, with relative sparing of other cognitive and affective functions until later in the disease course as well as independent functioning consistent with Cognitive Functional Status of mild cognitive impairment (MCI). As their illness progresses, most PPA patients lose independent functioning due to worsening cognitive-behavioral symptoms and progress to dementia. However, the field does not yet have robust methods for prognostication. The development of quantitative neuroanatomical prognostic biomarkers for loss of independent functioning would be of value in research and clinically (e.g., treatment recommendations, family education). GOALS. The goals of the present study were to (1) examine the role of functional brain networks implicated in executive function, memory, and socioemotional processes in predicting progression to dementia from the MCI stage of PPA, and (2) examine the independent or synergistic contributions of atrophy in the language network compared to atrophy in other networks. METHODS. Fifty PPA patients (17 agrammatic, 14 semantic, and 19 logopenic variant), who underwent a clinical and MRI evaluation at baseline and had at least 6 months of follow-up, were included in this study. For each patient, we measured the time between the first visit and the progression to dementia or last observation. We estimated individual network atrophy using surface-based analyses based on a parcellation of the cerebral cortex into seven canonical functional networks. We performed Cox regression analyses to test the hypothesis that baseline atrophy in networks subserving non-language, cognitive or affective functions would predict progression to dementia. RESULTS. Univariate Cox regression analysis showed that patients with greater atrophy outside the language network, including the left frontoparietal, salience, default mode, and ventral frontotemporal networks, had the highest risk of progression to dementia within a shorter period. Atrophy in the language network was also a predictor, although slightly weaker. CONCLUSIONS. Taken together, these results suggest that baseline cortical atrophy outside the language network is an important predictor of more rapid progression to dementia in a heterogeneous sample of PPA patients. This measure should be included in precision medicine models of prognosis in PPA.

Disclosures: M. Quimby: None. **Y. Katsumi:** None. **D. Hochberg:** None. **N. Carvalho:** None. **M. Brickhouse:** None. **B. Dickerson:** None. **A. Touroutoglou:** None.

Poster

P244. Biomarkers in Neurodegenerative Diseases II

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P244.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UCI MIND/WAM [01-2021]
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NIH/NICHD HDR01064993
NIH/NIA P50AG16573
NIH/NIA P30AG066519
NIH/NIA R01AG21912
NIH/NIA U01AG051412

Title: Estrogens and the brain: investigating the role of estrogen receptors in Alzheimer's Disease and Down Syndrome

Authors: *E. ANDREWS[1], A. MARTINI[2], M. PHELAN[2], E. HEAD[2,3,4];
[1]Dept. of Pathology & Lab. Med., Univ. Of California, Irvine Interdepartmental Neurosci. Program, Irvine, CA; [2]Dept. of Pathology & Lab. Med., Univ. of California, Irvine, Irvine, CA; [3]Dept. of Neurol., [4]Dept. of Pharmacol. & Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: Alzheimer’s disease (AD) is more prevalent in women, which is a critical concern as our aging population increases in number. This prevalence has yet to be characterized in people with Down Syndrome (DS), who are genetically predisposed to developing AD pathology. People with DS, who have full trisomy 21, inevitably develop AD neuropathology by the time they are 40 years of age. However, the initial signs of cognitive decline may not occur until almost a decade later. It is promising to note that up to 15% of elderly people who reach over 60 years of age with DS may not develop signs of dementia. Sex may play a significant role in the age of onset of cognitive decline, rate of progression and extent and type of neuropathology subsequently observed. Women with DS typically experience menopause between 44–46 years of age compared with an average of 51 years of age in the general population. Cognitive function in postmenopausal women with DS is worse than in men with DS at comparable ages, possibly owing to reduced bioavailability of estrogen in these women. Estrogens exhibit marked neuroprotective effects and disruption of its levels could have detrimental effects on the aging brain. Estrogens act on two primary receptors, ERα and ERβ,that are expressed throughout the hippocampus and frontal cortex, suggesting their role in regulating cognition and memory. I. Within the DS population, even fewer studies have investigated the role of estrogens and their receptors in the brain. Thus, lower levels of estrogen receptor expression could be associated with higher levels of AD pathology and neuroinflammation in women with DS compared to men. Our hypothesis is that AD pathology occurs at younger ages in women with DS, is more extensive in women as compared to men, and associated with down-regulation of ERα and ERβ. We acquired loads of estrogen receptors in the human frontal cortex, hippocampus, and posterior

cingulate cortex through immunohistochemical staining and quantification. Serial sections will be stained for tau neurofibrillary tangles and beta-amyloid plaques within a cohort of DS brains. Our study focuses on an area of research that is significantly understudied and critical for our understanding of risk factors for dementia in DS, and proposes a novel hypothesis that estrogen receptors are linked to AD pathology, cerebrovascular pathology and neuroinflammation.

Disclosures: E. Andrews: None. **A. Martini:** None. **M. Phelan:** None. **E. Head:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.01

Topic: C.03. Parkinson's Disease

Support: Spanish Ministry of Science and Innovation, Ref PID2020-120308RB-I00

Title: Blaming neuromelanin for Parkinson's disease: a new animal model of progressive nigrostriatal degeneration based on the AAV-mediated forced expression of tyrosinase in nonhuman primates

Authors: *J. CHOCARRO[1], A. FAJARDO-SERRANO[1], A. J. RICO[1], E. RODA[1], G. ARIZNABARRENA[1], E. LORENZO-RAMOS[1], S. ARRIETA[1], A. PEJENAUTE[1], A. HONRUBIA[1], A. VAZQUEZ[2], A. I. RODRIGUEZ-PEREZ[3], J. L. LABANDEIRA-GARCÍA[3], J. L. LANCIEGO[1]; [1]Neurosciences, CIMA - Univerisdad de Navarra, Pamplona, Spain; [2]Neurosurg., Servicio Navarro de Salud - Osasunbidea, Pamplona, Spain; [3]Res. Ctr. for Mol. Med. and Chronic Dis. (CIMUS), Univerisdad de Santiago de Compostela, Santiago de Compostela, Spain

Abstract: Neuromelanin (NMel) is a dark pigment characteristic of dopaminergic neurons in the human substantia nigra pars compacta (SNpc). Levels of NMel in humans are very high, thus enabling a direct macroscopical visualization of the SNpc. By contrast, most commonly used laboratory animals lack NMel. Although aged non-human primates (NHPs) also accumulate NMel over time, these levels are too low to be observed to the naked eye. Here we took advantage of AAVs coding for human tyrosinase (the enzyme mediating NMel synthesis) for driving a time-dependent NMel accumulation in dopaminergic neurons of the SNpc in NHPs up to similar levels as observed in elderly humans. Furthermore, NMel accumulation induced a synucleinopathy mimicking intracellular inclusions typically observed in patients suffering from Parkinson's disease (PD) known as Marinesco bodies (MBs; intranuclear aggregates) and Lewy bodies (LBs; intracytoplasmic inclusions). In parallel, a progressive nigrostriatal degeneration is observed in NMel-expressing dopaminergic neurons, together with a pro-inflammatory phenotype mediated by activated microglial cells and perivascular macrophages trying to digest extracellular NMel resulting from dopaminergic cell death. In summary, the conducted strategy resulted in the characterization and validation of a new NHP model of PD matching the known neuropathology of this disorder with unprecedented accuracy. Finally and most importantly, evidence was provided showing that intracellular aggregation of alpha-synuclein is triggered by NMel accumulation, therefore opening new interesting research avenues in the field of PD. In particular, any therapeutic approach intended to

decrease NMel levels may provide appealing choices for the successful implementation of disease-modifying therapeutics for PD.

Disclosures: J. Chocarro: None. **A. Fajardo-Serrano:** None. **A.J. Rico:** None. **E. Roda:** None. **G. Ariznabarrena:** None. **E. Lorenzo-Ramos:** None. **S. Arrieta:** None. **A. Pejenaute:** None. **A. Honrubia:** None. **A. Vazquez:** None. **A.I. Rodriguez-Perez:** None. **J.L. Labandeira-García:** None. **J.L. Lanciego:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.02

Topic: C.03. Parkinson's Disease

Title: AAV-induced overexpression of E46K-like α-synuclein mutants in substantia nigra results in nigrostriatal degeneration and motor dysfunction: a new rat model for Parkinson's disease

Authors: *Y. PI[1], *Y. PI[1], R. DRISCOLL[1], C. EHRENFELS[1], R. MASSOL[1], M. LIU[2], F. DU[2], M. H. ARNOLD[1];
[1]Biogen Inc, Cambridge, MA; [2]FD NeuroTechnologies Inc, Columbia, MD

Abstract: α-synuclein (αSYN) is a synaptic protein generally acknowledged to be linked to the etiopathogenesis of Parkinson's disease (PD). Over-expression of human A53T αSYN (hαSYN A53T) with adeno-associated viral vectors (AAV) reproducibly resulted in degenerative changes in substantia nigra and neuromotor functional impairment in rodents and non-human primates (NHP)(Trends in Neurosciences, 2016, 39(11):751; PLOS ONE 2016; Nature Rev Neurosci 2017, 18: 515). Transgenic mice expressing human αSYN E46K also exhibited motor symptoms and moderate loss of nigrostriatal dopaminergic neurons at 6 months of age (Neuron 2018; 100 (1): 75-90.). Here we report a new rat model of PD by expression of human E46K αSYN mutation or amplified homologous E→K mutation (E35/46/61K) in unilateral substantia nigra (SN) via a chimeric AAV1/2 viral vector. Rats expressing hαSYN E46K showed virus dose-and time-dependent progressive neuromotor dysfunction, assessed weekly using cylinder test, while rats with sham surgery exhibited no change in neuromotor function. We also observed AAV-hαSYN E46K viral dose- and time-dependent loss of tyrosine hydroxylase positive (TH+) neurons in the SN of rats within 5 weeks post-stereotaxic surgery. Intracellular aggregated αSYN inclusions were observed and pS129 α-SYN was also stained positive in the TH+ neurons of SN in these rats. Total microglia and astrocytes were significantly increased in ipsilateral SN compared to the corresponding region in contralateral SN, suggesting activation and proliferation of microglia and astrocytes in response to aggregation of human mutant αSYN in TH+ neurons. TH+ terminals showed degenerative changes in the ipsilateral striatum, accompanied by inflammatory gliosis. These changes were not observed in the SN of sham control or AAV-mCherry rats. Rats injected with AAV E46K αSYN homologous E35/ 46/61K mutation exhibited similar neuromotor dysfunction and nigrostriatal neurodegeneration. We conclude that AAV-mediated-expression of hαSYN E46K or hαSYN E35/46/61K in the SN of rats can recapitulate the primary pathological hallmarks of PD accompanied by progressive

neuromotor deficits within a relatively short time. This AAV- hαSYN rat model provides advantages over transgenic models for assessing efficacy of novel drug candidates that may modify the progression of PD.

Disclosures: Y. Pi: None. **R. Driscoll:** None. **C. Ehrenfels:** None. **R. Massol:** None. **M. Liu:** None. **F. Du:** None. **M.H. Arnold:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.03

Topic: C.03. Parkinson's Disease

Support: Department of Defense
Center for Development and Behavioral Neuroscience

Title: Characterization of Striatal Dopamine Dynamics in the Rat Alpha-Synuclein Pre-Formed Fibril Model of Parkinson's Disease

Authors: *A. CENTNER[1], I. DEL PRIORE[1], M. COYLE[1], J. GLINSKI[1], S. COHEN[1], M. TERRY[1], N. E. CHAMBERS[1], J. PATTERSON[3], C. KEMP[4], A. STOLL[4], K. LUK[6], K. MILLER[5], C. E. SORTWELL[5], C. R. BISHOP[2];
[2]Psychology, [1]Binghamton Univ., Binghamton, NY; [3]Michigan State Univ., Grand Rapids, MI; [4]Michigan State Univ., East Lansing, MI; [5]Translational Sci. and Mol. Med., Michigan State Univ., Grand Rapids, MI; [6]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Parkinson's Disease (PD) is a movement disorder characterized by striatal terminal loss and progressive death of dopamine (DA) neurons within the substantia nigra. Abnormal, misfolded accumulation of the synaptic protein alpha-synuclein (α-syn) has been implicated in the cellular dysfunction that precedes neurodegeneration and is a hallmark pathological marker of PD. Given the role of endogenous α-syn in neurotransmission and reuptake mechanisms, these abnormal α-syn aggregates have potential to disrupt DA dynamics and accelerate neuronal death. A recent and unique rodent model utilizes recombinant α-syn proteins that form short fragments which, when introduced to brain, trigger the conversion of healthy endogenous α-syn to its pathological form. This pre-formed fibril (PFF) rat model of PD replicates the progressive accumulation of α-syn aggregation, neuronal loss and motor dysfunction observed in PD, however α-syn-aggregate-induced alterations in basal and evoked DA release remain to be described. In the present study, adult male Sprague Dawley rats received unilateral injection of mouse α-syn PFFs or PBS, as control, at 2 striatal sites. In a between subjects' design, at either 4- or 8-months post-surgery, animals underwent *in vivo* microdialysis to evaluate basal extracellular striatal DA and metabolite levels, DA turnover, local KCl-evoked striatal DA release, and systemic L-DOPA-induced DA release. Motor impairments were assessed with forepaw adjusting steps test (FAS) the days prior to microdialysis testing. Baseline DA levels in all age and brain treatment groups were stable and did not differ across time. Interestingly, PFF-treated animals displayed lower DA evoked responses, showing significant deficits in neurotransmission which worsened further with increasing post-infusion. Acute L-DOPA administration yielded an equivalent overall rise in DA in both PFF and control rats at the 4-month

time point; however, at the 8-month time point PFF rats displayed lower L-DOPA induced DA levels. In addition, motor impairment was not detected until the 8-month time point. Ongoing postmortem histological analysis will examine nigral dopamine neuron phenotype and survival at both the 4- and 8-month time point. Taken together, the present study provides evidence that synucleinopathy in the nigrostriatal system in the PFF model results in progressive changes in DA dynamics suggesting early deficits in DA release. The rat PFF model offers researchers a platform to examine mechanisms behind pathological α-syn associated degeneration and neurotransmission dysfunction and test novel therapies at early timepoints when deficits are emerging.

Disclosures: A. Centner: None. **I. Del Priore:** None. **M. Coyle:** None. **J. Glinski:** None. **S. Cohen:** None. **M. Terry:** None. **N.E. Chambers:** None. **J. Patterson:** None. **C. Kemp:** None. **A. Stoll:** None. **K. Luk:** None. **K. Miller:** None. **C.E. Sortwell:** None. **C.R. Bishop:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.04

Topic: C.03. Parkinson's Disease

Support: Brain/MINDS

Title: Use of an infrared-monitored staircase device in analyzing symptom progression of preformed fibril- and virus vector-induced alpha-synuclein overexpression in the common marmoset

Authors: *L. R. UENO-NIGH, T. KANEKO, T. OISHI, K. INOUE, M. TAKADA;
Systems Neurosci., Kyoto Univ., Inuyama, Japan

Abstract: Previous research on Parkinson's disease (PD) common marmoset models has used the staircase task to quantify reaching and grasping ability. In the staircase task, marmosets are trained to reach with either hand to retrieve food rewards from a five-step staircase. Following induction of hemiparkinsonian symptoms, deterioration of marmosets' motor abilities can be measured based on the speed and accuracy of their retrievals. Advantages of this task include ease of training and dissociation of the spatial awareness from motor ability. However, manual recording and analysis of the task-related behavior is time-consuming and prone to human error, which makes it unsuited to frequent long-term use. As such, we newly developed a staircase device that automatically monitors the retrieval of reward from each step using infrared beams. Results are both easily obtained and accurate, with sensor data found to be consistent with retrievals recorded by high-speed video camera.
PD is known to be caused by aggregation of alpha-synuclein (α-syn) fibrils, which can be induced to create a PD model to test with the staircase device. However, injection of preformed α-syn fibrils alone, while promising for the study of synucleinopathy progression, does not seem to cause significant symptoms beyond moderate dopaminergic cell death. On the other hand, overexpression of α-syn using adeno-associated virus (AAV) vectors progresses slowly, making it inconvenient for research. A combined injection of AAV vector expressing α-syn and preformed α-syn fibril seeds into the substantia nigra pars compacta (SNc) has been found to exert synergistic effects, leading to more efficient and

drastic degeneration of dopaminergic cells.
Using advantages of the infrared-monitored staircase device, such as its ability to handle more frequent testing with finer resolution of retrieval times, we set out to precisely analyze the progression of symptoms manifested in marmosets exhibiting vector- and fibril-induced synucleinopathy. Results are currently pending and will be discussed in the presentation.

Disclosures: L.R. Ueno-Nigh: None. **T. Kaneko:** None. **T. Oishi:** None. **K. Inoue:** None. **M. Takada:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.05

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS109287

Title: Local overexpression of alpha-synuclein in the mouse prefrontal cortex leads to increased dendritic spine density and alters performance on cognitive behavioral tasks

Authors: P. J. BOSCH[1,3], G. DE CHOISY[2], R. C. COLE[2], S. NATHWANI[2], L. WAGNER[2], A. YOKIMISHYN[2], E. BAGNALL[2], Y. KIM[2], *G. M. ALDRIDGE[1,3];
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Abstract: Lewy Body Dementias (LBD), including Parkinson's disease dementia and Dementia with Lewy Bodies, are characterized by widespread intracellular alpha-synuclein (alphaSyn) protein deposits, including in the cortex. LBDs cause cognitive changes, including abnormalities in executive function and cognitive fluctuations. The cause of these symptoms is still unclear, but it is known that genetic duplication of alphaSyn increases the risk of developing Lewy Body disease. One hypothesis posits that accumulation of alphaSyn in the cortex perturbs synaptic and cellular function. To investigate the effects of cortical alphaSyn, viral overexpression of human alphaSyn protein confined to the prefrontal cortex (PFC) was employed. We used *in vivo* 2-photon microscopy, in conjunction with intracranial viral injections, cranial window implantation and head-fixed behavioral paradigms to assess the cellular and behavioral consequences of alphaSyn overexpression for an extended period. Live-imaging studies focused on dendritic spine density of Layer V pyramidal neurons using *Thy1-YFP-H* transgenic mice and calcium imaging of Layer II/III neurons using *Thy1-GCaMP6s* transgenic mice. In addition, we developed a tactile head-fixed behavior where mice are required to locate a correct tactile cue to receive a liquid sucrose reward. After cranial window implant and initial imaging, male and female mice were randomized to injection with virus coding for alphaSyn or mCherry alone. Imaging was conducted in awake mice in one-week intervals for 2 months to observe dynamic changes in dendritic spines. We found an increase in the relative dendritic spine density in mice with local overexpression of alphaSyn, beginning at 4 weeks after injection. The density changes were secondary to transient changes in the formation rate of spines 3-4 weeks after injection, with no change in elimination rate. In contrast to alphaSyn overexpression in other brain regions, our results suggest that PFC local overexpression does

not cause spine loss over a two-month period. Using our head-fixed behavioral task, we found that mice with local alphaSyn overexpression tended to learn a simple tactile discrimination task faster than mCherry-injected control animals ($p = 0.054$); however, they perform more poorly than controls with increasing task complexity. To apply these techniques to an alternate animal model for LBD, our ongoing studies are investigating the injection of human preformed fibrils, with efforts to understand progression of LBD via alphaSyn aggregate spread throughout the brain and the subsequent neurological effects on our cellular and behavioral paradigms.

Disclosures: P.J. Bosch: None. **G. de Choisy:** None. **R.C. Cole:** None. **S. Nathwani:** None. **L. Wagner:** None. **A. Yokimishyn:** None. **E. Bagnall:** None. **Y. Kim:** None. **G.M. Aldridge:** None.

Poster

P257. Alpha-Synuclein: Models II

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.06

Topic: C.03. Parkinson's Disease

Support: NSF-GFRP DGE:1746932

Title: Astrocytic Mitochondrial Calcium Dysregulation in the Striatum of an Alpha-synuclein Overexpression Model of Early-Stage Parkinson's Disease.

Authors: *T. HUNTINGTON, M. VALLE, R. SRINIVASAN;
Texas A&M Inst. for Neurosci., Texas A&M Univ., Bryan, TX

Abstract: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder affecting dopaminergic neurons in the nigrostriatal pathway. Recently, astrocyte dysfunction has been linked to early stages of neurodegeneration both in PD and other neurodegerative diseases; however, the underlying mechanisms linking astrocyte dysfunction with PD are not yet fully understood. Here, we study mitochondrial dysfunction in astrocytes of the dorsal lateral striatum (DLS) in a mouse model of early PD. To create this model, we performed a unilateral stereotaxic injection of adeno-associated virus (AAV) overexpressing alpha-synuclein (α-syn) in the substantia nigra pars compacta (SNc). When compared to mCherry-injected control mice, 4.5 months of AAV-mediated overexpression of α-syn was associated with a dysregulation of dopamine release and metabolism in the striatum. AAV-expressed human α-syn propagated from the SNc injection site to tyrosine hydroxylase (TH) positive terminals within the DLS, but induced minimal changes in TH content within the SNc. Using a previously characterized tool, we compared the kinetics of spontaneous Ca^{2+} influx between DLS astrocytic mitochondria from α-syn expressing mice and mCherry expressing control mice. We observed specific changes in spontaneous Ca^{2+} events between α-syn and mCherry overexpressing mice. Astrocytic mitochondrial Ca^{2+} influx also varied in response to dopamine receptor agonists. Together these data suggest that significant pathological alterations in spontaneous Ca^{2+} influx events occur in astrocytic mitochondria during early stages of PD.

Disclosures: T. Huntington: None. **M. Valle:** None. **R. Srinivasan:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.07

Topic: C.03. Parkinson's Disease

Support: NIH Grant 5R21NS098006-02

Title: Keap1 accumulation-induced defects in mitochondria drive dopaminergic neuron loss in VPS35 D620N transgenic mice

Authors: *S. MA, H. KO;
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Abstract: Keap1 accumulation-induced defects in mitochondria drive dopaminergic neuron loss in VPS35 D620N transgenic mice Shi-Xun Ma[1,2,†,] Bo Am Seo[1,2], Seung-Hwan Kwon[1,2], Senthilkumar S. Karuppagounder[1,2], Han Seok Ko[1,2*] [1]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America [2]Neurodegeneration and Stem Cell Programs, Institute for Cell Engineering, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America The vacuolar protein sorting 35 (VPS35) D620N mutation is known to be the major genetic cause of the late-onset, autosomal dominant familial Parkinson's disease (PD). However, the effects of VPS35 D620N on the function and survival of dopamine (DA) neurons still remains unclear. To address this, we developed tyrosine hydroxylase (TH) promoter-controlled tetracycline VPS35 D620N transgenic (Tg) mice expressing human VPS35 D620N mutation selectively in DA neurons. Behavioral, pathological, and biochemical analyses revealed that the VPS35 Tg mice recapitulated cardinal features of PD, which included an age-dependent substantial loss of DA neurons in the substantia nigra compacta and locus coeruleus and significant reductions in the levels of DA and its metabolites in the striatum. The loss of DA neurons in the VPS35 D620N Tg mice was accompanied by motor deficits, neuroinflammation, accumulation of pS129 α-synuclein and α-synuclein aggregates, and increased Tau phosphorylation in the midbrain. VPS35 D620N expression led to mitochondrial dysfunction, which included reduced mitochondria size and complex I activity, and increased reactive oxygen species (ROS) production, which was prevented by a short hairpin RNA knockdown of Kelch-like ECH-associated protein 1 (Keap1), leading to the restoration of the nuclear factor erythroid 2-related factor 2 (Nrf2) activity in SH-SY5Y cells . We are currently determining the neuroprotective effect of Keap1 knockdown in the DA neurodegeneration in the VPS35 D620N Tg mice. Taken together, this VSP35 D620N mouse model provides a valuable platform in deciphering the molecular mechanisms underlying VPS35-associated PD and for testing neuroprotective therapies. Additionally, the identification of Keap1 provides a molecular mechanism for DA neurodegeneration due to VPS35 D620N mutation in PD.

Disclosures: S. Ma: None. **H. Ko:** None.

Poster

P257. Alpha-Synuclein: Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P257.08

Topic: C.03. Parkinson's Disease

Support: NHI Grant HL055374
APDA

Title: Tissue plasminogen activator promotes dopaminergic neuron degeneration in an α-synuclein based mouse model of PD via a non-proteolytic interaction with the N-methyl-D-aspartate receptor

Authors: *D. TORRENTE[1], D. A. LAWRENCE[2];
[1]Dept. of Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Intrnl. Medicine, Div. of Cardiovasc. Med., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN). The causes of PD are unknown, however, there is evidence supporting the involvement of the immune response and excitotoxicity in the degeneration of DA neurons. Recently, we found that the protease, tissue plasminogen activator (tPA), is highly expressed in the SN. In the central nervous system, tPA is considered a neuromodulator, regulating events, such as excitotoxicity and microglia activation; events associated with DA neuron degeneration in PD. We found that in the SN of naïve WT mice, tPA colocalizes with the vesicular GABA transporter, a presynaptic marker of GABAergic axons. Retrograde tracing of axons innervating the SN using Cholera Toxin B in combination with a tPA-β-galactosidase reporter mouse showed that tPA-expressing neurons innervating the SN were mostly located in the striatum. This suggests that striatal neurons expressing tPA could affect DA neuron survival in the SN. To test this, we use an α-synuclein-based mouse model of PD, where a recombinant adeno-associated virus expressing human α-synuclein (AAV2-hα-syn) was injected into the SN. Mice lacking tPA ($tPA^{-/-}$) showed significant protection of DA neurons and recovery of lateralized sensory-motor integration in a corridor task compared to WT mice after AAV2-hα-syn injection. RNA-seq analysis in WT and $tPA^{-/-}$ mice after AAV2-hα-syn injection showed that overexpression of hα-syn in WT mice significantly upregulates the expression of genes involved in antigen processing and presentation such as *Ctss*, *b2m* and *FcgRIII*. In contrast, in $tPA^{-/-}$ mice expression of these genes was downregulated. RNA-seq data was validated by qPCR and immunohistochemistry. Mechanistically, injection of AAV2-hα-syn into mice overexpressing proteolytically-inactive tPA (tPA Ala) resulted in a significant increase in the degeneration of DA neurons compared to WT or $tPA^{-/-}$ mice. Using a neutralizing antibody that blocks the interaction of tPA with the N-methyl-D-aspartate receptor (NMDAR; Glunomab, a generous gift from Denis Vivien, Université de Caen Basse-Normandie), we found that Glunomab delivered directly into the SN protected DA neurons and significantly reduced the expression of MHC class I in the SN of tPA Ala mice compared to tPA Ala vehicle-treated mice. Overall, we discover a new population of tPA-expressing neurons in the striatum that innervates the SN and showed that tPA may play a direct role in DA neuron survival in the context of α-synuclein neurotoxicity via a non-proteolytical interaction involving the NMDAR and the upregulation of the MHC I-mediated immune response.

Disclosures: D. Torrente: None. **D.A. Lawrence:** None.

Poster

P257. Alpha-Synuclein: Models II

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Program #/Poster #: P257.09

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS069625
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Title: In vivo aggregation of presynaptic alpha-synuclein is not influenced by its phosphorylation at serine-129

Authors: L. J. WESTON[1], Z. T. COOK[1], T. STACKHOUSE[2], M. K. SAL[1], B. I. SCHULTZ[3], Z. J. C. TOBIAS[3], V. R. OSTERBERG[1], N. L. BROCKWAY[3], **S. SINGH**[3], G. GLOVER[3], *V. UNNI[1], T. A. WEISSMAN[3];
[1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Oregon Hlth. & Sci. University, Vollum Institu, Portland, OR; [3]Lewis & Clark Col., Portland, OR

Abstract: Alpha-synuclein is a presynaptic protein that abnormally aggregates in Parkinson's disease and other neurodegenerative diseases. Both the precise mechanisms that trigger alpha-synuclein aggregation and the role of synuclein pathology in disease progression are largely unknown. Using an in vivo zebrafish model to transiently express different forms of human alpha-synuclein, we show that alpha-synuclein localizes to presynaptic terminals and is phosphorylated at serine-129 by an endogenous polo-like kinase, as in mammals. By optimizing the fluorescence recovery after photobleaching (FRAP) technique and exploiting the visual advantages of transparency during zebrafish development, we were able to measure the levels of aggregation at presynaptic terminals. Mutations at serine-129 suggest that phosphorylation at this site alone does not directly alter alpha-synuclein mobility. Our results demonstrate that human alpha-synuclein can be expressed successfully in zebrafish and that disease-relevant post-translational modifications occur within neurons. Zebrafish provide a powerful model organism to study in vivo alpha-synuclein function and aggregation, and may help lead to therapeutic advances for neurodegenerative diseases.

Disclosures: L.J. Weston: None. **Z.T. Cook:** None. **T. Stackhouse:** None. **M.K. Sal:** None. **B.I. Schultz:** None. **Z.J.C. Tobias:** None. **V.R. Osterberg:** None. **N.L. Brockway:** None. **S. Singh:** None. **G. Glover:** None. **V. Unni:** None. **T.A. Weissman:** None.

Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.01

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS107318

Title: Soluble lymphocyte activation gene-3 Contributes to α-Synucleinopathy in the early Parkinson's Disease

Authors: *N. WANG[1,2], Y. KIMURA[1,2], S. BRAHMACHARI[1,2], L. ROSENTHAL[1], T. DAWSON[1,2], V. DAWSON[1,2], X. MAO[1,2];
[1]Dept. of Neurol., [2]Inst. for Cell Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The pathologic accumulation and aggregation of α-Synuclein (α-Syn) underlies Parkinson's disease (PD). We have recently identified lymphocyte activation gene-3 (LAG3) as a receptor that mediates pathologic α-Syn cell-to-cell transmission (Mao et al., 2016). Serum and cerebrospinal fluid (CSF) soluble LAG3 (sLAG3) levels have been demonstrated to be potentially associated with PD development and clinical phenotype. However, little is known about the mechanism of sLAG3 on the development of α-Synucleinopathy in PD. Here, we detected sLAG3 in the CSF of PD patients from the Johns Hopkins PDBP cohort by using ELISA. We found sLAG3 is significantly lower in the CSF of PD patients than that in control, which is consistent with previous study. Then, we purified the sLAG3 protein and determined the effect of sLAG3 on the endocytosis of α-Syn-biotin PFF in cultured cortical neurons. The results showed that sLAG3 can promote the endocytosis of α-Syn-biotin PFF in neurons. Given that a low dose of sLAG3 (α-Syn-biotin PFF / sLAG3 ratio > 10) is enough for facilitating α-Syn PFF transmission in neurons, sLAG3 may play an important regulatory role in PD progression. Accumulating evidence indicates that LAG-3 is an inhibitory co-receptor and plays pivotal roles in autoimmunity, sLAG3 may also be involved in inflammation caused by α-Syn PFF in the brain. To determine whether sLAG3 mediates PFF-induced activation of microglia, in the presence or absence of purified sLAG3, we examined mRNA levels of pro-inflammatory cytokines by Quantitative PCR and examined secreted cytokines in microglial conditional medium from PFF- or PBS- treated microglia with commercial protein multiplex arrays. We found that in the presence of sLAG3, PFF-treated microglia showed higher levels of cytokines relative to the PFF only group, while sLAG3 had no significant effect on PBS-treated microglia. The results indicate that the enhancement of PFF-induced microglia activation by sLAG3 may cause excessive immunity of microglia and promote the deterioration of α-Synucleinopathy. We also assessed α-Syn-induced pathology by monitoring the pS129 level in cultured neurons with sLAG3. We found that sLAG3 can also promote PFF-induced pS129 pathology, and showed an enhanced effect with increasing sLAG3 concentration. We propose that not only membrane-bound receptor LAG3, sLAG3 is also involved in α-Synucleinopathy and non-motor symptoms (e.g. sleep disorders) in PD. These microglial and neuronal response in the presence of sLAG3 may further interpret that sLAG3 may serve as a biomarker and enhancer of α-Synucleinopathy early during PD development.

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Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.02

Topic: C.03. Parkinson's Disease

Support: NINDS 1R01NS117968

Title: Role of NACore threonines in the aggregation and toxicity of human alpha-synuclein

Authors: *N. NATHAN KOCHEN, D. SEANEY, V. VASANDANI, E. E. LIAO, A. R. BRAUN, J. SACHS;
Biomed. Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Understanding the key molecular interactions that lead to alpha-synuclein (aSyn) oligomer and fibril formation are critical for bridging the knowledge gap between conformation and toxicity. Our previous work demonstrated that crystallographic waters within the aSyn NACore stabilize the fibrillar structure, with water-Thr75 interactions forming a water-wire that spans throughout the Tuttle et al. Greek Key aSyn fibril. We hypothesize that these water-threonine interactions are important in the fibrillogenesis cascade of aSyn.
Recent publications, totaling more than 10 new aSyn fibril structures, have allowed us to explore this water-stabilization phenomenon in an array of aSyn conformations. In this study, we show that Thr75, located in the amyloid-prone NAC core, interacts with water molecules to form a water-threonine network in the 2018 Li et al. Rod and 2020 Schweighauser et al. Multiple System Atrophy solved structures via all atom molecular dynamics simulations. Using recombinant protein, we show that mutating Thr75 to an alanine residue (T75A) - and thus eliminating its side-chain hydrogen bonding ability - leads to decreased monomer-only and pre-formed fibril seeded aggregation monitored via Thioflavin T.
Future experiments will assess the effect of the T75A mutation on *in cell* aggregation as measured by Förster Resonance Energy Transfer (FRET) measurements of our GFP-aSyn/RFP-aSyn fusion constructs. Finally, we will determine whether the decrease in aggregation of the T75A mutant leads to an increase in cytotoxicity relative to WT aSyn via overexpression in neuronal cell lines.

Disclosures: N. Nathan Kochen: None. **D. Seaney:** None. **V. Vasandani:** None. **E.E. Liao:** None. **A.R. Braun:** None. **J. Sachs:** None.

Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.03

Topic: C.03. Parkinson's Disease

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Rapid Response Innovation Award from MJ Fox Foundation

University of Miami Brain Endowment Bank
UCLA Human Brain and Spinal Fluid Resource Center

Title: Biological sex-dependence of DNA repair protein APE1 in mice and humans with alpha-synucleinopathy

Authors: *K. M. MINER[1], T. N. BHATIA[1], A. S. JAMENIS[1], R. N. CLARK[1], N. ABRAHAM[1], D. RAJASUNDARAM[2], S. SAUVAIGO[3], R. STETLER[4], J. CHEN[4], L. H. SANDERS[5], K. C. LUK[6], R. K. LEAK[1];
[1]Div. of Pharmaceut. Sci., Duquesne Univ., Pittsburgh, PA; [2]Dept. of Pediatrics, Rangos Res. Ctr., UPMC Children's Hosp. of Pittsburgh, Pittsburgh, PA; [3]LXRepair, Grenoble, France; [4]Dept. of Neurol., Univ. of Pittsburgh, Pittsburgh, PA; [5]Dept. of Neurol., Duke Univ. Sch. of Med., Durham, NC; [6]Dept. of Pathology and Lab. Med., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Lewy body disorders are characterized by proteostatic and redox disequilibrium, leading to deposition of α-synuclein in hallmark inclusions and oxidative damage to DNA. One common pathway for repair of oxidative DNA damage is base excision repair (BER), which involves the coordinated activity of several enzymes, including apurinic/apyrimidinic endonuclease 1 (APE1). Here, we report that knockdown of APE1 with two independent shRNA sequences or inhibition of APE1 DNA repair activity increased inclusions bearing pathologically-phosphorylated α-synuclein (pSer129) in preformed fibril-treated primary hippocampal cultures. Second, we examined APE1 expression in a mouse model of limbic-predominant α-synucleinopathy, in which α-synuclein fibrils are infused into the olfactory bulb/anterior olfactory nucleus (OB/AON). Six months later, we observed a fibril-induced decrease in APE1 expression in the brains of male mice and an increase in females. Similar patterns were noted for APE1 mRNA expression. Third, we demonstrated that the loss of APE1 in fibril-infused male mice *in vivo* is mediated by oxidative stress, as APE1 loss was abolished by dietary administration of the antioxidant N-acetylcysteine. Fourth, OB/AON tissues harvested from fibril-infused male mice displayed higher cleavage of synthetic DNA lesions on a novel biochip than tissues collected in parallel from fibril-infused female mice. However, OB/AON tissues harvested from fibril-infused female mice had higher DNA repair activity on the biochip compared to males. Assessments of open field activity measures and sucrose preference revealed a negative behavioral impact of α-synuclein fibril infusions in male but not female mice. Finally, APE1 expression was quantified in the human olfactory bulb and amygdala harvested from control subjects or patients with Lewy body disorders. Similar to fibril-infused male mice, men with Lewy body disorders displayed lower APE1 expression compared to women with Lewy body disorders. These findings reveal a sex-biased impact of limbic α-synucleinopathy on APE1 expression and function.

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Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

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Program #/Poster #: P258.04

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation
NIH/NINDS R03NS108229
Branfman Family Foundation
Indiana Clinical and Translational Sciences Institute (CTSI)

Title: Impact of post-translational modifications on membrane-induced alpha-synuclein aggregation in synucleinopathy disorders

Authors: *M. GUZMAN SOSA[1], O. ALI[1], S. DUTTA[1], A. SADEK[2], M. M. K. SYED[2], H. LASHUEL[2], J.-C. ROCHET[1];
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Abstract: Alpha-synuclein (aSyn) is a presynaptic protein that forms aggregates in the brains of individuals with Parkinson's disease (PD) and other synucleinopathy disorders. aSyn is thought to exist as a natively unfolded protein in the cytosol, but upon interacting with anionic lipids on cellular membranes it adopts an amphipathic helical structure that is likely critical for the protein's function in modulating synaptic vesicle release. Data from our group and others suggest that the aggregation of membrane-bound aSyn plays a central role in the protein's neurotoxicity in PD via a mechanism involving vesicle disruption. Increasing evidence suggests that the mechanism of membrane-induced aggregation is distinct from the more extensively studied process of aSyn aggregation in the absence of membranes. Although various post-translational modifications (PTMs) of aSyn identified in cell culture, animal models, or human brain have been shown to modulate aSyn aggregation in the absence of lipids, little is known about the effects of PTMs on membrane-induced aSyn self-assembly. We hypothesize that certain PTMs promote the protein's aggregation at the surface of phospholipid membranes, resulting in enhanced aSyn neurotoxicity, based on evidence that some PTMs alter the conformation of membrane-bound aSyn and/or perturb aSyn-membrane interactions. To address this hypothesis, aSyn variants with N- and C-terminal truncations previously identified in human brain were characterized in terms of their relative propensities to undergo membrane-induced self-assembly and elicit vesicle disruption. We found that aSyn variants with C-terminal truncations underwent more extensive oligomerization and accelerated fibrillization (yielding fibrils with altered morphologies visualized by EM) compared to WT aSyn when incubated with phospholipid vesicles at a low pH mimicking the acidic conditions of endocytic compartments. Moreover, the rate of aSyn-mediated vesicle disruption at pH 7 (relevant to cytosolic conditions) increased with the extent of the C-terminal truncation. N-terminal aSyn truncation mutants also formed fibrils more rapidly than WT aSyn in the presence of vesicles at low pH but had a reduced ability to elicit membrane permeabilization at pH 7. Current efforts are focused on characterizing our panel of aSyn truncation variants in terms of aggregation propensity and toxicity in neuronal cell culture models. The results of these studies will provide new insights into the role of aSyn PTMs and membrane-induced aggregation in the pathology of synucleinopathy disorders, setting the stage for developing therapies targeting aSyn in the brains of patients.

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Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

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Program #/Poster #: P258.05

Topic: C.03. Parkinson's Disease

Support: EMR/2018/000336

Title: Effect of lysine-directed PTMs on KTKEGV motifs in α-synuclein protein.

Authors: *J. GADHAVI, S. SHAH, S. GUPTA;
IIT Gandhinagar, Gandhinagar, India

Abstract: Parkinson's disease (PD) is one of the critical neuro-degenerative diseases. PD causes loss of dopaminergic neurons in the substantia nigra. The two major pathological hallmarks of PD include Lewy bodies and Lewy neurites in which the aggregated α-synuclein protein is found to be of major constituent. The α-synuclein protein is a 140 amino acid long natively unfolded protein and has 7 consensus imperfect repeats (KTKEGV) present in its sequence. In literature, it has been reported that the KEKEGV motif plays a crucial role in maintaining the native structure of α-synuclein. Also, the various post-translational modifications (PTMs) such as methylation, glycation, ubiquitination, sumoylation, acetylation, and carbamylation on the lysine site have been found to have a role in α-synuclein protein aggregation in PD. In the current work, we wanted to identify the role of a charge neutralizing PTMs (acetylation and carbamylation) on KTKEGV motif derived peptides present in α-synuclein protein and α-synuclein itself. Therefore, we performed in-situ acetylation and carbamylation modification on various KTKEGV motif-derived peptides are present in α-synuclein protein and α-synuclein. These peptides were synthesized by Fmoc based solid-phase peptide synthesis chemistry and further characterized by LC-MS. After synthesis, their aggregation kinetics behavior was studied by inducing PTMs (acetylation and carbamylation). Here, we observed the distinct aggregation kinetics pattern in various peptides of α-synuclein which was confirmed by biophysical assays such as ThT assay, ANS assay, congo-red birefringence microscopy, AFM, and SEM. We further identified that the carbamylation and acetylation played a site-specific role and induced amyloidogenesis in specific sites, while in other sites; it did not show aggregation. Our findings suggest that these site-specific charge neutralization by post-translational modification act as a seed for modulating α-syn protein aggregation. These findings could help to identify the site-specific role of PTMs in inducing the PD.

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Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.06

Topic: C.03. Parkinson's Disease

Support: NuRhoPsi
Lake Forest College

Title: Inisght into Parkinson's Disease from Yeasts: combined impact of genetic mutations and covalent modifications on alpha-synuclein

Authors: *C. T. BORLAND[1], Y. P. GANEV[1], C. N. MWALE[1], A. E. GRASSEL[1], F. BERTOLOTTI[1], R. J. OSSELBORN[1], T. C. NASSUNA[1], B. T. ZABAT[1], S. K. DEBBURMAN[2];
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Abstract: Parkinson's Disease (PD) is a human fatal and incurable neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy bodies, which are composed of misfolded α-synuclein protein. α-Synuclein is a highly post-translationally modified protein in both healthy and diseased states. Modifications on it include phosphorylation, nitration, SUMOylation, acetylation, and glycation. Regulation by lipids is also suggested to modify its toxicity. The toxicity of wildtype α-synuclein and six well-known mutant versions linked with familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) is well-modeled in budding yeast systems. In contrast, the toxicity mechanisms of three newer PD-linked α-synuclein mutants (A18T, A29S, and A53V) is poorly understood; particularly, the impact of post-translational modifications and lipid homeostasis on their toxicity is unknown. Using our lab's budding yeast model of PD, we investigated the toxicity potential of these three new mutants by assessing the impact of the mutations on yeast growth, protein localization, and expression in various yeasts strains. We report that: 1) All three mutants are toxic to yeast, but to different degrees and, surprisingly, less than wild-type α-synuclein; 2) Yeast strains with altered triglycerides reduce α-synuclein toxicity; 3) Yeasts strains with enhanced acetylation or reduced glycation environments rescue α-synuclein toxicity; 4) and, finally, enhanced SUMOylation is protective against α-synuclein toxicity. This study expands the evaluation of genetic α-synuclein mutants linked with PD in yeast models and supports the relevance of covalent modifications and lipid homeostasis on α-synuclein toxicity.

Disclosures: C.T. Borland: None. **Y.P. Ganev:** None. **C.N. Mwale:** None. **A.E. Grassel:** None. **F. Bertolotti:** None. **R.J. Osselborn:** None. **T.C. Nassuna:** None. **B.T. Zabat:** None. **S.K. Debburman:** None.

Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.07

Topic: C.03. Parkinson's Disease

Title: In vitro modelling of progressive α-synuclein aggregation in primary cortical cultures using a high throughput microfluidic co-culture platform

Authors: L. STRID ORRHULT[1], J. PIHL[1], Å. JÄGERVALL[1], K. WILLÉN[2], K. BJERREGAARD-ANDERSEN[2], K. FOG[2], S. ILLES[3];

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Abstract: Progressive loss of dopaminergic neurons within the substantia nigra as well as misfolded and aggregated α-synuclein (α-syn) within neurons throughout different regions of the brain, including cortex, are hallmarks in Parkinson's disease (PD). Several studies indicate that misfolded α-syn is released by neurons and taken up by recipient neurons where it acts as seeds to cause misfolding and aggregation of endogenous α-syn. To better understand processes involved in α-syn neuron-to-neuron spreading, we used a high-capacity microfluidic co-culture platform and high-content imaging on compartmentalized neuronal cultures to assess cellular uptake, axonal transport, somatic accumulation of α-syn seeds and aggregation of endogenous α-syn in transgenic mouse cortical neurons, overexpressing human α-syn. In detail, embryonic transgenic F28 mice cortical neurons were plated in the microfluidic co-culture plates allowing axons to grow into a cell-free interconnecting well. At 6 days *in vitro* (DIV), fluorescently labelled α-syn preformed fibrils (PFFs) or other preparations of α-syn seeds were applied to the cell-free axonal side. Cultures were maintained for up to 34 DIV and neuron-to-neuron spreading of α-syn were assessed using immunocytochemistry and high content analysis. We demonstrate that fluorescently labelled α-syn PFFs are taken up by the axons, are retrogradely transported, accumulate and remain within neurons close to the entrance area of the interconnected well. Axonal uptake of PFFs cause endogenous α-syn aggregation, appearing as perinuclear Lewy-body like accumulations and axonal speckles, in a concentration- and time-dependent manner. In addition, there were clear differences in seeding potency between the different PFFs tested resulting in varying degrees of aggregation that could be detected throughout the interconnected well. Since the microfluidic co-culture platform, containing an array of 96 experimental units, allows for local intervention of neuropathological processes, this assay platform can contribute to an increased understanding of processes leading to progressive α-syn aggregation in neurons. In addition, it allows for profiling of larger compound sets, in the search for molecules preventing progressive synucleinopathy with the potential to halt or delay the progression of PD.

Disclosures: L. Strid Orrhult: A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **Å. Jägervall:** A. Employment/Salary (full or part-time):; Cellectricon AB. **K. Willén:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S, Valby, Denmark. **K. Bjerregaard-Andersen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S, Valby, Denmark. **K. Fog:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S, Valby, Denmark. **S. Illes:** None.

Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.08

Topic: C.03. Parkinson's Disease

Support: Sealy Institute of Vaccine Science

Title: Potential Role of Alpha Synuclein Oligomeric Polymorphisms in Synucleinopathy Pathogenesis

Authors: *K. MOORE[1], U. SENGUPTA[2], M. KIDD[3], C. JEREZ[3], S. GAIKWAD[3], R. KAYED[2];
[1]Univ. of Texas Med. Br., Webster, TX; [2]Neurol., [3]Univ. of Texas Med. Br., Galveston, TX

Abstract: Neurodegenerative disorders are characterized by unique combinations of symptoms and pathological hallmarks of proteinaceous aggregates. Parkinson's disease (PD) and Dementia with Lewy bodies (DLB) are the two major synucleinopathies characterized by α-Synuclein (α-Syn) protein aggregates. Tauopathies, such as Alzheimer's disease (AD) and Progressive Supranuclear Palsy (PSP), also exhibit α-Syn pathology. Accumulating evidence suggests that an intermediate state of aggregates, oligomers, are the most potent neurotoxic species. Although multiple neurodegenerative diseases exhibit α-Syn aggregates, the behavioral phenotypes and neuropathology associated with each disease is distinct. Several studies have shown that amyloid aggregates, specifically fibrils of many amyloidogenic proteins such as α-Syn, amyloid β and tau represent considerable polymorphism at their molecular level. Our lab has demonstrated α-Syn can form distinct inclusions/conformations with distinct properties in the presence of different physiological inducers. Recombinant α-Syn oligomers modified by physiological inducers, dopamine or docosahexaenoic acid each exhibit distinct properties such as seeding propensity, aggregate size, and toxicity. By utilizing our lab generated α-Syn Toxic Conformation Monoclonal Antibodies (SynTCs) in a combination of biochemical and cellular assays, we provide evidence of distinct immunoreactivities as well as inflammatory responses associated with each oligomeric polymorphism. We also evaluate the effects of α-Syn oligomer immunodepletion in different cell types using cell-based assays and immunocytochemistry. These experiments provide cellular modeling of the effects of α-Syn oligomeric polymorphisms as well as if the therapeutic targeting of stable α-Syn oligomers can halt or reduce the neuropathological implications observed in synucleinopathies. We hypothesize amyloidogenic polymorphs may reflect the greater variability of disease phenotypes evident in synucleinopathies. With evidence showing oligomers as the most toxic species, neuroprotective intervention strategies targeting stable, toxic oligomers could be disease-modifying. Following in vitro analysis, our next step is to conduct an immunotherapy study with the SynTCs in a synucleinopathy mouse model. This immunotherapy study would evaluate the in vivo physiological effects of α-Syn oligomeric polymorphisms and if their therapeutic targeting can reduce or halt pathological implications and behavioral phenotypes associated with synucleinopathies.

Disclosures: K. Moore: None. **U. Sengupta:** None. **M. Kidd:** None. **C. Jerez:** None. **S. Gaikwad:** None. **R. Kayed:** None.

Poster

P258. Alpha-Synuclein: Aggregation and Pathogenesis

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P258.09

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R21AG068608-01
NIH Grant 1R15NS093539-01

Title: Novel Stabilizers of the Cytoskeleton in Lewy Body Disorders

Authors: *A. S. JAMENIS, T. N. BHATIA, K. M. MINER, K. KAKU, Y. SHAH, B. A. DEMARCO, R. N. CLARK, A. GANGJEE, R. K. LEAK;
Duquesne Univ., Pittsburgh, PA

Abstract: Lewy body disorders are associated with hallmark inclusions containing aggregated forms of the normally presynaptic protein α-synuclein. When α-synuclein aggregates in the synapse, it may be transported along axonal microtubular tracts to the soma for degradation or deposition into insoluble inclusions. However, during this transportation, α-synuclein aggregates may also adhere to the microtubules and impede the axonal transport of other cellular constituents. Axonal transport is known to depend upon the stability of the microtubule tracks, but the specific impact of α-synucleinopathy on microtubular dynamicity is not known. Here, we assessed markers of microtubule stabilization in olfactory bulb and amygdala samples harvested postmortem from men and women with Lewy body disorders and age-matched control subjects. Unexpectedly, we observed that women showed higher levels of detyrosinated α-tubulin (marker of microtubule stability) as well as higher levels of tyrosinated α-tubulin (marker of non-stabilized microtubules) compared to men. In order to test the impact of microtubule stabilization on the functional properties of α-tubulin, we measured inclusion formation in primary hippocampal cultures treated with novel heterocyclic microtubule stabilizers and challenged with preformed α-synuclein fibrils. As expected, the microtubule destabilizer nocodazole prevented the reduction in pathological inclusions that was observed with two of the novel microtubule stabilizers. Preliminary data assessing the influence of the biological sex on microtubule stability in validated male versus female primary neuron cultures suggest that the two microtubule stabilizers reduced the pathological inclusions—particularly in male neurons. These collective data suggest that biological sex affects microtubule stability, including in the context of Lewy body disorders.

Disclosures: A.S. Jamenis: None. **T.N. Bhatia:** None. **K.M. Miner:** None. **K. Kaku:** None. **Y. Shah:** None. **B.A. DeMarco:** None. **R.N. Clark:** None. **A. Gangjee:** None. **R.K. Leak:** None.

Poster

P260. Mechanism of Neurodegeneration II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P260.01

Topic: C.03. Parkinson's Disease

Support: France parkinson

Title: Effect of cannabis on motor and non - motor symptoms of Parkinson's disease: a behavioral and pharmacological study

Authors: *E. GIORLA[1], C. BAUNEZ[2];
[1]Inst. De Neurosciences De La Timone, Marseille, France; [2]INT CNRS & Aix-Marseille Univ., Marseille, France

Abstract: Interest in cannabis and cannabinoid research for treatment of neurological disorders have received growing attention over the past years. Although there is evidence from animal and human studies that cannabis has some symptomatic effects, many therapeutic challenges remain. Cannabis and

cannabinoid treatments require further evidence to refine the therapeutic applicability of cannabis-based medicines. Since the endocannabinoid system is largely expressed within the basal ganglia, most studies regarding Parkinson's disease (PD) and cannabis have focused on the cellular and molecular interactions between cannabinoids and dopamine. However, if cannabinoids have the potential to be beneficial for motor symptoms in various animal models of PD, the optimal treatment remains to be identified. The present study thus aims at highlighting the role of cannabis on motor and non-motor symptoms of PD. Despite the fact that there are evidences to suggest that cannabis could be beneficial for parkinsonian patients, the available data are inconsistent. One critical question remaining to be addressed is whether CBD alone could be sufficient or whether THC is required to obtain a therapeutic effect. Here we have addressed it using behavioural measures assessing motor and non- motor functions. We have run 2 different experiments. First, in our model of haloperidol-induced catalepsy, we found that the combination of THC + CBD seems to be efficient to alleviate motor symptoms. THC alone, but not CBD alone, also seemed to be beneficial on this measure. Then, in a rat model of Parkinson disease, induced by a bilateral 6-OHDA injection in the dorso-lateral striatum, we assessed both motor, attentional, impulsive and motivational processes in the 5 choice serial reaction time task. As for the catalepsy experiment, we here tested CBD alone, THC alone and CBD/THC mix. The preliminary results suggest that injections of THC+CBD seem to be the best treatment to reduce the deficits induced by the DA depletion, since it decreased impulsivity and improved attentional deficit, common deficits in our PD model, it shows no detrimental effect. In conclusion, although it is currently trendy to consider therapeutical use of cannabis, the exact composition of what is available on the market is critical for efficiency. Our results suggest that CBD alone will not be efficient enough and it is important to have THC in the mixture. This is thus still illegal in our country, but may be soon accessible.

Disclosures: E. Giorla: None. **C. Baunez:** None.

Poster

P260. Mechanism of Neurodegeneration II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P260.02

Topic: C.03. Parkinson's Disease

Title: The relevance of EEG biomarker in evaluating the anti-dyskinetic effect of drugs in Parkinson's disease.

Authors: *V. DUVEAU, A. EVRARD, J. VOLLE, C. ROUCARD, Y. ROCHE;
Synapcell SAS, St Ismier, France

Abstract: State-of-the-art clinical literature shows that motor symptoms of Parkinson's disease (PD) result from a dysfunction of the cortico-basal ganglia circuits. A hyper synchronization of beta rhythms in this circuit, positively correlated to motor symptoms, has been characterized in both parkinsonian patients and animal models. This aberrant excessive beta oscillation is suppressed by dopaminergic treatments, which simultaneously improve motor deficits. However, a chronic L-DOPA treatment induces abnormal involuntary movements (AIMs) and a prominent resonant gamma oscillation. This project aimed at investigating the effect of the antidyskinetic drug amantadine, which is routinely used in the clinic, on L-

DOPA-induced gamma oscillations in the 6-OHDA rat model of PD. In this poster, we will show that chronic administration of L-DOPA low dose (6mg/kg) induces specific gamma oscillations and AIMs which gradually increase with repeated treatments. We will demonstrate that a pre-treatment with amantadine dose-dependently reduces L-DOPA-induced gamma oscillations and AIMs score. Our data will illustrate how the preclinical study of cortical beta and gamma oscillations offers relevant and translatable EEG biomarkers that add significant value to drug development as stable, quantitative, and objective endpoints for the development of new antiparkinsonian and antidyskinetic neurotherapeutics.

Disclosures: V. Duveau: A. Employment/Salary (full or part-time):; SynapCell SAS. **A. Evrard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **J. Volle:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell SAS.

Poster

P260. Mechanism of Neurodegeneration II

Location: Virtual Only

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Program #/Poster #: P260.03

Topic: C.03. Parkinson's Disease

Support: NIH Grant P50-NS098573 (Udall)
NIH Grand R01-NS094206
F31 Fellowship 1F31NS108625-01 to AMD

Title: Differential effects of directional deep brain stimulation on parkinsonian gait in the parkinsonian non-human primate

Authors: *D. SULLIVAN[1], A. M. DOYLE[2], D. L. BAUER[3], Z. LAO[3], J. D. KRIEG[1], L. K. WILMERDING[1], M. BLUMENFELD[1], E. E. LECY[1], C. SPENCER[1], S. BEST[1], C. M. HENDRIX[3], J. WANG[3], J. L. VITEK[3], M. D. JOHNSON[1];
[1]Biomed. Engin., [2]Neurosci., [3]Neurol., Univ. of Minnesota, Minneapolis, MN

Abstract: Background: Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is a proven therapy to treat many of the motor signs of Parkinson's disease. Parkinsonian gait dysfunction, however, can be difficult to manage with conventional, quadripolar STN-DBS leads.
Objective: In this study, we compare changes in gait speed with targeted stimulation within and slightly dorsal to the STN in a non-human primate.
Methods: A directional DBS lead containing two vertically segmented rows with three radially segmented contacts per row was chronically implanted such that the top vertical row of contacts was slightly dorsal to the STN and within the lenticular fasciculus. The subject voluntarily navigated over a pressure walkway system. Data was collected before and after rendering the subject parkinsonian with systemic MPTP as well as during a monopolar review of DBS configurations.
Results: Gait speed was significantly decreased following MPTP treatment. DBS delivered at 0.2 mA through one of the three contacts investigated was found to significantly increase gait speed. This was not observed at higher stimulation amplitudes (0.3mA) that were closer to the internal capsule side effect

threshold.
Significance: Parkinsonian gait deficits, including gait speed, may be differentially affected with directional DBS lead technology and thus requires careful titration of stimulation amplitude to avoid confounding therapeutic effects.

Disclosures: D. Sullivan: None. **A.M. Doyle:** None. **D.L. Bauer:** None. **Z. Lao:** None. **J.D. Krieg:** None. **L.K. Wilmerding:** None. **M. Blumenfeld:** None. **E.E. Lecy:** None. **C. Spencer:** None. **S. Best:** None. **C.M. Hendrix:** None. **J. Wang:** None. **J.L. Vitek:** None. **M.D. Johnson:** None.

Poster

P260. Mechanism of Neurodegeneration II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P260.04

Topic: C.03. Parkinson's Disease

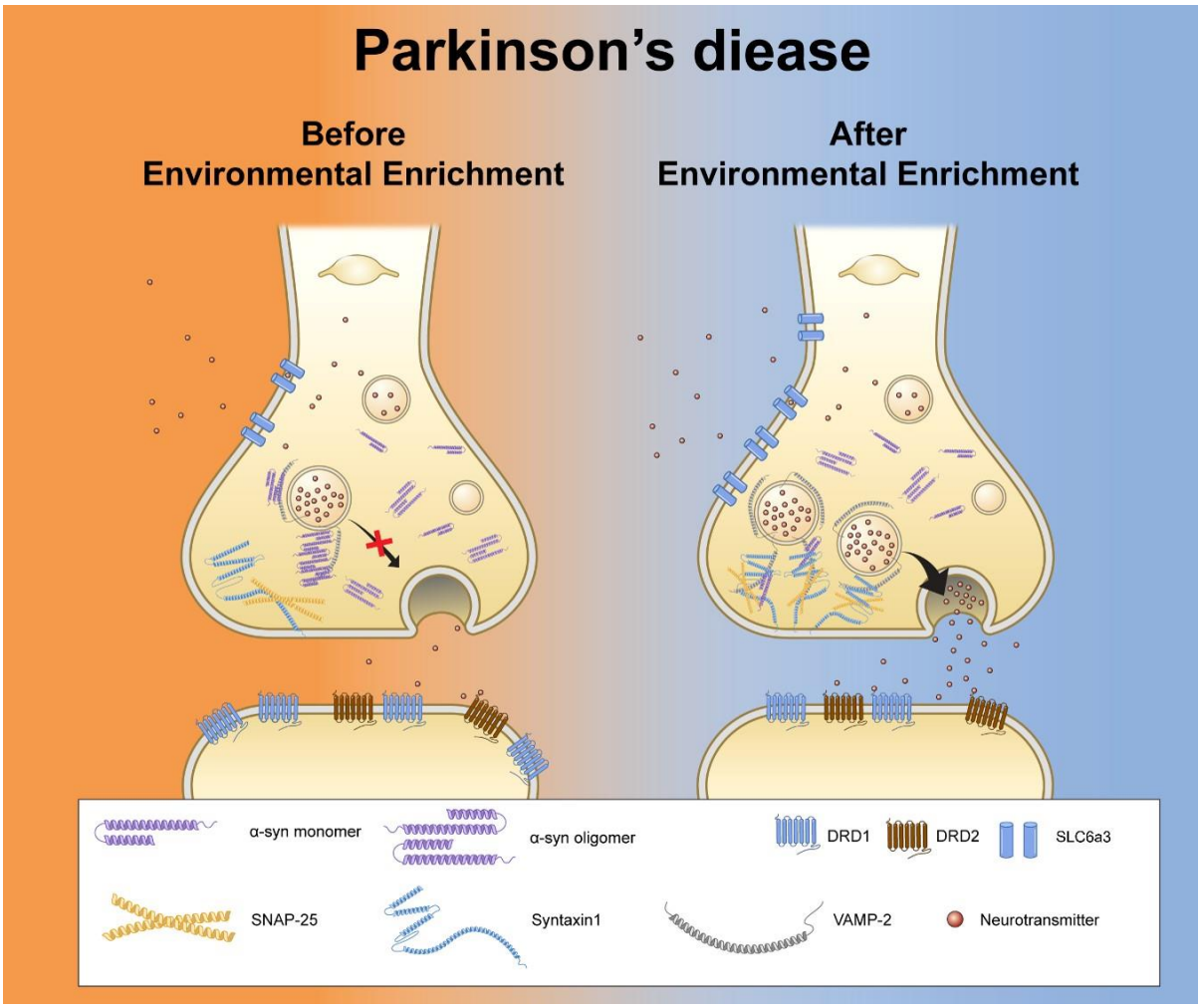
Support: The faculty research grant of Yonsei University College of Medicine (6-2020-0104)
The INNOPOLIS Jeonbuk Innovation Cluster, Korea Innovation Foundation (2020-JB-RD-0121)

Title: Reduced interaction of aggregated alpha-synuclein and VAMP2 by environmental enrichment alleviates hyperactivity and anxiety in a model of Parkinson's disease

Authors: *K. KIM[1,2], S. WI[6], J. SEO[3,7], S. PYO[3,7], S. CHO[3,7,4,5];
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Abstract: Parkinson's disease (PD) is a prevalent motor disease caused by the accumulation of mutated α-synuclein (α-Syn); however, its early stages are also characterized by non-motor symptoms, such as olfactory loss, cognitive decline, depression, and anxiety. The therapeutic effects of environmental enrichment (EE) on motor recovery have been reported, but its effects on non-motor symptoms remain unclear. Herein, we reveal the beneficial effects of EE on PD-related non-motor symptoms and changes in synaptic plasticity in the nucleus accumbens. To investigate its therapeutic effects in the early phase of PD, we randomly assigned eight-month-old mice overexpressing human A53T (hA53T) α-Syn to either the EE or standard condition groups for two months. Next, we performed behavioral tests and biochemical and histological analyses at 10 months of age. EE significantly alleviated locomotor hyperactivity and anxiety during the early stages of PD. It normalized the levels of tyrosine hydroxylase, phosphorylated and oligomeric α-Syn, and soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex-forming proteins, including synaptosomal-associated protein, 25 kDa, syntaxin1, and vesicle-associated membrane protein 2 (VAMP2). Moreover, the interactions between VAMP2 and

pSer129 α-Syn were markedly reduced following EE. The restoration of synaptic vesicle transportation status may underlie the neuroprotective effects of EE in hA53T α-Syn mice.



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Poster

P260. Mechanism of Neurodegeneration II

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P260.05

Topic: C.03. Parkinson's Disease

Support: R01 NS058945
R01 NS110613

Title: Detecting excessive daytime sleep in Parkinsonian non-human primates via local field potentials from deep brain stimulation leads

Authors: *A. K. VERMA, S. ACOSTA-LENIS, Y. YU, T. HAVEL, A. DENICOLA, H. YAO, E. MARSHALL, M. STOLLER, D. ESCOBAR SANABRIA, M. HOWELL, C. MACKINNON, J. L. VITEK, L. A. JOHNSON;
Univ. of Minnesota, Minneapolis, MN

Abstract: The propensity to become drowsy or fall asleep while conducting daily routines is common in people with Parkinson's disease (PD) and adversely impacts their quality of life. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and internal globus-pallidus (GPi) is an established treatment for motor symptoms of PD, however, the utility of local field potential (LFPs) recorded from DBS lead implanted in the STN and GPi for characterizing daytime sleep remains unclear. Physiological understanding of neural activity in the STN and GPi corresponding to daytime sleep can provide a rationale for engineering closed-loop DBS paradigm for detection and disruption of sleep-related neural activity. To this end, we recorded LFPs from STN and GPi via DBS lead implanted in two nonhuman primates (*macaca mulatta*) rendered parkinsonian by administrating neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Power in δ (1-4 Hz), θ (4-8 Hz), α (8-12 Hz), β (12-35 Hz), ϒ (35-90 Hz), and high-frequency (HF, 200-400 Hz) bands of STN and GPi LFPs (1-sec long for continuous detection) were extracted to test whether these features can discriminate awake and sleep states. Holdout cross-validation (70% training and 30% testing) technique was used to train a support vector machines classifier. The classifier yielded >85% sensitivity, specificity, and accuracy for discriminating awake and sleep states. Results suggest that LFPs recorded from both STN and GPi via DBS lead contain reliable neural signatures for discriminating awake and sleep states continuously. The findings could have implications in the development of personalized closed-loop DBS strategies for detecting and disrupting sleep-related neural activity in PD patients to promote wakefulness supplemental to providing aid to motor impairment.

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Poster

P260. Mechanism of Neurodegeneration II

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Program #/Poster #: P260.06

Topic: C.03. Parkinson's Disease

Support: Swedish Research Council
Swedish Brain Foundation
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Karolinska Institutet/National Institutes of Health PhD program in Neuroscience
NIH NINDS R01 NS095435
NIDA R01 DA07418

Simons and JPB Foundations

Title: Involvement of autophagy in levodopa-induced dyskinesia

Authors: *C. PLEWNIA[1], M. FEYDER[1], O. J. LIEBERMAN[2], G. SPIGOLON[1], A. PICCIN[1], L. URBINA[1], B. DEHAY[3], Q. LI[4], P. NILSSON[1], M. ALTUN[1], E. SANTINI[1], D. L. SULZER[2], E. BEZARD[3], A. BORGKVIST[1], G. FISONE[1];
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Abstract: Autophagy is one of the major degradation pathways in eukaryotic cells and plays an essential role in maintaining effective turnover of proteins and damaged organelles. It is intensively studied in cancer, metabolic and neurodegenerative diseases, but little is known about its role in pathological conditions linked to altered neurotransmission. In this study, we examined the involvement of autophagy in levodopa (l-dopa)-induced dyskinesia, a frequent motor complication developed by Parkinson's disease patients in response to dopamine replacement therapy. In Parkinson's disease, the loss of dopaminergic input to the dorsal striatum leads to the sensitization of dopamine D1 receptors (D1R) which confers on l-dopa the ability to activate the mammalian target of rapamycin complex 1 (mTORC1) in the striatal projection neurons of the direct pathway. The ability of rapamycin, an inhibitor of mTORC1, to counteract dyskinesia has been previously related to its action on mTORC1 downstream targets involved in the control of protein synthesis. However, virtually nothing is known about the impact on l-dopa-induced dyskinesia of dysregulated autophagy, which is another important downstream target of mTORC1. In this study, we used a mouse and a non-human primate model of Parkinson's disease to examine changes in autophagy associated with chronic l-dopa administration and to establish a causative link between mTORC1 inhibition of autophagy and dyskinesia. We found that l-dopa-induced dyskinesia is associated with accumulation of the autophagy-specific substrate p62, a marker of autophagy deficiency. Increased p62 was observed in striatal projection neurons of the direct pathway and depended on D1R-mediated activation of mTORC1. Inhibition of mTORC1 with rapamycin counteracted the impairment of autophagy produced by l-dopa and reduced dyskinesia. Importantly, the anti-dyskinetic effect of rapamycin was lost when autophagy was constitutively suppressed in D1R-expressing striatal neurons, through inactivation of the autophagy-related gene protein 7. These findings indicate that, in Parkinson's disease, augmented responsiveness at D1 receptors leads to dysregulated autophagy, and results in the emergence of l-dopa-induced dyskinesia. They further suggest the enhancement of autophagy as a therapeutic strategy against dyskinesia.

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Poster

P260. Mechanism of Neurodegeneration II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P260.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant HD092941
Loma Linda University GCAT-2020

Title: Identification of caspase and pro-inflammatory cytokines in a murine model for preterm hypoxic ischemic encephalopathy.

Authors: *T. C. HILLMAN, M. M. GHALY, C. G. WILSON;
Ctr. for Perinatal Biol., Loma Linda Univ., Loma Linda, CA

Abstract: Preterm hypoxic ischemic encephalopathy (pHIE) is a condition where blood and oxygen are prevented from reaching a fetus's brain resulting in neural inflammation and a spectrum of neurological conditions. Causes for pHIE vary creating a challenge for clinicians to diagnose the severity of an insult until after the damage is irreparable. Because most preterm HIE insults occur while the fetus is inside the mother, the signs, symptoms, and exact time of insults are often not clear. Current clinical interventions like therapeutic hypothermia and erythropoietin have decreased the severity of damage in full term infants; however, preterm infants do not respond to these treatments. Studying pHIE in a model where the insult started in utero has so far only been possible in large mammal models. Recently, however, use of a murine model which includes maternal factors has become available. The murine groups were divided into pHIE, three surgical control groups and a naïve group with tissue being harvested on the same post-gestational day for all groups. Using unbiased stereology, coronal brain slices were stained with caspase-9 and then counted to compare expression levels. The cortex of the right and left cerebral hemispheres were counted separately to identify if insult was bilateral or unilateral. Following caspase-9 staining 1.5 mm coronal brain sections were isolated and processed to investigate expression of pro-inflammatory cytokines IL-1B and TNF-α using an ELISA. The inflammatory pathway result for caspase-9, IL-1β and TNFα showed higher expression in pHIE than all controls. Caspase-9 expression in pHIE animals had higher positive cell counts per area in the cortex than the control animals. Expression of IL-1β and TNF-α had higher expression in 1.5 mm coronal cerebral hemisphere slices than the control animals. Expression of both the caspase marker and cytokines shows similarities to those seen in clinical reviews of human preterm infants. Additional analysis into the expression caspase-1 and other pro-inflammatory and anti-inflammatory cytokines needs to be conducted. Comparison between sex, sidedness, and target brain structure is underway. Looking at how murine pHIE pups in comparison to a murine full-term model in both inflammatory pathway proteins and miRNA will help direct more targeted therapies for preterm infants suffering from pHIE.

Disclosures: T.C. Hillman: None. **M.M. Ghaly:** None. **C.G. Wilson:** None.

Poster

P344. Brain Injury: Histology and Cellular Markers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P344.01

Topic: C.10. Brain Injury and Trauma

Support: NINDS U54 NS100064

NINDS NS091170
US Department of Defense W81XWH-13-1-0180

Title: Iron accumulation and intracerebral hemorrhage in the lateral fluid percussion injury model of post-traumatic epilepsy in adult rats: An EpiBioS4Rx Project 2 study

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Abstract: Severe traumatic brain injury (TBI) usually leads to intracerebral hemorrhages which result in iron accumulation. Iron deposits are risk factors of post-traumatic epilepsy (PTE) after TBI. In the EpiBioS4Rx Project 2 study, we investigated the temporospatial patterns of post-hemorrhagic iron deposits after lateral fluid percussion injury (LFPI) induced severe TBI. We used adult male 11-weeks old Sprague-Dawley rats: lateral fluid percussion injury (LFPI) (n=12), LFPI and deferiprone (DEF) (LFPI+DEF; n=9), sham (n=12) and naïve (n=4). Sham rats underwent a left parietal 5mm craniotomy only, whereas LFPI were also subjected to ~3.2atm pressure pulse. The LFPI+DEF group received DEF, an iron chelator, DEF 100mg/kg ip followed by 7.6mg/kg/day via a minipump infusion sc right after TBI and for 7 days (d). Rats were perfused at 2d, and 1, 2, 4, or 8 weeks (wk) after LFPI. Perfused brains were sectioned and stained with Perl's Prussian blue stain for iron using qualitative (distribution in the brain) and quantitative analyses, to determine the iron-stained areas (pixels/mm^2) of corpus callosum/external capsule (CC/EC). Additional rats underwent LFPI or sham surgeries (n=10/group) and subsequently MRI at 9d and 5 months (mo) post-surgery. Multi-echo gradient echo (MGE) 3D sequences, with outer volume suppression and fat suppression, were used. MGE data was used to calculate T2* maps, anatomical mixed contrast images and field maps. CC/EC, parasagittal and lateral cortices, hippocampus, striatum and thalamus of LFPI rats ipsilaterally to the lesion had high quantity of iron deposit. Iron deposits were rarely seen in sham, and never in naïve rats. LFPI group had more total iron pixels compared to control ($p=0.023$) or sham ($p=0.0073$), considering all timepoints. At 1wk post-injury, iron load in LFPI+DEF was significantly less than LFPI ($p=0.007$) and no significantly different than control or sham rats. A week after DEF discontinuation, LFPI+DEF had more total iron pixels than LFPI, control or sham rats ($p<0.01$). MRI revealed hypointensities on T2* consistent with hemorrhages at CC/EC in all LFPI rats at 9d and 5mo, and less frequently, at the left lateral cortex (9d) and left thalamus at 5mo post-LFPI. No hemorrhages were observed in sham rats in MRI data. All rats develop hemorrhages/iron deposits at the CC/EC fibers ipsilaterally to the injury side after TBI, which may be detectable up to 5mo. Continuous 1wk treatment partially reduced the iron load during the first week post-LFPI, but this was not sustained after treatment discontinuation, suggesting that longer DEF treatment would be needed to reduce iron load in the brain of LFPI rats.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P344.02

Topic: C.10. Brain Injury and Trauma

Title: Immunohistochemical expression of Nrf2-Antioxidant Response Element on rat brain of two models of epileptic seizures

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Abstract: Epilepsy is a neurological disorder that affects about one percent of the world's population and is characterized by an alteration in electrical activity that manifests itself in recurrent and spontaneous epileptic seizures (ES) within the central nervous system. One of the main cellular mechanisms of this neurological disorder is the oxidative stress (OS) which can be emulated in animal models through the use of chemical agents such as pethylenetetrazole (PTZ) and kainic acid (KA). A defense mechanism against OS cellular include the nuclear factor erythroid 2 related factor 2 (Nrf2), which is related to the regulation in the transcription of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. We studied the role of the transcription factor Nrf2 in experimental models of epilepsy, as well as its regulatory participation in the antioxidant system. Male Wistar rats were used, were divided into three experimental groups, a control group (Saline solution), KA group (10 mg/kg ip) and another administered with 3 doses of PTZ (25 mg/kg ip) in 15-minute intervals. Cresyl Violet stain and immunohistochemistry antibody for Nrf2 and Nitrotirosine (NNT), were applied. We have found that in rats treated with KA, there is a loss of pyramidal neurons of CA1 and CA3 6 h after the induction of ES and the presence of karyolysis and pyknotic cells becomes evident in a period of 6 at 48 h. Similar results were observed in rats treated whit PTZ at 12 h after the induction of ES and the presence of karyolysis and pyknotic cells but other times period of 12 at 72 h. The immunohistochemistry expression of Nrf2 starting at 12 h and reaching a maximum point at 24 h after the induction of ES and then gradually diminishing in the PTZ model; while that the immunohistochemistry expression of Nrf2 increases slightly 1 h reaching the maximum expression at 24 h after the induction of ES in the group treated with KA. NNT as a marker of OS, showed an increase in the immunoreactivity 1 h after the ES are induced, reaching their maximum point 24 h after the administration of PTZ, while that the reactivity to NNT was increased at the 12 and 24 h in group treated whit KA. The present results corroborate the OS as the main mechanism of seizures in animal models.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P344.03

Topic: C.10. Brain Injury and Trauma

Support: CIRM PC 13638 TLEANING

Title: Temporal characterization of the immune response following repeat mild traumatic brain injury

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Abstract: America is facing an epidemic with over 1.5 million individuals suffering from a traumatic brain injury (TBI) annually. While our understanding of TBI and its devastating effects is growing, less is known about a serious subtype of TBI called repeated mild TBI (rmTBI). Previous neurotrauma research suggests that immune cell activation is altered following injury. However, a comprehensive picture of immune cell infiltration and activation following rmTBI remains to be established. Therefore, this study will characterize the immune response at multiple timepoints following rmTBI using flow cytometry (FCM), immunohistochemistry, and stereological cell counting to establish a clear timeline for treatments to mitigate some of the damage seen in neurotrauma related conditions like chronic traumatic encephalopathy. Eight week old C57Bl6 male mice received five mild closed-skull hits once every other day for 10 days using a controlled cortical injury device. The mice were sacrificed 1, 3, 7, 14, 28, or 60 days post injury (dpi) with an average of 6 mice per time point. Fresh brains were dissected and a two millimeter thick coronal section from -1 to -3 bregma was cut. Bilateral 4mm diameter biopsy punches were made at the midline at the dorsal-most region to isolate the injury epicenter, which were then stained and processed by FCM. Macrophages/microglia, neutrophils, and T-cells were fluorescently labeled and counted via FCM. A subsequent study was performed and quantification of the immune cell populations within the tissue using immunohistochemistry and sterology are ongoing. An ANOVA and Tukey's post-hoc multiple comparisons tests showed significance between several timepoints in the FCM data. Macrophages/microglia were significantly different between 3 dpi and 28 dpi ($p=0.0235$), with an increase until 3 dpi, followed by a decrease until 28 dpi. A second significant time point occurred between 28 dpi and 60 dpi ($p=0.0008$), with a second peak at 60 dpi. Together, these findings suggest that the immune response after rmTBI is multiphasic, similar to that observed after spinal cord injuries. By establishing a profile of how the immune cells respond following injury, this may allow one to target specific cells within optimal time windows to ameliorate rmTBI.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Topic: C.10. Brain Injury and Trauma

Support: VA Merit Review Award I01RX001144
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Title: Aberrant fear extinction learning after mild traumatic brain injury in mice is associated with alterations in neural plasticity in the basolateral nucleus of the amygdala and medial prefrontal cortex

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Abstract: Mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD) have emerged as the signature injuries of the U.S. military who served in Iraq and Afghanistan, and frequently co-occur in both military and civilian populations. To better understand this co-occurrence, we utilized a mouse model of mTBI followed by auditory cued fear conditioning and fear extinction training (5 trials/day for 6 days). In addition to fear acquisition and extinction, we examined dendritic plasticity and neuronal count in the medial prefrontal cortex (mPFC) and basolateral nucleus of the amygdala (BLA), two regions critical for fear learning. Behavioral and brain endpoints in adult male C57BL/6J mice subjected to a lateral fluid percussion injury of 1.7 atmospheres of force (LFP mice) were compared to mice from two separate control groups: craniotomy controls (Sham mice) and unoperated controls (Unoperated mice). After surgery, no gross motor abnormalities or anxiety-like behavior were observed in Sham or LFP mice compared to Unoperated mice. Fear behavior was then compared between groups using linear mixed effects analysis. Acquisition of auditory cued conditioned fear (i.e. freezing to tone) was similar in all groups. Conditioned fear behavior decreased for all groups over the course of 6 days of extinction training, and the decrease across days was not impacted by experimental group. However, a significant interaction between within-session freezing behavior (i.e. across trials, collapsed across extinction test day) and experimental group was observed. Specifically, whereas freezing behavior in both Sham and Unoperated control mice did not change across trials, freezing behavior significantly increased across trials in LFP mice. These results suggest that brain injury produces an aberrant form of fear extinction learning with greater reactivity to the fear cue. Additionally, LFP mice demonstrated bilateral increased dendritic spine density in the BLA and decreased dendritic complexity in the mPFC, which could underlie the observed behavioral effects. These results have implications for patients with co-morbid mTBI and PTSD undergoing extinction therapy and suggest that aberrant learning and neuronal plasticity could be targeted for more effective treatment interventions.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Topic: C.10. Brain Injury and Trauma

Support: CONACyT 218556
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PAPIIT IN621147
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Title: Swimming reduces changes in cerebral anatomy and motor behavior caused by NMDA lesions in corpus callosum of the neonatal rat

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Abstract: The encephalopathy of prematurity is a pathology that can develop in premature babies due to several risk factors. These risk factors can cause cell death by excitotoxicity in the gray and white matter of the brain. Katona's neuro-habilitation procedures have been implemented in premature babies to reduce cerebral injuries and motor impairments, but we do not understand the mechanisms of recovery in the premature brain. We developed a rat model to study this problem. On the 5th postnatal day (PD) the corpus callosum of male rats was unilaterally lesioned with NMDA (5 µg in 2 µL), and a swim protocol from the 7th to 30th PD was followed. On PD 7 the rats were divided into six groups: Intact-sedentary (ISe), Intact-swim (ISw), Vehicle-sedentary (VSe), Vehicle-swim (VSw), Lesion-sedentary (LSe), and Lesion-swim (LSw). We evaluated the volume of the cortex (motor, cingulate and sensory), corpus callosum, and lateral ventricles on PD 20 and PD 30 of independent groups and, also, we counted the number of NeuN positive cells and the positive labeling of Myelin Basic Protein (MBP). We also evaluated the motor activity and learning in a water maze task from PD26 to PD30. On the 20th PD, the LSe group showed a decrease of cortical and callosal volume and an increase in the volume of the ipsilateral ventricle. We also found a reduced number of NeuN positive cells in the ipsilateral motor cortex. The MBP positive label was reduced in the ipsilateral cortex and corpus callosum. Importantly, in the LSw group, the number of positive NeuN cells in the contralateral cortex was not different from the Intact and Vehicle groups, and the labeling of MBP was not reduced in the contralateral cortex and corpus callosum. On the 30th PD the LSe group did not show the motor ability to stay on a rotarod and had high

latencies in a modified water maze task; by contrast, the LSw group had the motor ability to stay on the rotor and learned the water maze task similar to the control groups. In conclusion, swimming from the 7th PD to the 30th PD reduces the structural, motor behavior, and cognitive alterations produced by an excitotoxic perinatal injury in rats. We thank, Roberto A. Prado-Alcalá, Rogelio Arellano, Norma Serafín, Cristina Medina, Martín García, Alejandra Castilla, Nydia Hernández, Deisy Gasca, CONACyT (218556, 4971 and 251634; Scholarship 621147/43756) and PAPIIT-UNAM (IN621147, IN200917 and IN204118).

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Topic: C.10. Brain Injury and Trauma

Support: Start up funds: OHSU
Start up funds: Legacy Research Institute

Title: Impaired neurogenic response to a repeated head injury

Authors: A. WEINGARTEN[1], T. M. BAH[2], S. RAPHAEL[2], S. L. FELLER[2], ***L. E. VILLASANA**[1,2]; [1]Legacy Res. Inst., Portland, OR; [2]Apom, Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: In response to traumatic brain injury (TBI) neural stem cells undergo robust proliferation, increasing neurogenesis within the hippocampus, a brain region critical for learning and memory. Because new neurons develop properties similar to mature neurons and integrate into existing circuits, post-TBI neurogenesis is thought to contribute to hippocampal recovery. However, levels of neurogenesis eventually become depleted after TBI. Deficits in neurogenesis impair several processes of memory and mood regulation. Additionally, these deficits could significantly impact how the brain recovers from repeated TBI. Hence, in this study we addressed whether the hippocampus remains capable of eliciting increases in neurogenesis after a second TBI. We used a mild closed head injury that is similar to a concussive injury in two-month-old male and female POMC-GFP mice which transiently express GFP in immature hippocampal neurons. Mice were subjected to either a sham, single or a subsequent TBI (3wk treatment interval) and euthanized 18 days later to assess hippocampal neurogenesis. In comparison to mice with a single TBI, mice with a second TBI had significantly fewer GFP^+ cells which was further confirmed with a second marker of immature neurons, doublecortin. To determine whether proliferation is also impaired, we conducted a similar experiment but injected mice with the mitotic marker EdU 3 days after the second TBI and euthanized them the following day. The density of Edu^+cells and cells positive for Ki67, another proliferative marker, were lower in mice with a subsequent TBI compared to mice with a single TBI. Increasing the injury interval to 2 months did not restore the proliferative response. Using GFAP, SOX2, and Edu as well as Ki67 to label proliferating radial glia-like neural stem cells we observed that their proliferative response to the subsequent injury was also impaired. Importantly, there

were no differences in their overall density, suggesting these impairments are not merely due to reduced populations. Interestingly, we also observed attenuated increases in GFAP expression (intensity) within the hippocampus of mice with a second TBI, suggesting an adaptive process may be associated with these response deficits. Our results demonstrate that a history of concussion alters the proliferative behavior of neural stem cells and subsequently, the neurogenic response to a subsequent head injury which could in part explain why repeated TBIs have worse cognitive outcomes. These results point to a novel mechanism underlying vulnerability to repeated TBI.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Topic: C.10. Brain Injury and Trauma

Support: CNRM-70-8956
USU-PAT-74-3439
CDMRP W81XWH-13-2-0018

Title: Tbi leads to persistent structural and functional deficits in the cerebellum of a gyrencephalic animal model

Authors: *K. MANETZ, A. OBASA, S. C. SCHWERIN, S. L. JULIANO;
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Abstract: Traumatic brain injury (TBI) occurs frequently and leads to persistent problems. The cerebellum is critical to normal function, but understudied in response TBI. To create a more realistic TBI model in a gyrencephalic animal (the ferret), we used a combination of injuries consisting of multiple explosive blasts, interspersed with rotational head injuries (CHIMERA) over a period of 2 weeks, with or without stress. After survival of 4 weeks or 6 months and behavioral testing, we evaluated the cerebelli of animals receiving the combination injury. To assess cerebellar architecture, Purkinje cells, Bergmann glia, and astrocytes we used antibodies directed against GFAP and Calbindin. The animals surviving for 6 months showed substantial pathology including severe reduction of calbindin expression and limited ability to visualize Purkinje cells and their dendrites. In the injury plus stress condition, pathology occurred in the posterior lobe including strong reduction of calbindin expression in entire folia, including Purkinje cells and their dendrites. In other regions, visibility of Purkinje cells was intermittent and occurred in a striped pattern suggesting that zebrin-related units were reduced in function. The Bergmann glia appeared relatively normal and well oriented, and in most (but not all) instances maintained protective nests surrounding presumptive Purkinje cells. The animals surviving for 4 weeks post injury also showed pathology, but limited to restricted to spotty regions throughout the posterior lobe. Several folia exhibited a striped pattern of calbindin immunoreactivity from the Purkinje cell dendrites, again suggesting that functional cerebellar units were impacted. The deep cerebellar nuclei (DCN) showed

reduced calbindin immunoreactivity surrounding nuclei, especially in the animals surviving for 6 months post injury, indicating the influence of the Purkinje cell axons on the DCN was reduced. GFAP+ reactive astrocytes were observed in the granular layer and also surrounding Purkinje cells. Surprisingly, behavioral deficits for the injured animals were relatively minor and they did not display obvious motor deficits associated with cerebellar problems. Collectively, compared with Sham animals, the injured ferrets showed reductions in Open Field activities, decreased movements in the Light-Dark Box, and decreased ability to maintain Eye Contact. The injured animals also showed impaired Novel Object Recognition and Socialization tests. These findings reveal chronic neuropathology in the cerebellum after a combination TBI accompanied by behavioral deficits associated more with cognition and memory than motor activity.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Topic: C.10. Brain Injury and Trauma

Support: CNRM-70-8956, USU-PAT-74-3439
CDMRP Grant W81XWH-13- 2-0018.

Title: Differential effects of injury on multiple markers in a gyrencephalic animal.

Authors: *A. A. OBASA[1], **S. C. SCHWERIN**[1], S. L. JULIANO[2];
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Abstract: Traumatic Brian Injury (TBI) affects numerous individuals and leads to multiple persistent problems. We designed a model of TBI that included injuries incorporating repeated explosive blast and strong head rotation (CHIMERA), with or without stress. These types of combination injuries often leave functional issues that persist for years after the initial event, similar to those experienced by people. We wanted to compare the effects of this type of injury with animals receiving blast injury only. In order to effectively investigate this problem, we conducted a set of experiments using a gyrencephalic animal (the ferret), whose brain possesses many features similar to humans and are more likely to demonstrate responses that reflect those experienced by people. The injuries (and/or stress) took place over a period of two weeks; at the end of this time, the animals survived for either 4 weeks or 6 months. We evaluated several parameters including inflammatory markers (GFAP for astrocytic reactivity and aquaporin 4-AQ4), expression of tau-related markers including phosphorylated tau (pTau) and the isoforms of tau, 3R and 4R as well as prion protein (another marker often expressed in neurons of those with degenerative diseases). GFAP and AQ4 showed dramatic and significant increases at 4 weeks post injury, which persisted until 6 months post injury. Both GFAP and AQ4 showed especially strong reactivity surrounding blood vessels, for GFAP alone strong reactivity was seen in the subpial region, and at grey-white matter interfaces. Using western blot, pTau showed increases in the prefrontal and anterior

cingulate cortex at 4 weeks post injury, which persisted until 6 months post injury. Differences in the strength of the increase emerged between the animals with and without stress. Both the 3R isoform of tau and pTau showed stronger increases in the prefrontal cortex for the animals receiving stress compared with animals receiving the injury alone. The prion protein, however, showed stronger increases in the prefrontal cortex, the anterior cingulate cortex, and the hippocampus in animals that received the injury only. Overall, the ferrets receiving this combination injury showed astrocytic reactivity and increased expression of tau related proteins more quickly than the animals receiving blast alone. The pathology persisted for at least 6 months.

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Poster

P344. Brain Injury: Histology and Cellular Markers

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Program #/Poster #: P344.09

Topic: C.10. Brain Injury and Trauma

Title: Modifications of NeuN-RbFox3 expression pattern by monosodium glutamate in neonate rats

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Abstract: Anti-NeuN was generated using neuronal nuclei extracts to identify transcriptional regulation factors and cellular processes associated with development, differentiation and function of neurons. Now NeuN/RbFox3 is known as a splicing factor, which participates in mRNA maturation processes in neurons. Then, anti-NeuN may label neurons and their transcriptional state by showing nuclear DNA and RNA distribution and arrangement. On the other hand, glutamate-induced excitotoxicity is associated with neurodegenerative diseases and acute injuries of the central nervous system which results in neuronal death and modified NeuN immunoreactivity patterns. Monosodium glutamate (MSG) applied to newborn rats is an *in vivo* model that allows evaluating the consequences of excitotoxic neuronal damage throughout development. Then, to identify the changes in the expression pattern of NeuN/RbFox3 related to the rearrangements of nucleic acids produced by excitotoxicity, the anti-NeuN, DAPI and propidium iodide (PI) labeling were performed in brain slices on the postnatal day (PND) 14 after neonatal MSG treatment. MSG (4 mg/kg) was subcutaneously administered on PND 1, 3, 5, and 7 to male Wistar rats. At PND 14, treated and non-treated animals (n=4 for each group) were anesthetized and perfused with fixing solution, the brain was removed and coronal slices at level of the dorsal hippocampus (from 2.30 to 4.30 mm posterior to Bregma) were processed to immunohistochemistry and histological evaluation. The neurons of the cortex and hippocampus from MSG treated rats showed cellular damage (by IP labeling), dense chromatin bodies and a diffuse immunodetection pattern for NeuN/RbFox3 in the nucleus (DAPI) and cytoplasm. Whereas in non-treated group, NeuN/RbFox3 immunodetection pattern was intense in the

cytoplasm and showed typical speckles into the nucleus. Because NeuN/RbFox3 immunodetection pattern is modifying in response to excitotoxicity, its characterization offers a new perspective to study the neuronal damage. MSG-induced excitotoxicity modified the NeuN/RbFox3 expression pattern and chromatin rearrangements, which must be characterized as part of the early mechanisms involved in neuronal death.

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Poster

P366. Spinal Cord Injury: Recovery I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Nielson Foundation
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Washington State Spinal Cord Injury Research Fund
Mary Gates Endowment for Students

Title: Early detrusor application of botulinum toxin A reduces fibrotic bladder development and improves bladder compliance after severe thoracic spinal cord injury in rodents

Authors: *J. M. Y. BUSHNELL[1], J. R. BERGQUIST[1], L. N. CATES[1], T. PRASSE[1], J. E. HYDE[1], C. P. HOFSTETTER[1], C. C. YANG[2], Z. Z. KHAING[1];
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Abstract: After spinal cord injury (SCI), 80% of patients develop neurogenic bladders, which affects their quality of life significantly. Neurogenic bladders are associated with increased bladder infection, autonomic dysreflexia, and kidney damage. Altered spinal cord connectivity drastically impact activities of the bladder, which in turn can alter central nervous system plasticity in chronic SCI - for example, afferent C-fibers do not respond in intact animals to bladder distension, but are triggered by distension in chronic SCI animals. Currently, patients with neurogenic bladders are treated with oral anticholinergic medications once they begin to develop symptoms. However, there are significant negative side effects associated with peripheral and central anticholinergic drugs, which have also been associated with both physical and mental impairment. Furthermore, anticholinergic medications do not prevent the development of detrusor muscle hypertrophy which contributes to a non-compliant storage organ, high bladder pressure, and triggers autonomic dysreflexia. Onabotulinum toxin-A (BoNT-A) is currently approved for clinical use as a denervation agent after other treatment options fail. By that time, tissue hypertrophy has typically already caused permanent damage. We hypothesize that acute bladder chemodenervation with BoNT-A application into the detrusor muscle can prevent the onset of bladder wall hypertrophy after SCI, thereby improving bladder compliance and function post-SCI in a rat model.

Preliminary data shows that early (<1 hour post SCI) BoNT-A injections result in thinner bladder walls compared to early saline injected bladders (575.8 ± 40.4 μm vs. 1,094 ± 83.1 μm respectively; $p<0.0001$). BoNT-A injected bladders of SCI rats (SCI-BoNT-A) were significantly lighter compared to saline injected bladders of SCI rats (SCI-saline) (183 ± 42 mg vs 241 ± 25 mg respectively; $p<0.05$) as well. Bladder volume measurements post-injury also showed that SCI-BoNT-A group had their bladder reflexes return earlier than SCI-Saline. Initial cystometry data showed that patterns of detrusor activity during micturition functions in SCI-BoNT-A animals were similar to that of uninjured control animals. A current study is underway to compare early BoNT-A injections with late (defined as three weeks post injury) injections to confirm the benefits of novel acute BoNT-A injection.

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Poster

P366. Spinal Cord Injury: Recovery I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P366.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Imagine More Award 3309719

Title: Sensory cortical-locomotor pathway stimulation restores walking after spinal cord injury

Authors: *C. DOLICK[1], D. GRAHAM[1], D. REINHARDT[1], N. POPP[1], A. KRONER-MILSCH[2], C. M. OLSEN[3], S. K. KARADIMAS[4], K. SATKUNENDRARAJAH[2];
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Abstract: Spinal cord injury (SCI) often results in significant impairment in patients' locomotor abilities. Though there exists an increasing need for new ways of restoring function below the level of injury, treatment options remain limited. To date, motor cortex stimulation has only produced minimal improvements in functional recovery after SCI. A plausible explanation is that, in most cases, contusion injuries entirely disrupt the main corticospinal pathways originating from the motor cortex. The primary somatosensory cortex (SI) has direct neural control over the lumbar locomotor central pattern generator through cervical excitatory interneurons (SI locomotor pathway) independent of the motor cortex. We demonstrate the input-output architecture of the cervical projecting SI pyramidal neurons, and that part of this SI-locomotor circuitry is preserved after thoracic SCI. Furthermore, we used an intersectional viral approach to selectively stimulate the SI pyramidal neurons, that project to the cervical spinal cord (SI-cervical pyramidal neurons) after SCI. Chemogenetic activation of the SI-cervical pyramidal neurons after SCI restored a robust locomotor function without any adverse effects on movement, such as loss of balance or pain. Importantly, we demonstrate that the recovered locomotor function after SCI is attributed to the neuromodulation of this pathway. The modulation of the novel SI locomotor pathway not only enhances movement in health but emerges as a promising therapeutic approach for promoting locomotor recovery after SCI.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: This research is funded in part by Advancing a Healthier Wisconsin Endowment

Title: Promoting respiratory recovery in the chronic phase via cervical excitatory interneurons

Authors: *N. POPP[1], D. GRAHAM[1], D. REINHARDT[1], C. DOLICK[1], S. K. KARADIMAS[2], K. SATKUNENDRARAJAH[1];
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Abstract: Cervical spinal cord injury (cSCI) disrupts descending drive to the spinal respiratory circuitry resulting in significant respiratory compromise. Dysfunctional breathing is a significant cause of morbidity and mortality after cSCI, and although mechanical ventilation can support life, that can lead to further respiratory complications. The ability to restore breathing in the chronic phase after cSCI is an overwhelming yet essential goal. The diaphragm, the major inspiratory muscle, is innervated by phrenic motoneurons (PMNs) located in the cervical spinal cord (C3-C5). Cervical excitatory interneurons (eINs) synapse onto PMNs and discharge in synchrony with phrenic inspiratory motor output and modulate breathing. At the chronic stage, the respiratory network undergoes substantial modifications. This proposal builds upon our finding that chemogenetic stimulation of cervical eINs, while not necessary for normal breathing, plays an integral role in promoting plasticity and respiratory recovery immediately after cSCI despite a significant loss of PMNs. While there is tremendous evidence for a critical role for these neurons in modulating breathing in health and after pathological conditions, there are still critical gaps in our knowledge about the potential of these neurons to mediate plasticity and promote recovery of breathing after chronic spinal cord injury (SCI). Here, we demonstrate using art neuroanatomical techniques to detail the temporal changes in the connectivity of the respiratory neural circuitry following traumatic SCI, specifically looking at the plasticity of descending projections from premotor neurons in the brainstem to PMNs via eINs. Additionally, chemogenetic stimulation of cervical eINs, eight weeks after cSCI lead to significant enhancement of ventilation. Together, our findings demonstrate the capacity of cervical eINs in promoting respiratory plasticity and recovery after cSCI in the chronic state when promoting recovery is a daunting task.

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Poster

P366. Spinal Cord Injury: Recovery I

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Program #/Poster #: P366.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 1R01NS114007-01A1

Title: Effect of DREADDs activation of large diameter sensory afferents on recovery from contusion spinal cord injury in rats

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Abstract: Spinal cord injury (SCI) causes life-long neurological impairment with loss of sensory and motor function distal to the point of injury. There are approximately 300,000 patients living with SCI in the United States and currently no effective treatment, reducing quality of life. Epidural Electric Stimulation (EES), that is thought to excite large diameter sensory afferents (LDSA), has been found to improve recovery from spinal cord injury in conjunction with movement rehabilitation in rats and humans. We sought to develop an alternative approach for excitation of LDSA using the chemogenetic modulator of neuronal activity Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). DREADDs are activated by a putatively inert drug, clozapine-N-oxide (CNO), that crosses the blood brain barrier.
Long Evans rats were used in this study. Experimental animals had bilateral AAV2-DIO-hSyn-hm3dq-mCherry/Cre recombinase cocktail injections in L3-L5 dorsal root ganglia (DRG). Controls were injected with AAV2-mCherry into the same DRGs. 3 weeks post injection, all animals underwent a 200kDyn contusion on T10 spinal level. To assess recovery, The Basso Beattie and Bresnahan BBB locomotor rating scale, asymmetrical horizontal ladder and kinematics were scored before injury and at 3, 4, 6, 7 and 8 weeks after injury. Animals were exercised 3 times a week for 4 minutes with a 4mg/Kg intraperitoneal injection of CNO 30 minutes prior to exercise except for week 7. Week 7 was a CNO withdrawal week, seeking to determine if CNO is necessary for any observed changes in function at that time point. Horizontal ladder assays were scored on a hit/miss percentage system. Kinematics were extracted from video using DeepLabCut, and custom software written to derive parameters for each stride.
Preliminary results for 7 animals given excitatory DREADDs show a change in kinematics in week 7 with CNO withdrawal. Without DREADDs activation, these animals showed reduced minimum ankle height during the swing phase (1-way ANOVA across weeks 6, 7, 8; n=7 rats; p=0.025) and reduced anterior superior iliac spine (ASIS) height (test as above; p=0.016). CNO withdrawal on week 7 was associated with a trend towards worse ladder performance than the previous and following weeks. These results suggest that DREADDs activation may be necessary for changes in movement at longer times post injury. It does not rule out that plasticity in neural circuitry has occurred: plasticity may rely on afferent activation. As only 1 control animal completed the first study, statistical comparison of experimental animals to controls is not yet sufficiently powered; data collection is ongoing and will be added.

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Poster

P366. Spinal Cord Injury: Recovery I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01 NS101105 (WJA)
NIH Training Grant 5T32 NS077889, Neurobiology of CNS Injury and Repair

Title: Cervical spinal cord injury induces distinct changes in gut microbiome composition over time in rats

Authors: *J. S. NEWTON, C. E. TAYLOR, L. E. MENDENHALL, S. L. SPEED, C. M. CALULOT, W. J. ALILAIN;
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Abstract: Nearly 60% of all spinal cord injuries (SCI) occur at the cervical level. These high-level injuries can lead to quadriplegia, autonomic dysregulation, and interruption of the descending respiratory pathways required for breathing. As respiratory motor function is required for life, it is critical to restore breathing as soon as possible after cervical SCI. Indeed, therapeutic techniques in animal studies have been successful at restoring breathing function after SCI; however, these interventions appear to be more effective at chronic than acute timepoints post-injury. One potential cause for this observation is the impact the injury has on the gastrointestinal (GI) tract and gut microbiome, which have previously been shown to have detrimental effects on recovery outcomes, including lower limb motor function and emotional affect as indicated by increased anxiety-like behavior. However, the impact the gut microbiome has on the recovering spinal cord at different timepoints, levels, and injury severities still needs to be fully realized. We aimed to build upon these previous findings and investigate the impact of cervical SCI on the gut microbiome over time and up to chronic timepoints. We hypothesized that cervical SCI leads to transient changes in the gut microbiome, which are most severe acutely after injury impeding functional recovery of breathing, but resolve over time and thus eventually allow for more profound recovery. To test our hypotheses, we performed left C2 hemisections on adult female rats, collected fecal samples from injured, sham, and naïve animals, and assessed microbiome composition at various timepoints pre- and post-injury. Preliminary results suggest that following cervical SCI (up to 12 weeks post injury), robust differences in gut microbiome are apparent compared to non-injured animals. Future studies will classify bacterial identities and assess the impact of the post-injury gut microbiome on respiratory motor function and plasticity, as well as inter-institutional differences.

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Poster

P366. Spinal Cord Injury: Recovery I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 5R01HD081274

Title: Enhanced recovery of walking speed with combined adenosine A_{2A} receptor inhibition and daily acute intermittent hypoxia in persons with chronic incomplete SCI

Authors: *S. BARTH[1], C. TUTHILL[1], A. LINK[1], C. SLOCUM[1], G. S. MITCHELL[2], R. D. TRUMBOWER[1];
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Abstract: Acute episodes of low oxygen breathing (i.e., acute intermittent hypoxia; AIH) improve breathing ability and overground walking in persons with chronic incomplete spinal cord injury (iSCI). Based on studies in rodents, repetitive AIH elicits plasticity of spared axonal projections bypassing the injury site, thereby increasing respiratory and non-respiratory motor outputs in rats with hemisected, cervical iSCI. However, hypoxia also causes spinal extracellular adenosine accumulation, initiating a distinct mechanism that undermines AIH-induced motor facilitation. Studies in rats with iSCI found that adenosine A_{2A} receptor inhibition increases AIH-induced motor facilitation more than twofold. Thus, drugs removing the adenosine constraint to AIH-induced plasticity may improve motor function (e.g., walking) in persons with iSCI. The purpose of this study is to identify the extent to which caffeine, an adenosine A_{2A} receptor antagonist, may augment AIH-induced motor recovery in persons with iSCI. We conducted a cross-over, randomized clinical trial in a cohort of adults with chronic iSCI (injury onset 8±3.5 years, ±1.S.E). Participants received daily (5 days) treatments of caffeine (6mg/kg) 30-min prior to AIH (C+AIH) or room air (C+SHAM) and placebo prior to AIH (P+AIH) in a randomized order. A minimum of two weeks was allowed between AIH treatments (15, 1.5 min episodes; FIO2=0.10±0.02) or SHAM (15, 1.5 min episodes; FIO2=0.21±0.02). Participant vital signs were monitored throughout AIH and SHAM sessions to ensure safety. To evaluate motor recovery, overground walking speed (10-meter walk test, 10MWT) was assessed at baseline and day 5, as well as one week and two weeks post-treatment. Consistent with our hypothesis, caffeine augmented AIH-induced gains in walking performance in persons with iSCI. Participants' 10MWT time decreased following AIH alone (P+AIH: -1.9±2.0s) and C+AIH (-4.9±1.8s). The greatest reduction in walking time occurred with C+AIH, an effect that persisted for 2 weeks post-treatment (-6.3±1.8s, $p<0.01$) versus baseline. This enduring effect did not occur following C+SHAM (1.2±2.1s) or P+AIH (0.2±2.0s). We also found that the CYP1A2 genotype influences the potency of C+AIH. Persons who demonstrated the greatest gains in C+AIH walking speed possessed the homozygous (A/A) CYP1A2 genotype (fast caffeine metabolizers). These results are in part consistent with pre-clinical studies demonstrating that a selective adenosine A_{2A} receptor antagonist reduces crosstalk inhibition and enhances AIH-induced functional recovery of walking speed in persons with iSCI.

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Poster

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Program #/Poster #: P366.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS102920

Title: Sacral-coccygeal transcutaneous electrical stimulation for modulation of locomotion after spinal cord injury in humans

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Abstract: Following a spinal cord injury (SCI), the locomotor central pattern generator (CPG) loses supraspinal and propriospinal inputs leading to a loss of locomotor function. Our previous studies have shown improved locomotion after SCI using spinal cord transcutaneous stimulation (scTS) at the lumbar region (T11/T12 and L1/L2 vertebral levels). Yet, the effectiveness of scTS can be enhanced when paired locomotor training and/or pharmacological agents. In animals, the tail plays an integral role in locomotion, serving as an additional input to the locomotor CPG. While the tail is an atavism in human, the inherent anatomical connections between this area and locomotor-related neuronal network may still be present. Thus, it is possible that by stimulating the sacral-coccygeal region, we may influence the locomotor CPG. Here, we investigated the effect of stimulation over the Co1 vertebra on locomotor activity after spinal cord injury. Under approval of the University of Louisville Institutional Review Board, we conducted acute studies on non-disabled (ND) volunteers (n = 3) and a SCI volunteer with motor complete paraplegia. Continuous Co1 scTS was delivered by a constant current stimulator (BioStim5; Cosyma, Moscow) via transcutaneous electrodes using a cathode placed over the Co1 region and two bilateral anodes over the abdomen. Monophasic pulses were delivered at 30 Hz with a carrier frequency of 5 kHz, and a pulse width of 1 msec. Current amplitude was dictated by observed locomotor behavior and the absence of discomfort of the participant. Behavioral assessments in a gravity neutral setting showed that multiple muscles became active after Co1 scTS in the SCI group, increasing electromyography (EMG) power significantly ($p<0.001$). No change was observed in the ND group. Meanwhile, coefficient of variation of the EMG was lower in the SCI group ($p<0.005$) during Co1 scTS. Neurophysiological assessments using spinally evoked motor potentials (SEMPs) at the L1/L2 vertebral level during voluntary tasks with Co1 scTS showed no difference in the ND group, but showed inhibition in the SCI group when compared to control SEMPs ($p<0.005$). Furthermore, SEMPs evoked at Co1 showed an additional late response in the extensor muscles when compared against SEMPs at L1/L2. These results suggest that Co1 scTS targets the locomotor CPG through indirect pathways and this input can be considered as a modulator of locomotor function. These results establish a novel approach to scTS that may lead to increased rehabilitative effectiveness in improving locomotor recovery after SCI.

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Poster

P366. Spinal Cord Injury: Recovery I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: MnDRIVE Discoveries through Industry Partnerships Fellowship in Neuromodulation
Stem Cell Institute Predoctoral Award
Minnesota Spinal Cord Injury and Traumatic Brain Injury Grant

Title: Rapid Differentiation of iPSC Derived Dorsal Spinal Cord Progenitors for Use in Spinal Cord Injury

Authors: *A. HUNTEMER-SILVEIRA[1], D. MALONE[2], P. WALSH[2], A. PARR[3];
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Abstract: In the United States, there are approximately 18,000 new cases of spinal cord injury (SCI) each year, and more than half of these cases result in paralysis of two or more limbs, with individual economic costs in the millions. SCI can diminish or abrogate both motor and sensory systems. With the advent of human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), the future of regeneration of neurons in SCI is promising. In the past decade, deriving motor neurons (MNs) from both iPSCs and hESCs has increased our understanding of degenerative spinal motor diseases, as well as shown successful transplantation in rat models. However, comparatively little has been published to date applying the same strategies to the dorsal spinal cord and promotion of sensory recovery. This is critical, as the majority of SCI patients report both impaired sensory perception as well as debilitating chronic pain. Therefore, an imperative next step is to develop protocols to successfully differentiate stem cells into sensory neuron and interneuron populations. Unfortunately, this has been far less studied; a protocol to differentiate stem cells into these cell types in a short amount of time remains to be seen. We report here the preliminary results of our work generating a rapid differentiation protocol of region specific dorsal spinal cord progenitor cells in approximately 5-7 days from human iPSCs. Our ultimate goal is to combine these cells with our ventral MNs in a transplantation model in order to attain correct repair and reconnection at the site of injury, restoring both motor and sensory systems. These discoveries will push the field of spinal regeneration forward and offer hope to those affected by SCI.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS R01NS099076
Commonwealth of Pennsylvania 4100083087
NIH 1F31NS122245-01

Title: Rebuilding serotonergic regulation for cardiovascular functional recovery after spinal cord injury

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Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Cardiovascular dysfunction is one of the leading causes of mortality and morbidity among the population with spinal cord injury (SCI). Recently, transplanting embryonic raphe nuclei derived neuronal progenitors (RN-NPCs) into the rat injured spinal cord has been shown to mitigate disordered cardiovascular function. To determine if both host and graft-derived serotonergic ($5HT^+$) transmission mediate this functional restoration, we grafted embryonic day 14 (E14) RN-NPCs into the lesion of crushed spinal cord, which allows for better graft-host integration, at the 4th thoracic level. Rats receiving transplantation of E14 spinal cord-derived neural progenitor cells (SC-NPCs), or injury alone served as controls. Using radio-telemetric recordings, we analyzed resting hemodynamics, daily occurring spontaneous autonomic dysreflexia (AD) events, and the severity of colorectal distension (CRD)-induced AD. Subsequently, pharmacological and chemogenetic interventions were employed to elucidate reestablished supraspinal or intraspinal serotonergic machinery of cardiovascular function. The results demonstrated that RN-NPC grafts decreased tachycardia at rest, mitigated AD severity, and decreased the number of daily spontaneous AD events. Intrathecal (*i.t.*) administration of the $5HT_{2A}$ antagonist, Ketanserin, increased the resting heart rate in RN-NPC grafted rats, suggesting that the reduction in tachycardia is mediated in part through graft-derived serotonergic mechanisms. Unexpectedly, injections of Lenti-TPH-hM4Di-mCherry into the host raphe magnus to silence serotonergic neurons reduced the heart rate in RN-NPC but not SC-NPC grafted or injury only rats. This might be due to the interaction between host $5HT^+$ cells and grafted neurons. In addition, administration of the α-1 adrenoreceptor, Prazosin, significantly decreased AD severity, indicating the involvement of catecholamines in the reflexic response. Overall, it illustrates that grafted RN-NPCs-induced cardiovascular recovery is partially mediated through reconstituted supraspinal and graft-derived intraspinal serotonergic mechanisms. The results provide vital guidance to develop cell-based therapeutic approaches for cardiovascular recovery in SCI patients.

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Poster

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Program #/Poster #: P366.10

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Microfluidic high throughput screening platform to screen preclinical stage compound effects on neurite outgrowth of human motor neurons post injury

Authors: *J. RONTARD, A. BATUT, M. GLEYZES, D. DEBIS, M. LIBRALATO, L. DUBUISSON, J. VIEIRA, Y. CALDERINI, F. LARRAMENDY, T. HONEGGER;
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Abstract: Traumatic spinal cord injury (SCI) affects millions of people of all ages around the world and can potentially lead to irreversible cognitive and motor damage without any immediate therapeutics available. There is a significant demand for physiologically relevant models of SCI. The rise of Organ-on-Chip technologies combined with human cells opens new route to limit the number of animal experiments. The major modeling challenge is to accurately perform the injury only on the neurites without affecting cell viability and to apply the pre-clinical stage compounds on cell soma only. Microfluidic chip designs applied to neuroscience research are based on connection between compartmentalized neuronal populations through guiding neurite outgrowth by using microchannels. The longitude of microchannels acts as a selective barrier for the exclusive passage of axons over dendrites and it promotes the unidirectional growth of the neurites from one compartment to the other.We will present the design and fabrication of a compartmentalized microfluidic device with three compartments capable of both inducing a localized axotomy and a fluidly isolated cell chamber. The device allows quantification of axonal regeneration post-injury using an innovant and unique triangular design. Human-induced pluripotent stem cell-derived motor neurons are seeded and maintained up to 3 weeks in vitro. We performed a chemically-induced axonal injury on isolated axons in the middle compartment only. We then follow the dynamics of the axonal regeneration using the triangular methodology with and without tested neuropharmacological compounds in soma chamber. We show that this model can be sucessfully used for quantitative analysis of neurite outgrowth dynamics. We will finally present how this model can be used to record the functional activity using multielectrode arrays (MEA) coupled to the microfluidic device. The access to functional data during the injury and the recovery process provides relevant insight on the mode of action of pharmacological compounds. Our data suggest that this model can be used for high-throughput drug-induced axonal regeneration screening for preclinical stages pharmaceutical compounds. In conclusion, this study shows the added value of neurofluidic design strategies for the investigation of neurite length dynamics. To further strengthen the efficacy of those strategies, future work should focus using such methodology to evaluate the effect of pharmacological compounds on neurite elongation and orientation on maturing and mature human culture as well as proving the impact of hydrostatic pressure on neural architecture manipulation.

Disclosures: J. Rontard: A. Employment/Salary (full or part-time):; NETRI. **A. Batut:** A. Employment/Salary (full or part-time):; NETRI. **M. Gleyzes:** A. Employment/Salary (full or part-time):; NETRI. **D. Debis:** A. Employment/Salary (full or part-time):; NETRI. **M. Libralato:** A. Employment/Salary (full or part-time):; NETRI. **L. Dubuisson:** A. Employment/Salary (full or part-time):; NETRI. **J. Vieira:** A. Employment/Salary (full or part-time):; NETRI. **Y. Calderini:** A. Employment/Salary (full or part-time):; NETRI. **F. Larramendy:** A. Employment/Salary (full or part-time):; NETRI. **T. Honegger:** A. Employment/Salary (full or part-time):; NETRI.

Poster

P366. Spinal Cord Injury: Recovery I

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Program #/Poster #: P366.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Nielsen Foundation

Title: Bone loss following spinal cord injury: effects of age and time post injury

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Abstract: Following spinal cord injury (SCI), more than 80% of individuals develop osteopenia or osteoporosis. This unseen consequence of SCI renders these people 104 times more likely to have a bone fracture before the age of 50. Post-fracture complications then occur in 50% of cases, including venous thromboembolism, respiratory and urinary tract infections, and fracture nonunion, further increasing healthcare costs, morbidity and mortality. Despite the high prevalence of osteoporosis after SCI, and the overwhelming effects on quality of life, very few studies have focused on bone loss. It is critical that we understand how SCI affects bone. Further underscoring this pressing need, the SCI population is aging, and the age at which trauma occurs is increasing. Surprisingly, however, there have been no studies on the effects of age on bone loss after SCI. This study aims to address this gap in knowledge. We hypothesized that bone loss after SCI would increase with age and would be exacerbated with increased time post injury. To test this, we assessed bone loss in young (2-3 months) and old (9-10 months) male rats given a moderate spinal contusion injury. We collected the proximal tibia of the rats 1 and 6 months after SCI and assessed changes in the cancellous and cortical bone. Despite recovery of plantar weight-supported stepping, SCI rats had significantly less trabecular bone volume at both 1 and 6 months post injury when compared to age-matched shams. Both young and old rats also had higher osteoclast surfaces at one month post SCI. This increased osteoclast activity persisted until 6 months in the young rats, but was not present in older rats. Alarmingly, decreased bone formation also persisted even 6 months post SCI in both young and old rats. This means that in addition to the dramatic bone loss seen in acute SCI, osteogenic potential remains insufficient in the chronic stage. Together these results suggest that following SCI, regardless of weight-bearing, male rats exhibit decreased osteoblast and increased osteoclastic activity, leading to sustained bone loss even six months after injury. These data suggest that as the SCI population continues to age, the effects of bone loss on health and quality of life will also increase exponentially. It is critical that we identify the mechanisms mediating bone loss in this model, and begin testing novel interventions that improve bone integrity in people with SCI.

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Poster

P366. Spinal Cord Injury: Recovery I

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Program #/Poster #: P366.12

Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Polyethylene glycol attenuates secondary injury after spinal cord injury by preserving blood-spinal cord barrier (BSCB) in experimental rat model

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Abstract: Subsequent spinal vascular disruption following spinal cord injury (SCI) leads to breakdown of blood-spinal cord barrier (BSCB) which results in uncontrollable neuronal cell and glia necrosis and apoptosis. It is hard to prevent BSCB destruction because it occurs immediately after trauma and rapidly spread to rostral and caudal sites. Polyethylene glycol (PEG) is a hydrophilic polymer regarded to have fusogenic property which can seal the ruptured cell membrane and has been tried to use as a therapeutic substance for cell protection after SCI. In the present study, we investigated the effect of PEG on the vascular system after SCI, especially on the BSCB integrity. Spinal contusion was made at T11 segment in adult male SD-rats. Immediately after SCI, PEG was injected under the dura mater and 0.9% saline was injected for sham controls. Effect of PEG on BSCB integrity was proved with examining a leakage of molecules and number of blood vessel in lesion site by using Evans blue dye (EBD) and laminin staining in rats with contusive SCI. The damage of BSCB and blood vessels were assessed over time after spinal contusion (0, 3, 6, 12 and 24 hours after SCI). To confirm the actual function of blood vessels after SCI, we used 2,3,5-Triphenyltetrazolium chloride staining (0, 6 and 24 hours). Motor function was evaluated by using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale and combined behavioral score (CBS) (before and 1, 3, 5, 7, 10, 14, 21, 28, 35 and 42 days after SCI). Sparing tissues were analyzed with Luxol fast blue and cresyl violet staining after behavioral assessments. Leaked EBD from microvasculature started immediately after SCI and continued for 24 hours after SCI. In PEG group, Overall leakage of EBD was significantly decreased compared to sham control 0, 6, 12 and 24 hours after SCI. Blood vessels replaced more rapidly the lesion site at 6 and 24 hours after SCI in the PEG group compared to sham control and infarction sizes also were less in PEG group at 0, 6, 24 hours after SCI. In behavioral assessments, PEG group also showed earlier improvement of neurological locomotor function and prolonged recovery for 42 days post-SCI. The cavitation and shrinkage of spinal tissues in epicenter were also significantly less after PEG application. The present results demonstrated that PEG application in acute phase can attenuate ischemic injury in gray matter and improve earlier recovery of neurological functions through rapidly preventing the disruption of vascular system and preserving BSCB after SCI.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Modulation of astroglia-neuron trophic coupling and functional recovery after spinal cord injury by targeting the thrombin receptor

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Abstract: Excessive activation of the thrombin receptor, protease activated receptor 1 (PAR1) is implicated in diverse neuropathologies from neurodegenerative conditions to neurotrauma. PAR1 knockout mice show improved outcomes after experimental spinal cord injury (SCI), however information regarding the underpinning cellular and molecular mechanisms is lacking. Here we demonstrate that genetic blockade of PAR1 in female mice results in improvements in sensorimotor coordination after thoracic spinal cord lateral compression injury. We document improved neuron preservation with increases in Synapsin-1 presynaptic proteins and GAP43, a growth cone marker, after a 30 days recovery period. These improvements were coupled to signs of enhanced myelin resiliency and repair, including increases in the number of mature oligodendrocytes, their progenitors and the abundance of myelin basic protein. These significant increases in substrates for neural recovery were accompanied by reduced astrocyte (Serp1) and microglial/monocyte (CD68 and iNOS) proinflammatory markers, with coordinate increases in astrocyte (S100A10 and Emp1) and microglial (Arg1) markers reflective of pro-repair activities. Complementary astrocyte-neuron co-culture bioassays suggest astrocytes with PAR1 loss-of-function promote both neuron survival and neurite outgrowth. Additionally, the pro-neurite outgrowth effects of switching off astrocyte PAR1 were blocked by inhibiting TrkB, the high affinity receptor for brain derived neurotrophic factor. Altogether, these studies demonstrate unique modulatory roles for PAR1 in regulating glial-neuron interactions, including the capacity for neurotrophic factor signaling, and underscore its position at neurobiological intersections critical for the response of the CNS to injury and the capacity for regenerative repair and restoration of function.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Transplanting embryonic raphe nuclei-derived neural progenitor cells into the injured spinal cord improves cardio-electric disorders

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Abstract: High-level spinal cord injury (SCI) often interrupts supraspinal regulation of sympathetic activity to the heart. The loss of balance between autonomic components renders the occurrence of cardio-electric disorders such as arrhythmias. To reestablish serotonergic regulation of cardiac sympathetic activity, we transplanted embryonic day 14 (E14) raphe nuclei-derived neural progenitor cells (RN-NPCs) into the lesion of a crushed rat spinal cord at the 2nd thoracic (T2) level. Animals receiving E14 spinal cord-derived neural progenitor cells (SC-NPCs), injury alone or naïve served as controls. After 10-12 weeks, a radio-telemetric system was used to record electrocardiogram (ECG) and blood pressure (BP) for parameter analyses, including 24-h recording for heart rate variability (HRV), cardiac arrhythmias during colorectal distention (CRD) induced autonomic dysreflexia (AD) or dobutamine stress tests to mimic exercise. As a result, transplanting RN-NPCs significantly increased HRV which were characterized by increased values of root-mean-square of successive differences (RMSSD) in time domains and of low frequency (LF) in frequency domains, indicating enhanced sympathetic activity. The grafts decreased the occurrences of various arrhythmias during CRD-induced AD. When different doses of dobutamine were administered, the number of arrhythmias was significantly increased in rats grafted with SC-PNCs or injury alone but not those with RN-NPCs. Subsequently, pharmacological interventions showed that grafted RN-NPCs reconstituted sympathetic tone to the heart. Histological analysis revealed grafted serotonergic cell survival and well-integration with the host tissue. Numerous graft-derived serotonergic axons projected to the caudal autonomic regions innervating sympathetic neurons. The results indicated that RN-NPC transplants improve cardiac performance by possibly reestablishing serotonergic regulation for the recovery of sympathetic activity following SCI. Ultimately, this finding helps understand cardio-electric disorders in SCI subjects and provides insight on potential therapeutic strategies.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Topic: D.03. Somatosensation – Pain

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Title: Mapping the connections between motor cortex and pain circuits

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Abstract: The dual chronic pain and opioid epidemics have prompted an urgent search for alternative, non-addictive methods of analgesia. One promising alternative is non-invasive electrical or magnetic stimulation of the motor cortex (MC). While MC stimulation (MCS) has repeatedly been found to reduce chronic pain in human subjects and to decrease nocifensive behaviors in rodent models, how MC is connected with, and influences activity in, pain circuits remains unclear. To fill this gap in knowledge, we identified MC neurons active during pain and traced their connectivity by combining calcium imaging of thousands of cortical neurons in mice exposed to noxious stimuli with viral tracing from activity-determined MC nociceptive neurons. We identified a population of MC neurons that is distinctly more active during the application of a noxious stimulus than an innocuous stimulus. In particular, our calcium imaging studies revealed that the majority of MC nociceptive neurons activated following orofacial application of capsaicin are in the M2 subregion. Consistently, in TRAP2/Ai14 mice, in which neurons activated following capsaicin application express the fluorescent reporter tdTomato, we observed a population of tdTomato+ neurons in M2. The density of tdTomato+ neurons in M2 is comparable to that found in the primary somatosensory and anterior cingulate cortices (S1 and ACC, respectively), two cortical regions known to be important for pain perception. Finally, using viral tracing in TRAP2 mice, we labelled the outputs of M2 nociceptive neurons. Notably, we identify outputs to regions mediating the affective-motivational and cognitive-evaluative dimensions of pain experience, like the amygdala and medial thalamus, and regions involved in descending pain control such as the periaqueductal gray, through which motor cortex could influence nociceptive processing and pain perception. Altogether, our data suggests that motor cortex activity increases during pain and that this activity could influence downstream regions during pain perception. Determining how motor cortex influences pain experience could lead to improved stimulation protocols to relieve pain suffering in chronic pain patients.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Program #/Poster #: P385.02

Topic: D.03. Somatosensation – Pain

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Ministry of Sciences and Technology, Taiwan R.O.C. Grant#99-2811-B-001-072

Title: Functional Assessment of P2X7 activity alone the thalamocingulate pathway under nociceptive stimulation

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Abstract: Based from our previous works on the P2X7 and central post-stroke pain(CPSP), we have known that the P2X7 gets raised under CPSP condition and targeting P2X7 could vary the CPSP. Published reports that utilized mice with genetic deletion of P2X7 have shown reduced pain sensation. Although adenosine 5′-triphosphate (ATP) has been reported as a transmitter in the peripheral nervous system, and, a recording of evoked and miniature synaptic currents in the rat medial habenula have supported such a role in the central nervous system(CNS), whether ATP and its receptor directly involved in nociceptive transmission as well as its presence along the pain path in the CNS remain unclarified. In views of the mentioned significance of P2X7 involved in chronic/neuropathic pain and views of its role as a receptor for a known neurotransmitter ATP, we set to study the functional role of this receptor particularly during pain signaling in the thalamocingulate path with established pain models. We 1st utilized major *in vivo* and *ex vivo* neuropharmacological methods to record the effects of manipulating P2X7 receptors during neuron transmission with electrical stimulations(sciatic nerve stimulation, SNS) to mimic nociceptive inputs along the thalamocingulate path and synergistically analyzed the changes of downstream neurotransmitters or molecules following the SNS and P2X7 activation in wild type and P2X7 knockout mice(P2X7 KO) with combined microdialysis and high performance liquid chromatography (HPLC) methods. Secondly, we utilized live-Ca2+ imaging to verify the functional presence of P2X7 in the medical thalamus (MT) and anterior cingulate cortex(ACC). Our result revealed that upper MD application of P2X7 agonist or antagonists promoted or inhibited of both MT and ACC neuron activities. Under SNS, an elevated amount of Glu and ATP, ADP was detected in dialysate collected from the MT, whereas accompanied P2X7 antagonist application could reduce such an elevation in the combined microdialysis and HPLC assay. Brain slice Ca2+ imaging at MT and ACC Cg2 region reveals responsive calcium influx post P2X7 agonist BzATP application. In brief, the information provide in this study may help to address the role of P2X7 playing in the pain transmission along the major ascending pain path, thalamocingulate circuit. Furthermore, resolve the controversial unclearness of the presence of P2X7 alone the ascending pain transmission path in the central nerve system (CNS). These results may contribute knowledge for the pathophysiology to the onset of abnormal painful sensation and hence could contribute therapeutic potentials.

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Poster

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Title: Higher brain entropy predicts mindfulness meditation-based pain relief

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Abstract: Mindfulness meditation (MM) significantly relieves pain after minimal training through multiple neural mechanisms that are yet to be fully understood. Shannon brain entropy is a quantifiable measurement of uncertainty in the probability distribution of spontaneous neural dynamics. Within a hierarchical Bayesian inference cortical framework that matches ascending sensory signals with higher-order predictions, higher entropy reflects a dynamic neural state in which expectations are weakened to facilitate new predictions. Thus, brain entropy is a novel mechanistic target for self-regulatory mind-body approaches. Although recent work has shown that long-term MM practice increases electrophysiological markers of entropy, no known studies have examined if MM-induced pain relief is associated with entropy modulation. The proposed exploratory fMRI and psychophysical pain study investigated if mindfulness-based pain relief is associated with higher cortical Shannon brain entropy. After a baseline pain testing session, 40 pain-free participants (mean age = 30 years, 20 females) were randomized to four, 20-minute sessions of mindfulness meditation training or book listening. After successful completion of the regimens, fMRI scans were acquired during noxious heat (ten trials of alternating 12 seconds of 49°C) stimulation of the right calf during rest (all subjects) as compared to meditation (MM group) and rest (controls). After each scan, visual analog scale ratings of pain intensity (0 = no pain, 10 = worst pain imaginable) were collected. A 2 (rest vs. manipulation) X 2 (group) repeated measures ANOVA tested for group X manipulation differences on pain. Time series correlations between 48 distinct cortical regions were used to build functional connectivity matrices and thresholded (r = 0.40) to build networks during noxious heat scans. The Shannon entropy of networks' nodal degree distributions was compared across groups and conditions. To test the study hypothesis, MM-driven entropic changes were regressed onto residualized pain ratings. The significant interaction, $F(1,38) = 26.31$, $p < .001$, $\eta_p^2 = .41$) was driven by the reduction in pain intensity (-32%) by MM when compared to controls (+20%). Preliminary results show that MM significantly increased cortical entropy as compared to controls ($F(1,38) = 5.097$, $p = .030$, $\eta_p^2 = .12$). Further, higher MM-driven entropy predicted lower pain. We postulate that MM induces a high entropic state that lowers the influence of pain predictions to downregulate the experience of pain.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Topic: D.03. Somatosensation – Pain

Support: NIH BRAIN Initiative UH3 NS109556
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Title: Prediction of chronic pain state using intracranial neural biomarkers

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Abstract: Chronic, neuropathic pain syndromes are often refractory to treatment and impose significant suffering and disability. Chronic pain severity is often measured through subjective report, while objective biomarkers that may guide diagnosis, monitoring, and treatment are lacking. It is further unknown what brain activity underlies clinical chronic pain experiences on clinically relevant timescales or how this relates to experimentally evoked, acute pain. To identify neural substrates of chronic pain, four subjects with refractory, chronic neuropathic pain were implanted with intracranial electrodes and underwent long-term ambulatory recording of neural activity from the anterior cingulate (ACC) and orbitofrontal (OFC) cortex over months. Subjects longitudinally reported chronic pain metrics coincident with neural recordings obtained multiple times daily over months. We successfully predicted intraindividual chronic pain severity scores from direct neural activity with high sensitivity using machine learning methods. Chronic pain decoding relied on signals from a novel brain region, OFC, which tended to differ from patterns of neural activity associated with acute, evoked pain states during a task. Intracranial signals from OFC can successfully be used to predict spontaneous, chronic pain state over ecological timescales in patients.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Topic: D.03. Somatosensation – Pain

Support: DoD W81XWH-20-1-0790
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Title: Tiam1-mediated synaptic plasticity drives comorbid depressive symptoms in chronic pain

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Abstract: Chronic pain and depression are frequently comorbid, and their coexistence tends to worsen the severity of both disorders. Currently, the molecular mechanism underlying comorbid depressive symptoms in chronic pain is unclear. Ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, induces rapid and sustained antidepressant-like effects in chronic pain-induced depression in both patients and animal models. However, the mechanisms underlying ketamine's sustained antidepressant effects remain elusive. Here, we show that Tiam1, a Rac1-specific guanine nucleotide exchange factor (GEF) that was previously identified as a critical mediator of NMDAR-dependent dendritic spine development, is activated in the ACC in chronic pain mice displaying depressive-like behaviors. Conditional deletion of Tiam1 from postnatal forebrain excitatory neurons, specific deletion of Tiam1 from ACC neurons, or pharmacological inhibition of the Tiam1-Rac1 signaling pathway prevents chronic pain-induced depressive-like behaviors in mice. Biochemical, morphological, and electrophysiological assays reveal that Tiam1 orchestrates synaptic structural and functional remodeling in ACC neurons via actin cytoskeleton reorganization and synaptic NMDAR stabilization. This Tiam1-coordinated synaptic plasticity underpins ACC hyperactivity and drives chronic pain-induced depressive-like behaviors. Ketamine induces sustained antidepressant effects in chronic pain by blocking Tiam1-mediated synaptic structural and functional plasticity in ACC neurons. Our results reveal Tiam1 as a key factor in the pathophysiology of chronic pain-induced depression and in the sustained antidepressant effects of ketamine in ACC neurons. These findings highlight Tiam1 as a potential therapeutic target for the treatment of comorbid depressive symptoms in chronic pain.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Topic: D.03. Somatosensation – Pain

Support: IRC: Interfaculty Research Cooperation (IRC) "Decoding Sleep", University of Bern

Title: Neuronal Dynamics of the Sensory-Discriminative and Affective-Motivational Components of Pain during Sleep

Authors: *R. SANDOVAL ORTEGA, M. RENARD, P. DE LUNA, T. NEVIAN;
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Abstract: Painful somatosensation undergoes parallel processing. Thus, the pain response can be divided into a sensory-discriminative and an affective-motivational component, mediated by the lateral and the medial pain pathway, respectively. Yet, processing of these two pain components during sleep remains unknown. We performed multisite recordings in the ventroposterior nuclei of the thalamus (VPx) and the primary somatosensory cortex of the hindlimb (S1HL) to study the processing of the sensory component, and in the mediodorsal nucleus of the thalamus (MD) and the anterior cingulate cortex (ACC) to record the processing of the affective component. Freely moving implanted mice received either non-painful touch or painful pinprick stimuli to the hind-paws to identify differences between touch and pain processing in sleep and wake. We find the stimuli-evoked-dynamics of the sensory pathway to be different from the affective one. This is especially true in wake, where we have observed that top-down expectations activate the S1HL but not the ACC. However, Evoked Response Potentials (ERPs) in NREM sleep show that processing of pain is faster than touch and, contrary to touch, engages the sensory and the emotional component almost simultaneously. We further divided the data into the different behavioral responses evoked by the stimuli: presence or absence of paw withdrawal and awakening or maintained sleep. Non-painful responses activated both pain pathways in a similar fashion independently of the behavioral response or arousal state. On the contrary, pain-evoked neural dynamics were behavior-specific, waking up from sleep being the strongest response observed both in the S1HL and ACC, but not in thalamic areas. Finally, we assess how pre-stimulus neural activity affects the behavioral responses. In NREM sleep, high delta (1 - 4 Hz) power in the ACC had a protective effect on sleep, reducing the probability of waking up from painful stimuli, but not from non-painful ones. Unexpectedly, heightened ACC gamma (30 - 100 Hz) power was observed in maintained sleep trials in both stimulation types. S1HL neural activity did not influence the behavioral outcome in NREM trials but high gamma power in wake prior to the stimulation predicted paw withdrawal. These findings highlight for the first time the differences between the processing of the sensory and affective components of noxious and non-noxious somatosensory stimuli during sleep. Therefore, they open a door to understand how the processing of somatosensation during sleep may lead to the development and establishment of chronic pain, a disease which is still not fully understood and lacks standardized treatments.

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Poster

P385. Pain: Thalamic and Cortical Processing

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Title: Painful laser-evoked potential reflects pain catastrophizing

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Abstract: Numerous studies show pain catastrophizing — a cognitive process characterized by ruminating, magnifying, and/or experiencing helplessness about pain — is a powerful predictor for adaptation and response to treatment for chronic pain. In this study, we aim to determine pain-related electroencephalography (EEG) characteristics associated with pain catastrophizing. Ten healthy individuals (21.8±1.9 yrs, 5 female) were recruited to the study. The 13-item Pain Catastrophizing Scale (PCS) was administered. A Nd:YAP laser stimulator was used for pain induction such that each laser stimulation induced a pin-prick acute pain challenge (about 40 to 50 pain on a scale of 0 to 100, where 0 indicates “no pain at all” and 100 indicates “maximum pain possible”). Thirty triplet (inter-stimulus interval 1 second, inter-triplet intervals 7-9 seconds) stimulations were delivered to the dorsum of the left hand. During the study, subjects wore protective goggles, rested comfortably on a couch, and kept their eyes open. To maintain stable attention, subjects were asked to actively appraise pain levels during each stimulus, and report them after each triplet stimulation trial. Evoked potentials were recorded by placing disc electrodes over the Fz, C3, C4, Cz, Pz, T7, and T8 locations (10-20 electrode placement referenced to linked earlobes). Analogous to the laser stimulation, non-painful electric shock stimulation (40-50 stimulus intensity) was also used in a separate session for pain versus non-painful comparisons. We measured the mean amplitude of the evoked potential after manual removal of artifacts. Overall, the amplitude of painful laser and non-painful electric shock evoked potentials attenuated significantly within each triplet stimulation where the first stimulation within the triplet evoked the largest potentials, then the second and followed by the third ($p < 0.01$). Furthermore, greater amplitude attenuations between the first and the second laser stimulation on the midline frontal Fz, as well as bilateral sensorimotor C3 and C4 correlated with higher pain catastrophizing scale (Spearman's rho > 0.73, $p < 0.05$). No significant correlation was found between PCS and non-painful electric shock. These results may help to better understand brain mechanisms of pain catastrophizing in relation to acute painful stimuli. Accordingly, we propose that if these EEG characteristics are modifiable and could be extended to chronic pain models, this knowledge could also inform the development of new neuromodulatory interventions for preventing and managing chronic pain.

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Poster

P385. Pain: Thalamic and Cortical Processing

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P385.08

Topic: D.03. Somatosensation – Pain

Title: The influence of participant posture on laser evoked potentials

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Abstract: *Introduction:* Laser evoked potentials (LEP) are commonly employed to assess spinothalamic tract function within the human somatosensory system. Painful laser stimuli are typically delivered in the periphery, with responses recorded from multiple brain regions via electroencephalography (EEG).

Interestingly, there are discrepancies among research groups in the posture/positioning of participants during LEP assessments, be that either seated or lying. Our primary aim was to investigate the influence of altering participant posture (lying, sitting, standing) on LEP outcomes.
Methods: Twenty (20) healthy participants (Age 24.3±4.6) received noxious laser (Nd:YAP) stimuli on the left forearm and the left thigh, at participants' pain threshold (range 2.25-3.5 J), in three postural conditions (lying, sitting, standing). Participants received 20 stimuli at each location and in all three postures, in a randomized order. Participants reported their perceived pain following each laser stimuli, via a 0-10 numerical rating scale (NRS). Brain activity was recorded using 32 EEG electrodes, according to 10-20 international positioning. EEG data was band-pass filtered 0.5-30Hz, with baseline corrected EEG epochs (100ms pre-laser to +1000ms post-laser) averaged to produce N2P2 waveforms. We used linear mixed models to assess differences between postural conditions for N2P2 waveform amplitudes and latencies as well as NRS responses to laser stimuli.
Results: For leg stimulations, a main effect of postural condition was observed for N2 latency ($F_{(2,33.1)}$=5.28, p=0.01). We observed significantly shorter N2 latencies in sitting compared to standing (t=3.19, p=0.009), with similarly shorter N2 latencies in sitting compared to lying, albeit not significant (t=2.19, p=0.10). There were no significant differences for N2 latencies between lying and standing (t=1.1, p=0.95), nor were there any significant differences in any other LEP outcomes or NRS responses. There were no significant effects of postural condition for arm stimulations.
Conclusions: Previous studies have observed reducing N2 latencies following experimental pain induction, suggesting our reduced N2 latencies during sitting may be indicative of a heighted nociceptive response. For those employing LEPs, our findings suggest the choice of participant posture does indeed influence LEP outcomes, with the greatest influence on N2 latencies derived from the lower limb.

Disclosures: L.D. Linde: None. **O. Ortiz:** None. **J.L.K. Kramer:** None.

Poster

P385. Pain: Thalamic and Cortical Processing

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Program #/Poster #: P385.09

Topic: D.03. Somatosensation – Pain

Support: Grunenthal Foundation - Young Pain Researcher
FLAD - R@D grant
CCDRN [Norte-08-5369-FSE-000026]

Title: Presurgery limbic brain structural properties predict pain persistence after joint replacement surgery for osteoarthritis

Authors: *J. BARROSO[1], P. BRANCO[2], J. PINTO-RAMOS[3], A. VIGOTSKY[2], T. J. SCHNITZER[2], V. M. GALHARDO[4], A. V. APKARIAN[5];
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Abstract: Osteoarthritis (OA) is one of the most prevalent musculoskeletal diseases, affecting an estimated 10 percent of the world's population over the age of 60 and its prevalence is projected to increase - with an estimated 130 billion people affected by the year of 2050. Joint replacement surgery is a successful intervention, treating pain and OA-related disability, however a substantial proportion of patients (10-37%) still report moderate to severe pain after surgery. Mechanisms of persistent pain after surgery remain unclear. In this prospective longitudinal study, we studied structural properties of the subcortical brain, together with clinical and demographic indices, as possible predictors of pain persistence 6 months after surgery.We followed a population of 81 knee OA (kOA) patients from before total knee replacement surgery (TKR) until 6 months after the intervention. Longer pain duration, higher levels of pre-surgical anxiety and a neuropathic pain profile were predictive of pain persistence after surgery. Subcortical volumes were also predictive of the outcome: larger volumes of the bilateral thalamus, amygdala and left hippocampus were associated with pain persistence. Next, by studying shape properties, a more granular measure, we uncovered that an outward displacement of the right amygdala and right anterior hippocampus were also associated with pain persistence. Finally, we queried if the clinical/psychological predictors and subcortical properties had unique value to explaining the outcome. To do so, we built sequential regression models to explain the magnitude of post-surgical pain. We uncovered that adding brain parameters to clinical predictors led to a significant increase in the predictive value of the model (final model, R^2 0.44, $p<0.001$).Our results demonstrate that the predictive value of subcortical anatomic indices on post-surgical pain is additive to the clinical predictors and revealed a final model able to explain 44% of the variance of post-surgery pain intensity. Current notions of persistent pain after a technically successful TKR surgery have focused on clinical/psychological dimensions, without a clear mechanistic link to pain physiology. We show that structural properties of the brain's limbic circuitry are predictors of pain maintenance after TKR surgery. These results support the importance of limbic neuroanatomical factors in the persistence of chronic pain and open a new avenue not only for studying post-surgery pain mechanisms but also regarding clinical care of OA pain patients.

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Poster

P421. Olfactory Coding: Second Order Regions

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Program #/Poster #: P421.01

Topic: D.05. Olfaction and Taste

Support: NIH BRAIN U01-NS108637

Title: Ultrastructure of the chemosensory rhinophore ganglion and its connective in the nudibranch mollusc Berghia stephanieae reveals an unexpectedly complex anatomical organization

Authors: B. D. DRESCHER[1], Y. MEIROVITCH[2], C. TAIT[3], ***H. H. SANT**[3], E. PAVARINO[2], R. SCHALEK[2], S. WANG[2], Y. WU[2], J. W. LICHTMAN[2], P. S. KATZ[3];
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Abstract: Nudibranch molluscs use their rhinophores, a pair of dorsally positioned cephalic sensory appendages, to detect chemical cues in their environment. Little is known about the structure and function of the rhinophore ganglion itself, which is positioned at the base of each rhinophore. We used a volume electron microscopy approach to elucidate organization of the rhinophore ganglion and the connective to the cerebral ganglion, in the nudibranch *Berghia stephanieae*. The rhinophore connective carries the axons of primary sensory neurons and interneurons from the rhinophore and the rhinophore ganglion into the brain. Efferent neurons from elsewhere in the brain also project axons through the rhinophore connective into the rhinophore ganglion and further into the rhinophore. A single rhinophore ganglion and connective were serially sectioned at 33 nm and imaged at 4 nm resolution. Stitched and aligned sections from the connective were segmented using machine learning and proofread manually. The rhinophore ganglion neuropil contained a high density of vesicle-filled varicosities, which may be multi-neuronal complex synapses, as well as numerous vesicle-free neurite tracts. The ganglion contained almost 9000 neuronal nuclei, which were mostly clustered along the periphery. Thus, each rhinophore ganglion had nearly twice as many neurons as the rest of the brain (cerebropleural and pedal ganglia). The connective contained approximately 30,000 axon profiles with varied staining densities, clustered into distinct fascicles, which were surrounded by fewer than 50 large glial cells. While the range of axon cross sections was 90 nm to 500 nm, most of them were about 200nm. Two axon fascicles had distinct ultrastructure and extremely thin processes (~100nm); we determined that these were a set of primary sensory afferent axons from the rhinophore that bypass the rhinophore ganglion and project directly into the brain. These findings highlight the complexity of the rhinophore ganglion and connective. This is a first step in documenting the structural organization underlying chemosensory processing in *Berghia*. Completion of a full rhinophore ganglion connectome will greatly enhance our understanding of chemosensation in nudibranchs.

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Poster

P421. Olfactory Coding: Second Order Regions

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Program #/Poster #: P421.02

Topic: D.05. Olfaction and Taste

Support: NIH R01 DC016293-01
NIH R21 DC015873-02

Title: Physiology of a specific local interneuron population in the Drosophila antennal lobe reveals non-spiking characteristic due to lack of voltage gated sodium current

Authors: *J. E. SCHENK, Q. GAUDRY;
Biol., Univ. of Maryland, College Park, MD

Abstract: Local interneurons (LNs) within the *Drosophila melanogaster* antennal lobe (AL) generally serve inhibitory functions, accomplished by spiking-mediated release of GABA at the first synapse of the olfactory relay. Here, we have identified a population of non-spiking LNs (nsLNs) within the *Drosophila* AL. While common in other insect species, nsLNs are a novel observation in this *Drosophila* brain region. To characterize these cells, we performed *in vivo* whole cell patch clamp electrophysiology and wide field calcium imaging with exposure to odor panels consisting of private and public odors. While nsLNs are still responsive to odor stimulation, we did not detect sodium current in this population of neurons. Additionally, we utilized fluorescent *in situ* hybridization and cell-specific protein tagging in the nsLNs to assess the expression of the insect voltage gated sodium channel, Para. The unique nature of these cells could lend itself to understanding functions not well characterized in *Drosophila* olfaction and odor coding. Moreover, the confirmation of nsLNs in the *Drosophila* AL suggests a commonality across many insect species, warranting further investigation.

Disclosures: J.E. Schenk: None. **Q. Gaudry:** None.

Poster

P421. Olfactory Coding: Second Order Regions

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Program #/Poster #: P421.03

Topic: D.05. Olfaction and Taste

Support: DBT/Wellcome Trust India Alliance IA/I/15/2/502091
SERB grant CRG/2020/004719

Title: Understanding olfactory processing in the antennal lobe in aedes aegypti

Authors: *P. SINGH, S. GOYAL, S. GUPTA, S. GARG, V. RAJPUT, A. TIWARI, A. K. GUPTA, N. GUPTA;
Indian Inst. of Technol., Kanpur, India

Abstract: Antennal lobe, the primary olfactory processing center in the insect brain, receives odor information from the olfactory receptor neurons present in the sensory layer. Projection neurons (PNs) and local neurons (LNs) are the two major classes of neurons in the insect antennal lobe (AL). We used whole-cell patch-clamp recordings and post-hoc dye filling to study the physiology and morphology of antennal lobe neurons in the yellow fever mosquito, Aedes aegypti. A panel of odors were presented to the olfactory organs of immobilized insects and responses were recorded from the cell body of AL neurons. We obtained ~1200 PN-odor response pairs and ~250 LN odor response pairs. Additionally, we were able to observe the morphology of ~200 projection neurons and ~50 local neurons and classify them further into morphological sub-classes. Based on glomerular innervation, we found that projection neurons are majorly uni-glomerular but could also be bi- or multi-glomerular. On the other hand, the innervation patterns of LNs could be categorized as pan-glomerular, all-but-few, patchy, or continuous. We also extracted different electrophysiological features such as spike amplitude, spike half-width, spike adaptation, spike amplitude accommodation, and the size of after-hyperpolarization from the recordings. Pairwise distance matrix revealed that PN and LN clusters are well separated. Based on these parameters,

we were able to classify a cell as a projection or a local neuron with about 90% accuracy. Further, we analyzed the obtained odor-responses of uni-glomerular PNs. We compared the change in firing rate of sister PNs in response to the panel of odors. The odor-generated activity patterns of sister PNs were only weakly correlated, indicating functional diversity among sister PNs in mosquitoes. We also performed behavioral experiments using a custom-built set-up to quantify the preference of mosquitoes for each odor in the panel. The behavioral valence was then correlated with the PN-response trajectory of the odor. Next, we analyzed the role of local neurons in olfactory processing. Local neurons have been found to be neuromodulatory in other insect species. We performed immuno-histology against GABA and found some of the local neurons to be GABAergic. Additionally, we observed that in some cases, the inhibitory responses were abolished or small excitatory responses were revealed in the presence of GABA antagonists. Altogether, our study provides a comprehensive characterization of the mosquito antennal lobe neurons and will serve as a foundation for understanding the olfactory processing in the mosquito brain.

Disclosures: P. Singh: None. **S. Goyal:** None. **S. Gupta:** None. **S. Garg:** None. **V. Rajput:** None. **A. Tiwari:** None. **A.K. Gupta:** None. **N. Gupta:** None.

Poster

P421. Olfactory Coding: Second Order Regions

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P421.04

Topic: D.05. Olfaction and Taste

Title: Ultrastructural distribution of dense-core vesicles from electron microscopy images in Drosophila olfactory projection neurons

Authors: *M. KIM[1], S. GERHARD[2], H. E. SOMHEGYI[1], A. S. BATES[1], T. M. NGUYEN[1], G. S. X. E. JEFFERIS[3], W.-C. A. LEE[1];
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Abstract: Internal physiological states and sensory processing are thought to be modulated by neuropeptides. Neuropeptides are a class of signaling molecules that are released from dense-core vesicles (DCVs) and mediate slow-onset, long-lasting modulation of synaptic transmission. In *Drosophila*, olfactory processing begins with olfactory sensory neurons (OSNs) which converge onto projection neurons (PNs) that innervate the central brain. However, the organizational principles of how neuropeptides modulate early olfactory circuits remain unclear. To investigate the localization pattern of neuropeptide-containing DCVs, we utilized machine learning to automatically identify DCVs in large-scale electron microscopy datasets and map their locations across the antennal lobe. This approach enabled us to investigate aspects of circuit modulation and flexibility from static wiring diagrams. We found that DCVs are preferentially localized in the presynaptic sites of feedback synapses from PNs back onto OSNs, suggesting that this peptidergic feedback modulation may modulate sensitivity within specific glomerular channels. Our work suggests that co-transmission of neuropeptides and small-molecule

transmitters provides additional modulatory mechanisms that increase the flexibility of neural circuit function.

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Poster

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Program #/Poster #: P421.05

Topic: D.05. Olfaction and Taste

Support: DBT/Wellcome Trust India Alliance IA/I/15/2/502091
SERB grant CRG/2020/004719

Title: Responses of the antennal lobe neurons to carbon dioxide in mosquitoes

Authors: *S. GOYAL, P. SINGH, S. GUPTA, S. S. SINGH, M. GUPTA, A. K. GUPTA, N. GUPTA; Biol. sciences and bioengineering, Indian Inst. of Technol., Kanpur, India

Abstract: Mosquitoes are vectors of some of the deadliest human diseases across the world. Female mosquitoes need a mammalian blood meal for oviposition. They rely on various olfactory cues to locate suitable hosts. Carbon dioxide (CO_2), exhaled in human breath, is crucial for host seeking. Disrupting their CO_2-based host-seeking behavior may help in combating the growing threat of mosquito-borne diseases. Previous studies, using single sensillum recording, showed that CO_2 is detected by sensory neurons present in the capitate peg sensilla housed in the maxillary palps of the dengue mosquito, *Aedes aegypti*. We wanted to study how CO_2 is processed downstream of the sensory neurons. We measured the response of antennal lobe neurons (~200 projection neurons and ~40 local neurons) to CO_2 using *in vivo* whole-cell patch recordings. We found that ~25% of the projection neurons and ~42% of the local neurons responded to CO_2 in varying patterns. The responses ranged from purely excitatory or purely inhibitory patterns to combinations of both. Flying mosquitoes encounter fluctuating plumes of CO_2 in the environment, possibly affecting how the mosquito brain processes CO_2. We measured the responses of the antennal lobe neurons to CO_2 delivered in different temporal patterns: homogeneous versus non-homogeneous, single pulse versus multiple pulses. We found no significant difference in projection neuron responses to CO_2 when delivered as a homogeneous or a non-homogeneous plume. In contrast, local neurons showed slightly elevated responses to multi-pulse stimuli compared with a single pulse. Apart from CO_2, mosquitoes encounter different human skin volatiles and use them to orient towards the host in the natural environment. We measured the response of antennal lobe neurons to a skin volatile, lactic acid, and its binary mixture with CO_2. Analysis of single odor and mixture responses revealed that some mixture processing occurs in the projection neurons for the binary blend of lactic acid and CO_2, possibly mediated by lateral interactions. Overall, our study provides a better understanding of mosquito-host interaction by looking at the antennal lobe responses to an important olfactory cue, CO_2, and its synergy with other host volatiles.

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Poster

P421. Olfactory Coding: Second Order Regions

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Topic: D.05. Olfaction and Taste

Support: NIH BRAIN U01-NS108637

Title: Multimodal, distributed connectivity of the chemosensory appendage the nudibranch mollusc, Berghia stephanieae suggests non-canonical olfactory processing

Authors: *C. C. TAIT, D. RAMIREZ, P. S. KATZ;
Biol., Univ. of Massachusetts, Amherst, Amherst, MA

Abstract: The neuroanatomy of olfactory systems shares structural aspects across standard model organisms; specialized brain regions receive information from sensory neurons, with multimodal integration occurring in upstream processing centers. We explored the neuroanatomy of the distance-chemosensory appendage, the rhinophore, of the nudibranch mollusc *Berghia stephanieae*. The rhinophores emerge from the dorsal surface of the animal's head, each with a dedicated ganglion at its base. Extending into each rhinophore from the rhinophore ganglia are two thick nerves that branch extensively and contain thousands of fibers, as seen with tubulin immunohistochemistry. We identified populations of putative sensory neurons expressing histamine and APGWamide that project axons to the brain via these nerves. Neurobiotin fills of the cut rhinophore nerves revealed tracts terminating in the brain both ipsilaterally and contralaterally, indicating communication between opposite sides of the brain. One rhinophoral fiber tract ended in a neuropil region in the cerebral ganglion implicated in multimodal integration, where histaminergic mechanoreceptor hair cells also terminate. Thus, axons projected from the rhinophores directly to diverse brain areas. We also identified efferent neurons in the brain that project axons into the rhinophore. Among these were: 1) a single ipsilateral photoreceptor from each eye, suggesting interactions between chemosensation and vision occur in the periphery; 2) five neurons in each buccal ganglion, which plays a role in feeding behavior; 3) a single pair of cerebral serotonergic neurons, which projected bilaterally to the rhinophore tips; and 4) a single pair of cerebral neurons immunoreactive to Small Cardioactive Peptide, which projected to a specific region of the rhinophore ganglion. This region also had terminals immunoreactive to Neuropeptide Y, which seemed to emerge from cells intrinsic to the rhinophore ganglion itself. Thus, overall, *Berghia* neuroanatomy differs from canonical olfactory systems in that there is less convergence of input to central regions, more input from diverse central neurons into the chemosensory appendage itself, potentially more multimodal integration in the periphery, and distinct neuromodulatory innervation to specific areas. Although we do not yet know how stimuli are processed, these neuroanatomical details indicate that molluscan chemosensation may be fundamentally different from what is known in other taxa.

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Poster

P421. Olfactory Coding: Second Order Regions

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Program #/Poster #: P421.07

Topic: D.05. Olfaction and Taste

Support: KVPY Fellowship
IISER Pune

Title: Intermittent inputs reveal invariant odor representations

Authors: R. MOHANTA, ***C. ASSISI**;
Biol., Indian Inst. of Sci. Educ. and Res., Pune, India

Abstract: Olfaction, like other sensory systems, uses the timing of spikes to encode incoming sensory input. The identity of an odorant that arrives in a steady stream can be reliably ascertained by examining the spatiotemporal sequence of spikes that are generated by brain networks involved in olfaction. However, odor inputs come, not as a steady stream, but riding upon chaotically pulsed plumes of air. Each time an input arrives, it follows a unique temporal pattern. As a consequence, the spatiotemporal spike sequences that encode the odor must also be different every time an animal encounters temporally varying odor input. It really is a wonder then that animals are capable of decoding sensory cues and navigating highly complex and turbulent 'odorscapes'. Why, despite varying inputs, are odor percepts invariant (alternatively, why does a rose always smell like a rose)? What are the neural invariants of stable olfactory percepts? We address these questions in a computational model of the locust olfactory system. We show that when time-varying odor inputs intermittently perturb subsets of neurons in the antennal lobe network, the activity of the network reverberates in a manner that depends on both the nature of the inputs it receives and the structure of the neuronal sub-network that these inputs stimulate. We demonstrate that it is possible to decipher the structure of the perturbed sub-network by examining transient synchrony in the activity of the neurons. Follower neurons in the mushroom body are sensitive to coincident input and thus uniquely placed to pick out episodes of transient synchrony in antennal lobe projection neurons. We find that the ability to reconstruct the sub-network structure is vastly improved when odor inputs arrive or are sampled in an intermittent manner. Our model suggests, antennal flicking, a strategy employed by locusts when sampling a steady stream of air, injects intermittency in the input and might hasten the formation of an invariant odor representation. The exact temporal pattern in which intermittent perturbations arrive does not affect our reconstruction. Thus, the structure of the stimulated sub-network itself serves as a unique invariant code that represents the odor.

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Poster

P456. Retinal Circuitry III

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P456.01

Topic: D.07. Vision

Support: NIH Grant EY026614
NIH Grant EYE031631

Title: Requirement for Lhx3 in the differentiation of bipolar cells and the inner retinal circuitry

Authors: *L. HUANG[1], L. GUO[2], X. XIE[1], X. DONG[1], L. GAN[1];
[1]Dept. of Neurosci. and Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA; [2]Col. of Life Sci., Zhejiang Univ., Hangzhou, China

Abstract: Retinal bipolar cells (BCs), the late-born interneurons in the retina, are located in the inner nuclear layer (INL) and act, directly or indirectly, to transmit visual information from photoreceptors to ganglion cells. The two major BC subclasses, ON-bipolar cells and OFF-bipolar cells based on their opposite responses to glutamate release, are classified into more than ten subtypes. How these subtypes are specified during retinogenesis is poorly understood. Previously, we have shown that the expression of LHX3, a LIM-homeodomain (LIM-HD) transcription factor, starts from postnatal day 4 (P4), peaked at P8 and maintained through adulthood. Its expression overlaps that of ISL1 and LHX4, two key LIM-HD factors for the differentiation of BC subtypes, in the developing retina. In this study, we further showed that LHX3 is selectively expressed in type 3a OFF-cone bipolar cells, type 5 ON-cone bipolar cells, and a subgroup of type 2 OFF-cone bipolar cells. To investigate the role of *Lhx3* in the specification of BCs, we conditionally deleted *Lhx3* in the developing mouse retina using *Six3-Cre* mice that express Cre recombinase in the developing retina and forebrain. In the absence of *Lhx3*, the b-wave and oscillation potential amplitudes of light-adapted electroretinogram (ERG) were significantly attenuated, suggesting a disruption in the cone-driven pathway. In *Lhx3*-null retinas, the number of rod bipolar cells and type 2 OFF-cone bipolar cells was reduced significantly while type 3a OFF-cone bipolar cells increased. Conversely, *Lhx3* over-expression in retinal progenitors during retinogenesis significantly promotes the generation of BCs. In addition, loss of *Lhx3* resulted in an increase in the number of Müller cells and a reduction in AII amacrine cells. Together, *Lhx3* plays an important role in regulating the differentiation and function of BCs, especially the cone-driven retinal circuitry.

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Poster

P456. Retinal Circuitry III

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Program #/Poster #: P456.02

Topic: D.07. Vision

Support: EY018139
EY028033

EY030554

Title: Trans-synaptic mechanism of cone photoreceptor wiring

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Abstract: Our vision depends on two types of photoreceptors in the retina, rods and cones. Rods are superb at detecting extremely low level of light and essential for vision under dim conditions. In contrast, cones operate within an incredible broad range of light intensity and are responsible for most aspects of our daytime visions including color detection, visual acuity and contrast. To form vision, the information encoded in photoreceptors must been accurately transmitted to the correct downstream bipolar neurons. The faithful relay of information between photoreceptors and their corresponding ON-bipolar cells (ON-BCs) hinges upon the synaptic connection established between the two parties, a process known as the synaptic wiring. Increasing studies have shown that synaptic wiring of neurons is controlled by various families of trans-synaptic cell adhesion molecules (CAMs), which are cell-surface molecules critical for establishing cell-cell contacts and mediating subsequent intracellular signaling.Using an unbiased proteomics strategy, we identified a CAM, ELFN2, which is selectively expressed by cone photoreceptors and targeted at cone synapses. We found that elimination of ELFN2 did not lead to observable structural and functional change at cone synapse, probably due to the upregulation of ELFN1 in the cones. We next eliminated both ELFN1 and ELFN2 using several different conditional KO mouse models and demonstrated that the synaptic transmission between cones and ON-CBCs is completely abolished while the synaptic architecture remains normal in conditional double KO retinas.Mechanistically, we found that both ELFN1 and ELFN2 bind to the postsynaptic glutamate receptor, mGluR6, via an *in trans* fashion. Using cell-based assay, we showed that this trans-cellular interaction between ELFNs and mGluR6 decreased the potency and efficacy of glutamate induced signaling of mGluR6. Moreover, by using several mouse models where different levels of ELFN proteins are expressed at cone synapses, we discovered that the synaptic content of post-synaptic mGluR6 is tightly correlated with the synaptic content of pre-synaptic ELFN proteins, and more importantly, with the amplitude of cone synaptic transmission. Together, we have uncovered the molecular mechanism underlying the functional wiring of cone photoreceptors by showing that a pair of CAMs, ELFN1 and ELFN2, work collectively at cone synapses to trans-synaptically modulate the surface content and pharmacological property of post-synaptic mGluR6 and that the synaptic content of this trans-synaptic ELFN/mGluR6 complex is one critical factor determining the synaptic strength of cone photoreceptors.

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Poster

P456. Retinal Circuitry III

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Title: Loss of Trpm1, the gene for the On bipolar cell transduction channel, in 15q13.3 microdeletion syndrome contributes to central behavioral deficits

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Abstract: 15q13.3 microdeletion syndrome is characterized by a broad spectrum of psychiatric disorders. Seven genes are located in the target region of chromosome 15 (MTMR10, FAN1, TRPM1, MIR211, KLF13, OTUD7A, and CHRNA7). While the contributions of several of the genes to the disorder have studied using mutant mouse models, no single mouse model has been able to recapitulate the whole behavioral spectrum of human 15q13.3 microdeletion syndrome.Trpm1, one of the genes located in the target region of 15q13.3 microdeletion syndrome, has been implicated as a retinal ON bipolar cell visual signal transduction channel. Trpm1 has not been investigated concerning this syndrome because the visual impairment in Trpm1$^{-/-}$ mice may confound the results of behavioral tests involving vision. Also, Trmp1 is reported to be exclusively expressed in the retina in the central nervous systems. We performed a comprehensive behavioral test battery using Trpm1 null mutant mice to investigate the role of Trpm1 in the central nervous system, and to examine the relationship between TRPM1 and 15q13.3 microdeletion syndrome. Our data demonstrate that Trpm1$^{-/-}$ mice exhibit abnormal behaviors that may explain some phenotypes of 15q13.3 microdeletion syndrome: including reduced anxiety-like behavior, abnormal social interaction, attenuated fear memory, and, most prominently, hyper locomotor activity. While the ON visual transduction pathway is impaired in Trpm1$^{-/-}$ mice, we did not detect compensatory higher sensitivities for other sensory modalities. The pathway for visual impairment is the same between Trpm1$^{-/-}$ mice and mGluR6$^{-/-}$ mice, but hyper locomotor activity has not been reported in mGluR6$^{-/-}$ mice. Unexpectedly, the data suggest that the phenotype of Trpm1$^{-/-}$ mice extend beyond that predicted from visual impairment alone. Here, we present the first evidence associating TRPM1 with impairment of cognitive function similar to that observed in phenotypes of 15q13.3 microdeletion syndrome.

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Poster

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Research to Prevent Blindness Unrestricted Grant

Title: Pathways for processing local and global motion in primate retina

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Abstract: When observing a visual scene, the image perceived by the eye is rarely static. Movement by the observer causes the visual world to pan across the eye, creating global motion on the retina. Global motion creates a two-part encoding problem for visual perception. First, form and position of objects must stay constant during global motion. Second, local motion of objects must be distinguished from globally moving counterparts. The neural pathways that mediate visual perception during global motion are not well understood. In many vertebrates, retinal ganglion cells separate object motion from global motion through interactions between their receptive field center and surround. In primates, however, many pathways of the retina have been insofar difficult to study, and it is unknown whether such specialized motion processing occurs in the primate retina. Here, we probe receptive fields of many lesser-studied ganglion cell types in the primate retina to understand how global motion affects visual encoding. Specifically, we first assess how global motion affects signal integration, and then measure each cell type's selectivity for local motion relative to global motion.Spike responses or whole-cell synaptic currents were recorded from several types of primate retinal ganglion cell in an intact, in vitro preparation of the macaque monkey retina. Custom light stimuli were used to probe sensitivity to global motion. Global motion activates the receptive field surround of many primate retinal ganglion cell types. However, the effects of global motion processing in the surround differs across cell types, ranging from facilitation of cellular responses to suppression of responses. We also report that at least three primate retinal ganglion cell types show selectivity for local motion.Our results indicate that selective processing of local and global motion in the primate visual system begins in the retina. The receptive field surround parsed global motion inputs in several ganglion cell types, resulting in increased or decreased cellular sensitivity based on cell type. Moreover, three ganglion cell types were selective for local motion. Prior to our study, the primate visual system was thought to reserve complex motion computations for the cortex. We show here that the primate retina is more computationally powerful than previously thought.

Disclosures: T. Appleby: None. **F.M. Rieke:** None. **M.B. Manookin:** None.

Poster

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Title: Surround stimulation in the scotopic light regimen produces non-classical center-surround antagonism in the primate retina

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Abstract: Center-surround antagonism in the mammalian retina has long been appreciated to alter how retinal ganglion cells (RGCs) sample spatial inputs in bright light conditions but has appeared to be absent in dimmer environments. Consistent with this, we find that classical center-surround antagonism is present in primate RGC spatial receptive fields during mesopic and photopic conditions but is absent in scotopic light conditions. Despite the apparent absence of surround inhibition, the receptive field center of ON parasol RGCs still narrowed at scotopic light levels as background intensities increased. We confirmed pharmacologically that the changes in receptive field size persist without horizontal cell feedback. To explore possible mechanisms mediating this unexpected change in receptive field size, we measured the size of receptive field subunits. Subunits were 3-4-fold larger at dim vs bright light levels. We used modeling to explore how subunits combine to produce the classical difference of gaussians receptive field profile. This will allow us to determine whether overall changes in receptive field dimensions can be explained by changes in subunit size. Ongoing experiments are exploring the origin of larger subunit sizes measured in scotopic conditions. In addition to effects on spatial receptive fields, we also found that surround stimulation in scotopic backgrounds leads to surround-dependent temporal filtering. Both the time to peaks of the response generated by short steps and the linear filters extracted from noise sequences are speeded in scotopic backgrounds when the surround is driven with same polarity contrasts as the center. These results are particularly interesting since they occur in the absence of classical surround inhibition and because rod photoreceptors have relatively slow kinetics. Together these changes in receptive field features are likely to have important effects on an organism’s ability to perform complex visual tasks in scotopic environments especially those which depend on correlations between space and time (e.g. motion detection).

Disclosures: N. Ingram: None. **F. Rieke:** None.

Poster

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Title: A perturbative approach uncovers context-dependent processing of natural scenes in the retina

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Abstract: Neurons in the early visual system are supposed to extract specific features from natural scenes. However, many works have shown that this processing depends on the visual context. It is thus not clear if the neurons extract always the same feature, and therefore a stable representation of the visual world, across different contexts. In the retinal output, some types of ganglion cells respond selectively to light increase (On cells), while others respond to light decrease (Off cells). However, it is unclear if this selectivity, characterized with synthetic stimuli, is maintained when they are stimulated with natural scenes. Here we address this issue by recording the responses of ganglion cells in salamander and mice to stimuli composed of natural images slightly perturbed by patterns of random noise. We measured a receptive field from the responses to many checkerboard patterns superimposed on the same natural image, i.e. an image-dependent receptive field. For the same cell, these receptive fields strongly depended on the natural image. When changing the image, the receptive field could switch its polarity from On to Off. Standard, linear models could not reproduce this result. However, a convolutional network model learned on the responses to many natural images could predict these context dependent receptive fields, and suggest that it is the result of the convergence of several circuits onto the same ganglion cell. This strong dependence of the On-Off polarity on the context makes it challenging to decode luminance from these ganglion cells. However, more abstract features could be reliably decoded. Our perturbative approach thus uncovered the selectivity of retinal ganglion cells to more abstract features, and could be used in other sensory areas to characterize the selectivity of neurons during natural scene processing.

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Poster

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Title: Contributions of retinal direction-selectivity to predation in mice

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Abstract: Mice engage in complex, visually guided hunting behaviors. Circuits in superficial superior colliculus (sSC) link visual inputs from the retina to predation (Hoy et al., 2019). Yet, the contributions of specific visual circuits in the retina to predation remain unclear. Mice keep insect prey in their binocular visual fields during pursuit and capture (Johnson et al., 2021). Direction-selective narrow-field (NF) cells in sSC are necessary for efficient predation, suggesting a role for direction-selectivity (DS) in the behavior. Here, we test the hypothesis that retinal DS signals orient mice toward their target and maintain moving prey within their binocular visual fields.
Retinal DS originates in starburst amacrine cells (SACs) and is encoded in the spikes of direction-selective ganglion cells (DSGCs). We selectively ablated SACs by performing intraocular injections of diphtheria toxin (DT) into mouse eyes expressing the DT receptor only in SACs; we controlled for injection artifact by injecting saline in a subset of mice. We used immunohistochemistry to confirm SAC ablation and rule out off-target effects following DT injections. Patch-clamp experiments show that DSGCs in SAC-ablated retinas do not encode motion direction; similarly, the gaze-stabilizing optokinetic reflex generated downstream of DSGCs is absent in these mice. We trained these mice to hunt crickets in an arena and quantified various aspects of the behavior, as previously described (Johnson et al., 2021). DS in sSC is derived from the retinal DS circuitry (Shi et al., 2017). We show that DSGCs innervate NF cells in sSC; thus, we hypothesize that the NF cells in sSC of SAC-ablated mice will no longer be DS. If the DS feature of NF cells in sSC is necessary for orienting toward and keeping prey within the binocular field, we expect the distribution of the crickets in the head-centric visual field to broaden and capture times to increase. We are currently evaluating these parameters and comparing effects of chronic and acute suppression of retinal DS.

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Poster

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Title: Physiological function of Alzheimer's-linked Aβ oligomers in the developing CNS

Authors: *S. BARTLEY[1], H. XIA[2], J. ZHU[2], E. HO[2], M. A. BICCA[2], H. D. SECKLER[3], K. L. VIOLA[2], W. L. KLEIN[2];
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Abstract: Amyloid beta oligomers (AβOs) are known to be toxic peptides that instigate multiple types of brain damage, *e.g.*, synapse loss, selective nerve cell death, and inflammatory gliosis. AβO buildup in adult brain is regarded a central toxic event in Alzheimer's disease. Results described here, however,

show that AβOs are not just pathogenic agents of brain damage. It has been found that AβOs are expressed physiologically for a brief period during CNS neural development and are essential for proper placement of neurons. Physiological expression of AβOs was discovered in retina of the embryonic chick, which forms an Aβ peptide identical to that of humans. Retina AβOs first appear in the optic nerve layer and then spread outward into specific cell bodies and synaptic layers. They subsequently down-regulate as the retina matures, becoming restricted to the outer retina. AβO expression is thus like a molecular wave progressing from inner to outer retina, virtually disappearing when formation of neural circuitry is completed. Identification of AβOs has been confirmed by Western blots and mass spectrometry. Intriguingly, use of different AβO selective antibodies indicates the presence of several proteoforms with different patterns of localization and developmental control. These differences appear to be linked to correspondingly different patterns of AD-type pTau expression, detected by AT8 and PHF1. If AβOs are lowered prematurely in embryos cultured *ex ovo*, the retina shows gross disruption of nerve cell placement. The distortions of retina laminar structure caused by intravitreal injection of a BACE-1 inhibitor or an AβO-selective antibody resemble the retina dysplasia previously described for various pathological conditions. Results suggest the hypothesis that embryonic AβOs constitute a new type of peptidergic hormone with a short-lived developmental role, perhaps triggering the same types of changes caused by their re-expression at the onset of Alzheimer's. A transient role for AβOs in CNS development of species with human sequence Aβ42 may be one reason evolution has conserved a peptide that manifests deleterious gain-of-function properties in the aging brain.

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Poster

P463. Physiological and Functional Properties of Visual Circuits

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Title: Reading decreases foveal stimulation of ON visual pathways

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Abstract: Visual experience plays a major role in the development of visual diseases associated with refractive error such as myopia and amblyopia. It is well known that the risk of developing myopia increases with the time spent reading and decreases with outdoor activity, however, the stimulus

parameters driving the disease remain unclear. To address this gap in knowledge, we compared the visual stimuli feeding the retina of humans that performed two tasks associated with different risks of myopia progression, reading and walking indoors. Human subjects (2 females, 6 males, 29.6 ± 6.1 years old) performed the two tasks while wearing glasses with cameras and sensors that recorded visual images and visuomotor activity (Tobii Pro Glasses 2). When compared with walking, reading reduced temporal contrast in central vision (5 degrees from fixation) and increased it in peripheral vision (8-60 degrees from fixation), leading to a pronounced reduction in the ratio of central/peripheral strength of visual stimulation (fovea/periphery temporal contrast: 24 ± 11 / 60 ± 19 when reading, 47 ± 4 / 39 ± 4 when walking, n = 2000 image pixel samples per subject and task, $p < 0.0001$, Wilcoxon test). Reading also made the luminance distribution heavily skewed towards negative dark contrast in central vision and positive light contrast in peripheral vision, leading to a pronounced reduction in the ratio of the central/peripheral stimulation of ON visual pathways (fovea/periphery luminance skewness: -2.8 ± 1.2 / 0.9 ± 1.5 when reading, 0.5 ± 0.2 / 0.5 ± 0.4 when walking, n = 2000 image pixel samples per subject and task, $p < 0.0001$, Wilcoxon test). Reading also reduced the average fixation distance (reading/walking 0.5 ± 0.3 / 1.1 ± 2 meters, $p < 0.0001$, Wilcoxon test), pupil size (reading/walking: 3.2 ± 0.5 / 4.3 ± 0.7 millimeters, $p < 0.0001$, Wilcoxon test), blink rate (reading/walking: 10.2 ± 7 / 31.6 ± 11.2 blinks/minute, $p < 0.0001$, Wilcoxon test), head velocity (reading/walking: 1.7 ± 0.7 / 14.4 ± 2.6 degrees/second, $p = 0.0002$, Wilcoxon test), and amplitude of the vestibulo-ocular reflex (reading/walking variation in eye position: 0.6 ± 0.3 / 1.2 ± 0.4 degrees, $p = 0.038$, triggered by variation in head velocity: 2.2 ± 0.8 / 13.3 ± 5.6 degrees/second, $p = 0.0002$, Wilcoxon tests). However, the reduction in fixation distance, pupil size, blink rate, and eye movements should be associated with relatively modest changes in the strength of visual responses. Therefore, we conclude that reading causes a pronounced reduction of the foveal/periphery ratio of visual stimulation driving ON visual pathways. These results are consistent with the hypothesis that ON visual pathways play an important role in myopia progression.

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Poster

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Topic: D.07. Vision

Title: A bi-monocular cortical theory for color (including brightness) sensations in human vision

Authors: *C. Q. WU;
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Abstract: Color is the carrier of visual consciousness (VC). James Clark Maxwell expresses this idea succinctly: “all vision is color vision”. Thus, color sensation is an essential part of VC. Color sensation is primarily monocular. Hermann von Helmholtz claims this point as follows: “the content of each separate [monocular] field comes to consciousness without being fused with that of the other field by means of organic mechanisms; and that, therefore, the fusion of the two fields in one common image, when it does

occur, is a psychic act." Mapping the above point onto the neuroanatomical organization of the primate visual system, I assert that the thalamic recipient layer of the primary visual cortex (V1-L4) is the neural substrate for color sensation. Specifically, I propose the following six-pack model for this layer: Tangentially, it consists of different ocular dominance columns (ODCs) receiving thalamic inputs from the two eyes respectively; Vertically, it consists of three sublayers corresponding to the three primary color sensations: blue, red, and green. As to Helmholtz's notion of psychic fusion of the three primary color sensations for creating a whole gamut of perceivable colors, I map its physiological mechanism to single-moment synchronized firings of spiny stellate neurons within V1-L4. In this view, the magnitude of a sensation directly correlates with the number of cells within the sync-firing cell assembly; and monocular and binocular fusions are of the same type. Furthermore, I suggest that color complementarity (the Helson-Judd effect) is also created in this layer: Within each local area corresponding to one LE's ODC and its RE's counterpart, when the neural activity level of an eye's image is below the binocular adaptation-level within the locality, color complementarity will occur. Afterimage (AI) has traditionally been treated as retinal, but I claim that it is cortical. Also, +AI and -AI have usually been taken as due to different causes. William McDougall posits that both +AI and -AI are due to the same cause; here I further develop this concept: They are both due to the persistence of some neural activity (or potential) in V1-L4; an AI is positive if its activity level is over its adaptation level and is negative otherwise; an AI is of the same hue if the polarity between its activity-level and adaptation-level remains the same as in the primary stimulation and is complementary otherwise. Finally, I propose that AI is not only cortical but also a part of visual short-term memory (STM): Theoretically, it is possible to prolong an AI as long as one wishes. In this regard, visual STM is on a par with verbal STM where an acoustic item can be rehearsed as long as one wishes.

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Poster

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Title: Daily oscillation of the excitation/inhibition ratio is disrupted in two mouse models of autism

Authors: *M. BRIDI[1], N. LUO[1], G. KIM[1], C. O'FERRALL[2], R. PATEL[2], S. J. BERTRAND[2], S. KANNAN[2], A. KIRKWOOD[1];
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Abstract: Autism spectrum disorder (ASD) is an increasingly prevalent neurodevelopmental disorder involving sensory processing abnormalities. Alterations to the balance between excitation and inhibition (E/I ratio) are postulated to underlie behavioral phenotypes in ASD patients and mouse models. However, in primary visual cortex (V1) of wild type mice, the E/I ratio is not a fixed value. Rather, it oscillates

across the 24h day. Therefore, we hypothesized that the E/I oscillation, instead of the overall E/I ratio, may be disrupted in ASD mouse models. We tested this hypothesis in fragile X mental retardation protein knockout (*fmr1* KO) and BTBR *T+ Itpr3^{tf}/J* (BTBR) mice, models of syndromic and idiopathic ASD, respectively. We measured the E/I ratio at multiple times of day using whole-cell patch clamp recordings. We found that the E/I ratio in the V1 layer 2/3-2/3 pathway is dysregulated in both models, but in different ways: the oscillation is flattened in *fmr1* KO and phase-shifted in BTBR mice. These phenotypes cannot be explained by altered sleep timing, which was largely normal in both lines. Furthermore, we recorded miniature excitatory and inhibitory postsynaptic currents (mE/IPSCs) in V1 at multiple times of day and found that E/I dysregulation occurs due to alterations in both excitatory and inhibitory synaptic transmission: mE/IPSC frequency matched the dysregulated E/I pattern observed in each line. These findings provide a crucial perspective on the E/I ratio in ASD, suggesting that ASD phenotypes may be produced by a mismatch of E/I to the appropriate behavioral state, rather than altered overall E/I ratio *per se*.

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Poster

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Title: The endocannabinoid system in the primary visual cortex of the vervet monkey

Authors: *C. MICAELO-FERNANDES[1], S. MORYOUSSEF[1], H. HAÏMEUR[1], J. BOUSKILA[1], J.-F. BOUCHARD[1], M. PTITO[1,2];
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Abstract: Cumulating evidence highlights the contribution of the endocannabinoid (eCB) system to visual perception. The primary visual cortex/V1 represents the first cortical stage of visual information processing and the presence of the cannabinoid receptor type 1 (CB1R) at this level has been previously reported for mice, macaque monkeys and humans. In this work, we aimed at reproducing and extending these findings, by performing a more comprehensive neuroanatomical and neurochemical characterization of the eCB system in V1 of the vervet monkey. Five young male vervet monkeys *(Chlorocebus sabeus)* were used in this study. The combined immunohistochemical labelling patterns of the neuronal nuclear antigen (NeuN), the neurofilament H non-phosphorylated (SMI-32), parvalbumin (PV), and the vesicular

glutamate transporter 2 (VGLUT2) were used to define the lamination of V1. The same markers were also applied in double immunofluorescence to study the distribution of CB1R and the eCB-synthesizing and degrading enzymes N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and Fatty Acid Amide Hydrolase (FAAH) respectively. The six-layered organization of V1 was clearly identified. Similarly to previous findings, CB1R-immunoreactivity was the greatest in the most superficial (L2-3) and the deepest (L5-6) layers of V1, with low labelling of L4. CB1R was present in axonal fibers rich in varicosities, surrounding (but not colocalizing with) NeuN-, SMI-32- and PV-positive cell bodies. CB1R-positive axons had very limited overlap with VGLUT2-positive axons. In contrast, NAPE-PLD and FAAH were expressed along the cortical depth of V1, in the somatodendritic compartment of diverse neurons, including SMI-32-positive pyramidal cells and PV-positive interneurons. Our results suggest a presynaptic localization of CB1R, in axons terminating in the superficial and deep layers of V1. L2-3 and L5-6 constitute precisely the main output layers of V1, whereby CB1R-positive fibers found on these layers might correspond to feedback projections originating from their cortical and subcortical targets, respectively. Since the degree CB1R/VGLUT2 colocalization appears to be minimal, the likely inhibitory, i.e., GABAergic nature of these projections is currently being investigated.

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Topic: D.07. Vision

Title: A whole-brain monosynaptic input connectome to neuron classes in mouse visual cortex

Authors: *S. YAO, Q. WANG, K. E. HIROKAWA, B. OUELLETTE, P. BOHN, T. L. DAIGLE, T. ZHOU, M. MORTRUD, A. WILLIFORD, P. A. GROBLEWSKI, M. D. NAEEMI, M. MCGRAW, L. POTEKHINA, P. R. NICOVICH, W. WAKEMAN, S. MIHALAS, B. TASIC, A. H. CETIN, J. A. HARRIS, H. ZENG;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Identification of the structural connections between neurons is a prerequisite to understanding brain function. We have developed a pipeline to systematically map brain-wide monosynaptic inputs to specific neuronal populations using Cre-driver mouse lines and the recombinant rabies tracing system. We first improved the rabies virus tracing strategy to accurately identify starter cells and to efficiently quantify presynaptic inputs. We then mapped the presynaptic inputs to different excitatory and inhibitory neurons in the primary visual cortex and five higher visual areas. Our results reveal quantitative target-, layer- and cell-class-specific differences in the retrograde connectomes, despite similar global input patterns to different neuronal populations in the same anatomical area. The retrograde connectivity we define is consistent with the presence of the ventral and dorsal visual information processing streams, and supports a hierarchical, modular organization of the mouse visual circuit. This study expands our knowledge of the brain-wide inputs regulating visual areas and demonstrates that our improved rabies

virus tracing strategy can be used to scale up the effort in dissecting brain-wide connectivity of genetically defined cell populations in the whole mouse brain.

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Poster

P463. Physiological and Functional Properties of Visual Circuits

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P463.06

Topic: D.07. Vision

Support: CIHR grant MOP-119498

Title: Laminar functional connectivity in primary visual cortex

Authors: *J. NING[1], C. L. BAKER[2];
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Abstract: Laminar structure is a distinctive feature of cerebral cortex, which is broadly conserved not only across cortical areas but also across species. It comprises 6 layers characterized by cellular organization, specific inputs and projection targets. Previous studies have shown anatomical connectivity across laminae (Harris and Shepherd, 2015), but how different laminae are connected physiologically is still unclear. Here, by using a series of functional connectivity methods, we investigate association and causal relationship across laminae in primary visual cortex. While responding to visual stimuli, neurons across cortical depth in A17/18 of the anesthetized and paralyzed cat were recorded with a 32-channel linear array probe (NeuroNexus). Multiunit activity (MUA) was extracted from recorded neuronal responses for each channel, as times of level-crossings at 3 standard deviations of the bandpass digitally filtered (300 Hz - 3.0 kHz) signal. Current source density (CSD) analysis was applied to approximately locate recording sites into 3 layers (supra-granular layer, granular layer and infra-granular layer) (Mitzdorf and Singer, 1978). We implemented a series of functional connectivity methods in Matlab, including mutual information, Pearson correlation, and Granger causality, to measure statistical dependence of MUA across recoding sites. Since common input and indirect influence could introduce spurious connectivity, we applied conditional Granger causality, which could remove variance explained by other variables when estimating pairwise functional connectivity, using a version of the method designed to analyze spiking responses (Chen et al., 2006; Dhamala et al., 2008). For validation, we tested these methods on simulated spiking data from a small network of leaky integrate-and-fire models. These methods showed patterns of functional connectivity across laminae, suggesting association and causal relationships between neuronal layers of cortex. The results from mutual information and Pearson correlation exhibited a similar relation to the laminar structure measured by CSD, and Granger causality

provided indications of directionality. In simulated data, conditional Granger causality outperforms Granger causality in minimizing the effect of spurious correlations such as confounders and indirect influence, and therefore better reveals potential underlying mechanisms. In conclusion, these three functional connectivity measures, including mutual information, Pearson correlation and Granger causality, suggest how neurons in the primary visual cortex process sensory inputs in a laminar-dependent manner.

Disclosures: J. Ning: None. **C.L. Baker:** None.

Poster

P463. Physiological and Functional Properties of Visual Circuits

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Topic: D.07. Vision

Support: NIH R01. EY011488

Title: Developmental changes in the temporal and laminar structure of responses to oriented gratings in primary visual cortex following eye opening

Authors: *A. A. LEMPEL, D. FITZPATRICK;
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Abstract: Cortical circuits develop in two main stages: an early stage driven by endogenous mechanisms that precedes sensory experience, and a later stage where maturation is driven by sensory input. Orientation maps in ferret primary visual cortex (V1) have served as a powerful model for studying these different phases of cortical maturation. The development of orientation maps begins before eye opening, where neuronal responses to oriented gratings are poorly selective yet organized in spatial patterns. Visual experience transforms these immature response patterns into a reliable representation of orientation. Response patterns elicited by gratings have so far been studied with calcium imaging techniques that provide low temporal resolution and are limited to superficial layers. Therefore, whether the temporal and laminar structure of these response patterns changes across development remains unknown. By combining imaging techniques with electrophysiology, we revealed that the poorly selective patterns of responses to gratings seen before eye opening emerge in superficial layers with long latency and do not extend to deeper layers. In particular, neuronal responses recorded in layer 4, the main target of thalamo-cortical input, showed poor correlation with and lower orientation selectivity than response patterns seen in layer 2/3. These results strongly suggest that, before eye opening, responses to gratings are shaped by recurrent mechanisms within layer 2/3 that generate spatial patterns and increased selectivity. After eye opening, responses became strongly selective with short latency across all cortical layers, consistent with the established view that mature orientation selectivity in V1 of carnivores is computed through feed-forward mechanisms in layer 4. This developmental difference in the laminar and temporal structure of responses to gratings could be due to the lack of experience with stimuli that include sharp edges before eye opening. If so, responses to stimuli that can be perceived through closed eyes should present a mature temporal and laminar structure before eye opening. To test this, we analyzed responses to homogeneous

changes in luminance across development. Indeed, responses to these stimuli showed high selectivity with short latency across all layers both before and after eye opening. Taken together, our results suggest that early in development neuronal responses to novel stimuli are structured across the cortical network by recurrent mechanisms that provide some degree of selectivity. Further experience with the stimuli would re-shape feed-forward connectivity leading to mature cortical representations.

Disclosures: A.A. Lempel: None. **D. Fitzpatrick:** None.

Poster

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Research To Prevent Blindness

Title: Layer-dependent modulation of gamma-band oscillations by stimulus size in primate visual cortex

Authors: *A. M. CLARK[1], M. BIJANZADEH[2], *A. ANGELUCCI[1];
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Abstract: Sensory processing is affected by context. In primary visual cortex (V1), a commonly studied form of this contextual modulation is surround suppression (SS), in which responses to stimuli inside a cell's receptive field (RF) are suppressed by nearby stimuli (Angelucci et al 2017). Previous studies have shown that in primate V1 stimuli that activate both the RF and surround increase the power of local field potential (LFP) gamma-band oscillations (Gieselmann, et al, 2008; Jia, et al, 2011). There is evidence that inter-areal feedback (FB) connections contribute to SS and modulate gamma oscillations. Specifically, surround stimulation in monkey V1 evokes the earliest LFP signals in FB-recipient V1 layers (Bijanzadeh et al, 2018), and inactivation of V2-V1 FB reduces SS (Nassi et al. 2013; Nurminen et al. 2018). Inactivation of V2/V3 FB also reduces the power of gamma oscillations in V1 (Hartmann et al, 2019). Because the strength and tuning of SS, as well as the pattern of FB connections, varies across V1 layers, we wondered whether V1 layers exhibit differences in SS-modulated gamma. To study laminar differences in stimulus-evoked LFP gamma power, we recorded across all V1 layers within a cortical column in macaque monkeys using linear electrode arrays oriented normal to the cortical surface. Stimuli were gratings of optimal position, orientation and spatiotemporal frequency that varied in diameter. Consistent with prior work, across all layers, V1 gamma power was size tuned and the peak frequency of the gamma oscillation decreased with increasing diameter. However, unlike in prior accounts, size tuning curves were suppressed for the largest stimuli. Furthermore, the effect of stimulus size on gamma power

varied across layers. In supragranular layers, gamma power peaked for stimuli about the size of the recorded multi-unit (MU) RFs; much larger stimuli suppressed both MU activity (MUA) and gamma power. Conversely, in granular and infragranular layers, gamma power peaked for diameters that far exceeded those eliciting the greatest MUA; thus stimulation of the surround suppressed MUA but increased gamma power. Across all layers, gamma size tuning peaked for smaller stimuli in the later portion of the response, further suggesting FB modulation of the gamma oscillation. In accordance with these findings, we did not observe a difference across layers in the orientation tuning of gamma power for stimuli that did not activate the RF surround. The above suggests models of cortical gamma in which excitatory-inhibitory interactions are modulated by a global feedback signal must be refined to take into account laminar differences in lateral, interlaminar and FB connectivity.

Disclosures: A.M. Clark: None. **M. Bijanzadeh:** None. **A. Angelucci:** None.

Poster

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Support: NEI RO1 EY027383
NEI R21 EY027946
McDonnell Center for Systems Neuroscience

Title: A modular organization of looped interareal and thalamocortical pathways in mouse visual cortex

Authors: *R. D'SOUZA, W. JI, A. BURKHALTER;
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Abstract: The dorsal lateral geniculate nucleus (dLGN) and pulvinar, the two main thalamic nuclei that innervate visual cortex, send strong axonal projections to layer 1 (L1) of mouse primary visual cortex (V1) in addition to their respective dense innervation of L4 and L5 of V1. L1 of mouse V1 is characterized by a modular organization wherein the afferents from dLGN and pulvinar terminate respectively in two spatially segregated, interdigitating zones termed ‘patches’ and ‘interpatches’ (D’Souza et al., 2019). Because dLGN and pulvinar inputs to L1 play diverse roles in the computation of predicted and unpredicted changes in the visual scene during locomotion (Roth et al., 2016), we hypothesized that patches and interpatches demarcate two distinct, specialized networks, each comprising preferential interareal and thalamocortical connections. Using a combination of anterograde and retrograde viral tracing of projection neurons in dLGN, pulvinar, V1, and several higher-order areas in wild type and Ai9-Cre mice of both sexes, we find that interareal and thalamocortical connectivity is governed by a ‘like-to-like’ rule: the postsynaptic targets of projection neurons residing in patch and interpatch zones preferentially send projections back to patches and interpatches, respectively. Patches and interpatches were identified by immunostaining tangential cortical sections for the M2 acetylcholine receptor. ‘Patch circuits’ included V1 neurons that projected to laterally located, higher visual areas LM (lateromedial), RL (rostrolateral), and AL (anterolateral), all of which, in turn, preferentially innervated

V1 patches. RL was recently shown to be specialized for processing posterior motion inherited from the retina (Rasmussen et al., 2020). Moreover, the apical dendrites of L5 and L6 cells that sent descending projections to dLGN were also preferentially located in patches, the preferred target of axons emanating from the dLGN shell. 'Interpatch circuits' included V1 neurons projecting to PM (posteromedial), whose direction selectivity likely depends on non-retinal mechanisms (Lien and Scanziani, 2018), the pulvinar, and the respective, reciprocal inputs back to L1 of V1. Furthermore, the axons of local V1 pyramidal cells and somatostatin-expressing interneurons were significantly denser in interpatches. Together, these connection motifs suggest the existence of two distinct brain-wide circuits: a patch network containing areas of the ventral stream (LM) including the posterior parietal branch of the dorsal stream (AL, RL), and an interpatch network containing the medial branch of the dorsal stream (PM).

Disclosures: R. D'Souza: None. **W. Ji:** None. **A. Burkhalter:** None.

Poster

P463. Physiological and Functional Properties of Visual Circuits

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Title: Vision is required for cell type specification in the visual cortex

Authors: *S. BUTRUS[1], S. CHENG[2], V. XU[2], S. SAGIREDDY[1], K. SHEKHAR[1], S. ZIPURSKY[2]; [1]UC Berkeley, Berkeley, CA; [2]UCLA, Los Angeles, CA

Abstract: Postnatal development of the visual cortex requires vision. However, how vision regulates gene expression in individual cortical cell types during this period is poorly understood. To this end, we assembled a postnatal developmental atlas of the mouse primary visual cortex (V1) using single nucleus RNA-sequencing of 225,000 neurons across six developmental stages between P8 and P38 and four light rearing conditions: normal rearing, dark rearing between P21-28 and P21-38, and dark-rearing between P21-28 followed by brief ambient light exposure. We used unsupervised machine learning approaches to identify molecularly distinct cell types at each age and developed a supervised learning framework to assess their postnatal maturation. We discovered that, under normal rearing conditions, the glutamatergic cell types in upper cortical layers (L2/3/4) were only specified following eye opening. By contrast, lower-layer glutamatergic (L5/6), GABAergic, and non-neuronal types were specified before this period. Using fluorescent in situ hybridization for L2/3 type markers identified in the atlas, we found that L2/3 glutamatergic types were organized in a sublaminar fashion that was established following eye opening, Furthermore, most genes that distinguished L2/3 types were expressed in a graded fashion across the three types, including markers that regulate axon projection specificity and inhibitory synapses. Finally, our dark rearing experiments revealed that early postnatal visual experience is required for both the establishment and maintenance of this continuous variation in L2/3 cell type identity. Visual deprivation disrupted both the transcriptional profiles of L2/3 neuronal types and their in situ organization, both of

which were partially recovered when visual stimulation was restored during the critical period. However, the maturation of L5/6 glutamatergic, GABAergic, and non-neuronal types was independent of vision. This selective influence of vision on cellular organization within L2/3 aligns with recent functional studies showing that only L2/3 neurons require vision to shape their tuning properties (Tan et. al., Neuron, 2020). In summary, our study provides an experimental and computational framework for investigating the role of experience in shaping the molecular, structural, and functional organization of the vertebrate brain.

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Poster

P463. Physiological and Functional Properties of Visual Circuits

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Topic: D.07. Vision

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Title: Cone-specific orientation sensitivity in macaque primary visual cortex

Authors: *M. A. SAVAGE, C. V. DIENI, P. D. GAMLIN, L. C. SINCICH;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Color and orientation sensitivity are two fundamental aspects of vision encoded in primary visual cortex (V1). Early work suggested that these features are specific to anatomically segregated regions of primate V1, with color sensitive neurons residing in cytochrome oxidase (CO) patches and orientation sensitive neurons in CO interpatch regions, but recent research has shown that such a functional segregation is not so strict. We investigated the interaction of cone-specific signals and orientation tuning in macaque V1 with 2-photon calcium imaging and classified the recorded neurons by CO compartment. One animal was injected with a fluorescent calcium reporter (AAV1-syn-gCamp7s). After 3 months transfection time, we imaged through a cranial window while the animal was anesthetized and under neuromuscular blockade. Visual stimuli consisted of drifting cone-isolating gratings (L, M or S) of 6 different orientations. Postmortem CO histology was aligned with the imaged field using vascular landmarks. We imaged 252 transfected neurons within a 460 μm diameter field at 200 μm depth and found that 62% were in a CO interpatch area and 33% were in CO patches. Half of the labeled neurons were visually responsive (Z score > 2.5), with a median orientation tuning width of 26°; of these cells 58% were highly orientation selective (1-circular variance > 0.5). The CO patch and interpatch neurons displayed similar median orientation tuning widths, 28° and 24° respectively, consistent with recent reports. The cohort of 125 responsive neurons exhibited either L cone dominant weighting (60% L/M ratio > 1) or M cone dominance (40% L/M ratio < 1). When comparing S cone vs LM cone inputs, the

responses were more skewed, with 32% S cone dominant (S/LM ratio > 1) and 68% LM cone dominant (S/LM ratio < 1). Orientation tuning width was similar for each group of cone dominant neurons. Cone weighting ratios were compared in relation to CO patch or interpatch regions, and the same prevalence of L vs M cone dominance was found in each region as in the overall population. The S vs LM cone inputs differed slightly, with the CO patches having 41% S cone dominance and 59% LM cone dominance while the CO interpatch neurons were less S cone dominant (27%) than LM cone dominant (73%). Notably, in a subset of neurons, orientation tuning changed by >30° depending on the cone-isolating stimulus. We found 18% of CO patch and 20% of CO interpatch neurons displayed shifts in orientation tuning based on which cone class was being modulated. Our results show that cone-isolating stimuli drive well-oriented responses in CO patch and interpatch areas of V1, with some neurons apparently displaying cone-specific orientation tuning.

Disclosures: M.A. Savage: None. **C.V. Dieni:** None. **P.D. Gamlin:** None. **L.C. Sincich:** None.

Poster

P463. Physiological and Functional Properties of Visual Circuits

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Title: Holographic activation of neural ensembles reveals both space and feature based cortical microcircuitry

Authors: *I. A. OLDENBURG, W. D. HENDRICKS, H. ADESNIK;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Visual perception involves the coordinated effort of thousands of interrelated and often genetically similar neurons. Privileged interconnectivity between excitatory cells in co-active ensembles can amplify sensory input and facilitate perception. However, as these ensembles are physically intermingled, understanding the causal influence that ensembles of cells exert on other neurons requires new advanced technologies. We use multiphoton holographic optogenetics (3D-SHOT) to gain temporally precise, individual cell resolution control of groups of neurons in vivo. We drive specific ensembles of excitatory neurons in L2/3 of mouse primary visual cortex to determine their influence independent of sensory stimulation. We find, across hundreds of different stimulated ensembles, that most groups reliably recruit recurrent inhibitory circuits, but that individual responding neurons may be excited or inhibited depending on both their physical proximity and feature preference similarity to the stimulated ensemble. Furthermore, the selection of which cells make up a stimulated ensemble impacts the inhibition

observed. Together, these space- and feature-dependent rules refine our understanding of the cortical microcircuit, reconciling the Hebbian ‘like to like’ connectivity, with smooth spatial rules, and a balanced role of inhibition.

Disclosures: I.A. Oldenburg: None. **W.D. Hendricks:** None. **H. Adesnik:** None.

Poster

P463. Physiological and Functional Properties of Visual Circuits

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Title: High-density recordings with flexible electrodes in macaque primary visual cortex

Authors: *L. MERKEN, M. SCHELLES, F. CEYSSENS, P. JANSSEN;
KU Leuven, Leuven, Belgium

Abstract: Chronically implanted multi-electrode arrays are capable of recording multiple neurons for several months. However, in most applications, rigid electrodes are used which cause scar tissue formation over time. In order to upscale to a large number of electrodes, scar tissue formation should remain minimal. Another limitation of some multielectrode arrays is the limited length of the electrodes, which precludes investigating cortical areas that are buried in sulci. We developed ultra-thin flexible electrode arrays for long-term single- and multi-unit recordings that can also reach deeper cortical areas.The multi-electrode arrays were designed in a comb-like shape, with one to three electrodes on each needle, and a needle spacing of 700 µm. This allows insertion of multiple electrodes at the same time, while also spanning a large area of cortex. The electrode arrays consisted of a 10-20 µm thin flexible, biocompatible polymer (polyimide) with metal traces and iridium oxide as electrode material. Ongoing in vitro accelerated lifetime experiments have already demonstrated a lifetime of over 1.5 years. To allow the array to pierce the pia mater, it was temporarily reinforced with resorbable PLGA. A coating technique combined with a dedicated electrode array design was developed to create a sharp tip (< 10 µm²) needed for insertion. In a first in vivo test we implanted one macaque monkey with 92 electrodes in the primary visual cortex. Preliminary electrophysiological measurements were performed and histological analysis (NeuN, GFAP, CD 68, H&E stainings) was completed 3 months after implantation. We observed minimal scar tissue formation and viable neurons up to 10 microns from the site of implantation. In another macaque monkey, we implanted 139 electrodes and performed awake recordings while the monkey fixated during presentation of flickering checkerboards of 1 to 4 degrees. Over a time period of 2 months (10 sessions), we recorded multi- and single-unit activity from up to 68% of the active electrodes. In total, we observed 66 to 92 channels with a significant visual MUA response (Wilcoxon rank sum test comparing pre- and post-stimulus; $p<0.05$). The receptive fields were located in the lower contralateral visual field at eccentricities of 1 to 4 degrees, and measured between 1 and 3 degrees in diameter. In conclusion, we achieved long-term recordings of neural activity with highly flexible arrays in

primary visual cortex, which induced minimal scar tissue formation. These electrodes can be upscaled to 1000 electrodes to cover a large volume of cortex, including cortex in sulci, which is crucial for developing a high-resolution cortical visual prosthesis.

Disclosures: L. Merken: A. Employment/Salary (full or part-time):; Laboratory for Neuro- and Psychophysiology, KU Leuven, Leuven, 3000, Belgium. **M. Schelles:** A. Employment/Salary (full or part-time):; KU Leuven, Electrical Engineering Dept. (ESAT), Micro- and NanoSystems (MNS), Leuven, Belgium. **F. Ceyssens:** A. Employment/Salary (full or part-time):; cMACS, KULeuven, Belgium / ReVision Implant NV, Belgium. **P. Janssen:** A. Employment/Salary (full or part-time):; Laboratory for Neuro- and Psychophysiology, KU Leuven, Leuven, 3000, Belgium.

Poster

P463. Physiological and Functional Properties of Visual Circuits

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Program #/Poster #: P463.14

Topic: D.07. Vision

Support: Simons Grant 543019

Title: Mapping activity in macaque primary visual cortex using simultaneous micro-ECoG and depth arrays

Authors: *R. T. RAGHAVAN[1], K. A. KATLOWITZ[2], M. A. LONG[3], J. A. MOVSHON[1];
[1]Ctr. for Neural Sci., [2]Neurosci., New York Univ., New York, NY; [3]Neurosci. institute, NYU Sch. of Med., New York, NY

Abstract: Understanding the spatial precision of ECoG signals and the fidelity with which they reflect neuronal activity is critical to evaluating their utility as a recording method in both basic and clinical settings. This has grown more relevant with the development of high resolution ECoG arrays (micro ECoG) which have electrode spacing similar to intracranial silicon probes. We used micro-ECoG arrays to measure evoked activity in the visual cortex of anesthetized macaques, a circuit in which the content and spatial scale of sensory responses is well understood. We used sinusoidal grating stimuli to measure spatial frequency and orientation selectivity, and the spatial extent of visual activation that could be resolved on individual micro-ECoG array contacts. Stimulus-evoked responses had maximal SNR in the gamma band (40-300 Hz). Variations in the spatial frequency selectivity of gamma band signals agreed with the scale of spatial frequency maps in visual cortex as measured with calcium imaging (Nauhaus et al. 2012). Receptive field sizes from individual contacts were similar to intracranial spiking activity that we recorded simultaneously using laminar silicon arrays, and were roughly 3x smaller than reported for macro-ECoG recordings over primate cortex (Dubey and Ray 2019). These signals also exhibited strong surround suppression, a characteristic of superficial layer cortical activity. 48 hr post-implantation, sites continued to show tuning for both orientation and spatial frequency, as did intracranial spiking activity from these regions of surface visual cortex. We determined the stability of these measurements in one animal by recording over 6 days. Receptive field size remained stable over this time, while spatial frequency and orientation selectivity broadened, suggesting increasing pooling of underlying cortical

signals. Together, these results reveal conditions under which micro-ECoG arrays provide an excellent readout of cortical population activity. Moreover, they suggest micro-ECoG arrays can approximate the spatial resolution afforded by intracranial recording electrodes, but with a significantly less invasive footprint.

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Poster

P463. Physiological and Functional Properties of Visual Circuits

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Program #/Poster #: P463.15

Topic: D.07. Vision

Title: Validating White Matter Tractography using Topographic Mapping

Authors: *C. PEDERSINI[1], N. MILLER[2], K. DESIMONE[1,3], A. TEMUDO[1], K. K. SREENIVASAN[1], O. ABDULLAH[1], B. ROKERS[1];
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Abstract: Methods for identifying and assessing the structure of white matter pathways in the brain have advanced significantly in recent years. However, it is still difficult to determine if a method captures a tract in its entirety. Here, we present a pipeline to assess tractography methods by leveraging population receptive field (pRF) mapping data, which estimates topographic organization in gray matter.
We collected neuroimaging data of 7 healthy participants in a 3T MRI scanner. We extracted an estimate of the optic radiation (OR) white matter tract based on either probabilistic (Constrained spherical deconvolution) or deterministic (Generalized q-space imaging) methods. We extracted LGN, pulvinar and V1 ROIs based on anatomical templates (Freesurfer, Neuropythy), identified connecting streamlines, and cleaned the results when necessary. For each streamline we assigned a preferred polar angle and eccentricity based on the median value of the pRF estimates of V1 voxels it innervated. To validate this procedure, we checked the extent to which the estimates assigned to each streamline reproduced a relatively uniform spatial representation. Finally, we propagated tract-based estimates to LGN and pulvinar and visualized the resulting spatial representation. Thus we assessed the ability of the pipeline to recover the retinotopic organization of thalamus based on the combination of V1 retinotopy and white matter tractography.
Overall we observed a uniform representation of the contralateral visual field and fewer streamlines represented locations in the periphery rather than the central visual field, mirroring the pRF mapping results in gray matter, although this pattern was better preserved when using the probabilistic rather than the deterministic method.In thalamus we observed that the tract-based estimates provided a greater representation of the angular locations around the horizontal midline, consistent with previous studies. Both methods were slightly biased towards locations in the upper visual field and showed a greater representation of spatial locations around 2-5 degrees of eccentricity. These results highlight the potential and limitations of methods that estimate the retinotopic organization of the thalamus based on retinotopic organization in V1.

In conclusion, these results provide a means for leveraging functional data to identify and validate white matter pathways in topographically organized brain areas, and provide a means to compare tractography methods based on functional imaging data.

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Poster

P484. Representation of Objects and Scenes III

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Title: Causal testing of a topographic code in macaque V1 using a model-assisted all-optical read/write experimental platform

Authors: *S. KOBAYASHI, Y. Y. CHEN, X. X. WEI, E. SEIDEMANN;
Univ. of Texas At Austin, Austin, TX

Abstract: The encoding of coarse-scale visual features such as shape must involve pooling of information across populations of neurons with small receptive fields (RFs). Previous studies suggest that under some circumstances this may be done by exploiting topography in primary visual cortex (V1)—namely retinotopy, where neurons are organized by their RFs in visual field. We hypothesize the existence of a topographic decoder that can parse shape via the spatial structure of mean evoked V1 activity. To test this hypothesis, we trained macaque monkeys to discriminate aspect ratio (AR)—an important determinant of shape—by reporting the AR of bright 2-D Gaussians on a gray background. We used an encoding/decoding model of V1 with realistic noise, retinotopy, and tuning diversity to see how V1 may process information relevant to this task. We created decoders accessing different scales of encoded information—a purely retinotopic decoder only accesses the shape of mean activity across cortex, while a "labelled line" decoder accesses all information, including individual unit tunings. We find retinotopic decoders perform the AR task well, despite discarding substantial task-relevant information that is otherwise retained by a labelled line decoder. Macaques are sensitive to minute differences in AR, being able to correctly report AR of stimuli only slightly elongated from circular. Analysis of physiology of macaque V1 population activity via widefield voltage-sensitive dye and calcium imaging show that stimulus AR can indeed be decoded from the retinotopic shape of V1 activity, with sensitivity comparable to that of the animals. The ability to decode AR from retinotopic information is not sufficient to prove it is actively used by the visual system. We wish to test our hypothesis more directly using an all-optical platform to simultaneously record and manipulate population activity in primate V1 via co-expression of genetically encoded green calcium indicators and red-shifted opsins. By adding a projector to spatially pattern the evoked activity, we can inject retinotopic-only information into V1—activity indiscriminate to

individual tunings, only holding information in the shape of activity across cortex—while animals perform the AR task. We plan to run an experiment where we seek to bias perception using the above platform—if a purely retinotopic decoder truly exists, the injection of retinotopic-only information would bias perception. The results will be interpreted together with the models described above. Our model-assisted read/write methods in awake behaving macaque will allow for a causal approach in understanding visual processing.

Disclosures: S. Kobayashi: None. **Y.Y. Chen:** None. **X.X. Wei:** None. **E. Seidemann:** None.

Poster

P484. Representation of Objects and Scenes III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P484.02

Topic: D.07. Vision

Support: NIH/NEI grant R01EY016454

Title: A fast and robust retinotopic-scale representation of occluding edges in macaque V1 suggests an active role for V1 in scene segmentation

Authors: *S. KUMAR, Y. Y. CHEN, E. SEIDEMANN;
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Abstract: Despite the complex and cluttered environment that often surrounds us, our visual system rapidly and accurately interprets natural scenes and supports visually-guided behaviors. There are two competing hypotheses regarding the role of primate V1 in scene segmentation, a key component of scene interpretation. The segmentation computation may be partially implemented in V1, leading to a fast V1 representation of occluding edges that is invariant to the local features in the figure and background. Alternatively, V1 represents only the local features, the segmentation takes place downstream from V1, and delayed segmentation V1 signals reflect post-segmentation top-down modulations. To distinguish between these possibilities, we are studying V1's representation of camouflaged targets, where a figure obscures a background of identical texture. We trained two macaque monkeys to detect a small 2°x2° rectangular figure that occludes a large background. The target and figure contain identical sine-wave gratings that differ only in their phase. The target appears on half of the trials at a known location at an eccentricity of 2°, and the monkey reports target presence by making a saccade to the target location and target absence by maintaining fixation. As expected, the monkeys' performance improves with increasing target-background phase difference. Detection phase-difference thresholds are ~60° at 6 or 8 c/°. Behavioral masking experiments reveal that segmentation can be completed based on 80 ms of pre-mask edge stimuli, suggesting a rapid segmentation computation. To measure V1 population responses to occluding edges, we chronically expressed GCaMP6f in excitatory V1 neurons and recorded neural responses during passive fixation and behavioral detection tasks using widefield imaging. We find fast and robust elevated V1 population response along the retinotopic representation of the occluding edge that monotonically increases with phase difference and is largely insensitive to the local target and background features and to the behavioral task (passive vs. active). Decoding analysis reveals that these

responses can support fast and accurate camouflaged target detection and that V1 activity is elevated at the expected edge location on false-alarm trials relative to correct rejections. In summary, our results reveal a fast mechanism that represents occluding edges at the retinotopic scale in V1, supporting the hypothesis that V1 plays an active role in the segmentation computation. This conclusion is further supported by the finding that the edge-related V1 representation is correlated with variability in perceptual decisions.

Disclosures: S. Kumar: None. **Y.Y. Chen:** None. **E. Seidemann:** None.

Poster

P484. Representation of Objects and Scenes III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P484.03

Topic: D.07. Vision

Title: A comparison of top-down and bottom-up representations of visual objects in the human brain

Authors: *V. WADIA[1], A. MAMELAK[2], U. RUTISHAUSER[2], D. Y. TSAO[1,3];
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Abstract: A comparison of top-down and bottom-up representations of visual objects in the human brain. Mammalian visual processing has long been thought of as a combination of top down and bottom up processing. An extreme instance of top-down processing occurs in imagination, when a subject can be directed by verbal cues to perceive a stimulus in the absence of any bottom-up input. Animal studies have yielded rich insight into neural mechanisms for bottom-up processing. However, the neural mechanisms for top-down processing have been more elusive, in part due to the impossibility of verbal instruction in animals. Here, we performed single-neuron recordings in epilepsy patients implanted with modified depth electrodes that contain embedded microwires. These patients are implanted for the purpose of localizing the source of their focal epilepsy. We use this rare opportunity to examine the neural mechanisms underlying visual imagination in humans by directly comparing top down and bottom up representations of visual objects at a single neuron and population level across two different recall tasks (cued and free). Subjects were required to view images and, after a visual search distraction period, recall the images in either a cued (alternating tones specifying which two images to cyclically visualize) or a free (verbal description) manner. We find cells that were selective during encoding and maintained that selectivity during recall, corroborating previous findings (Kreiman et al, 2000; Gelbard-Sagiv et al, 2008; Khuvis et al, 2021). However, we report the existence of two additional cell populations distributed across multiple brain regions: cells that were exclusively active during viewing, and surprisingly, cells that were exclusively active and selective during recall periods either cued or free. These three functional groups perform complementary functions to give rise to perception and memory as we experience it.

Disclosures: V. Wadia: None. **A. Mamelak:** None. **U. Rutishauser:** None. **D.Y. Tsao:** None.

Poster

P484. Representation of Objects and Scenes III

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P484.04

Topic: D.07. Vision

Support: HHMI

Title: Chronic recordings reveal the face cell's cross-category encoding model

Authors: *Y. SHI[1], P. BAO[2], D. Y. TSAO[1];
[1]Caltech, Pasadena, CA; [2]Peking Univ., Beijing, China

Abstract: Inferior temporal (IT) cortex is considered the final stage for object recognition in the ventral visual stream. Macaque IT cortex contains 6 face-selective patches where most cells respond much stronger to faces than to other objects. Interestingly, these face cells also respond differently to different non-face objects, thus raising the question: What is a face cell's full encoding model to all object categories? It has long been thought that face cells use a specialized coding mechanism dedicated to faces, but with the advent of deep neural networks, a general-purpose coding mechanism becomes plausible. Specifically, can we predict the responses of face cells to faces using their weak responses to other objects? Previously our lab found that face cells encode faces by projecting each face stimulus onto a preferred axis in the face space (Chang & Tsao, Cell 2017). To address the question raised above, we mapped the preferred axes of cells for both faces and non-face objects in order to perform a further comparison. Traditional acute recording only allows a few thousand stimuli to be shown to the monkey within a recording session, which is not enough to build an accurate cross-category model. We thus used chronic brush arrays (McMahon & Leopold, J Neurophys 2014) to record from the same cells for days and even months, allowing us to show an order of magnitude larger number of stimuli to the monkey. Preliminary results suggest that face cells use different models for faces and non-face objects. We hypothesize that the chimeric encoding behavior may arise from local circuit plasticity shaped by early developmental experience.

Disclosures: Y. Shi: None. **P. Bao:** None. **D.Y. Tsao:** None.

Poster

P484. Representation of Objects and Scenes III

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Program #/Poster #: P484.05

Topic: D.07. Vision

Support: HHMI

Title: Neural representation of continuous, visual experience in the primate hippocampus

Authors: *K. MOHAN, J. LU, D. Y. TSAO;
Caltech, Pasadena, CA

Abstract: The mammalian brain is remarkably efficient at building memories of our conscious experience. We effortlessly reconstruct experienced events, and we are able to establish and maintain detailed episodic memories even after single, one-shot episodes. This ability to rapidly create a coherent internal model of the world is thought to rely on the hippocampus and its interactions with the cortex. Decades of experimental work have emphasized the role of the rodent hippocampus in constructing a spatial map of the environment but the underlying hippocampal code for representing visual experience, beyond simple awareness of egocentric spatial location, remains unknown. To tackle the question of how the primate hippocampus represents rich, naturalistic visual experience, we recorded neural population activity in the hippocampus (N=247) with 24-channel V Probes. During recordings, animals navigated a 3D immersive virtual reality (VR) environment tiled with visual objects at distinct spatial locations. Using VR headsets customized for macaques, animals actively explored the environment using a two-axis joystick to receive juice rewards. In addition to active experience during exploration, the same visual objects were presented passively to explore how predictable, spatially organized experience is learned. We also compare neural responses of the same cells to the same visual objects during active versus passive experience. We characterized the selectivity of individual hippocampal neurons to environmental variables (such as object identity, spatial location of animal, spatial location of currently viewed object, etc.), behavioral variables (such as joystick position, eye position, reward, etc.), as well as interactions between these variables. Single neurons showed spatially selective activity around salient events in virtual space, such as arena start, arena end, and approach towards objects in the arena, suggesting that hippocampal cells encode key events in continuous experience. We test the hypothesis that the hippocampus represents the ingredients of a visual scene - multiple objects and their locations - through an abstract, compositional representation. Overall, our results provide an understanding of visual representations in the hippocampus during exploration of object-rich environments.

Disclosures: K. Mohan: None. **J. Lu:** None. **D.Y. Tsao:** None.

Poster

P484. Representation of Objects and Scenes III

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Program #/Poster #: P484.06

Topic: D.07. Vision

Support: NIH/NIMH/IRP

Title: Reversible silencing of primary visual cortex with a chemogenetic system in rhesus monkey

Authors: *M. SMITH, M. ELDRIDGE, W. LERCHNER, M. MCDOUGALL, J. SHIM, B. RICHMOND;
Section on Neural Coding and Computation, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Chemogenetic silencing is a powerful tool in systems neuroscience research because it allows for selective and reversible silencing of neuronal activity. Ivermectin-gated chloride channels (GlyCl)

have been used to silence neurons and modify behavior of freely-moving mice. The goal of this study is to test whether the GlyCl-ivermectin system can be used to reduce neuronal activity in non-human primates (NHPs), using a behavioral task sensitive to inhibition of primary visual cortex (V1). A modified ivermectin-gated chloride channel was expressed unilaterally in V1 of a single monkey, using a mixture of two viruses, AAV2-syn::GluCl2a-YFP and AAV2-syn::GluCl2b-YFP, which respectively expressed the α and β units of a glutamate-gated chloride channel (GluCl). The virus was injected at 0.5μL per second in a 3x3 grid. In the contralateral hemisphere, an aspiration lesion was performed as a positive control. A saccade-based visual detection task was used to determine the locations in the visual field that corresponded to the placement of the virus and lesion-induced scotoma. Gabor patches of varying frequency and contrast were then presented at four sites in the visual field: two control locations, the location corresponding to viral expression and that corresponding to the permanent scotoma. Contrast sensitivity curves were derived from the results obtained following ivermectin injection vs. vehicle injections. After vehicle injections, contrast sensitivity at the two control sites and the viral site were indistinguishable, whereas sensitivity was significantly lower at the scotoma site. Ivermectin injections significantly reduced sensitivity at the viral expression site without affecting the other three sites. Thus, the GlyCl-ivermectin inhibition in V1 caused an observable behavioral impact, suggesting that this chemogenetic tool may be suitable for reversible silencing of neuronal activity in NHP cortex (pending replication in a second subject).

Disclosures: M. Smith: None. **M. Eldridge:** None. **W. Lerchner:** None. **M. McDougall:** None. **J. Shim:** None. **B. Richmond:** None.

Poster

P484. Representation of Objects and Scenes III

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Program #/Poster #: P484.07

Topic: D.07. Vision

Support: NIMH/NIH/HHS

Title: Dissociation of function of visual areas TEO and TE in tests of visual recognition memory and perceptual categorization

Authors: *M. A. G. ELDRIDGE[1], T. SETOGAWA[2], J. E. PEARL[3], B. J. RICHMOND[1];
[1]NIMH, Bethesda, MD; [2]Univ. of Toyama, Tsukuba, Japan; [3]Harvard Univ., Cambridge, MA

Abstract: It is widely accepted that a set of interconnected cortical brain regions running from the occipital pole to the ventral temporal lobe underlie the ability to perceive and recall visual stimuli.This pathway, labeled the ‘ventral visual stream’, consists of architectonic areas starting with primary visual cortex (V1) in the occipital lobe through V2, to V4, to the inferior temporal cortex areas TEO and TE. Although it has been established that there are reciprocal anatomical connections between areas, this system is often modeled as a multi-layer, feed-forward network (a deep network).
We performed two experiments to study the contributions of two areas thought to be at the final stages of complex image processing, areas TEO and TE. In a visual perceptual categorization task (the monkeys

had to judge whether a morphed image was more dog-like or cat-like) bilateral removals of either area TEO or area TE led to a modest impairment in performance, and when both TEO and TE were removed, the deficit was severe. Thus, the two regions seemed to contribute to the ability to categorize stimuli accurately, and each could at least partially compensate for the loss of the other. Conversley, in a visual recognition task (the monkeys had to indicate whether a series of novel images were being presented for the first or second time within a session), TEO removal had no effect on performance, whereas TE removal caused a severe impairment. The combined TE + TEO removal produced no additional deficit to that observed in the group with TE removals.
Both of these results demonstrate that TE receives high resolution visual information even when TEO has been removed. Further, the dissociation in the pattern of effects observed in these two studies demonstrates specialization of function in areas TE and TEO.

Disclosures: M.A.G. Eldridge: None. **T. Setogawa:** None. **J.E. Pearl:** None. **B.J. Richmond:** None.

Poster

P484. Representation of Objects and Scenes III

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Program #/Poster #: P484.08

Topic: D.07. Vision

Support: NIH/NIMH/IRP

Title: Retrograde viral tracing demonstrates bifurcating V4 projections to areas TEO and TE in the rhesus monkey

Authors: *B. RICHMOND, **N. MIYAZAKI**, B. LI, M. A. ELDRIDGE, W. LERCHNER;
Lab. of Neuropsychology, NIMH, Bethesda, MD

Abstract: The classic hierarchical structure of visual processing (V1 -> V2 -> V4 -> TEO -> TE) posits that visual information reaches TE via TEO. A previous behavioral study from our lab suggests that visual categorization can be performed in areas TEO and TE in parallel. These findings challenge the classic hierarchical structure of the ventral visual stream. Previous anatomical studies show that a direct projection from V4 to TE exists, independent of the V4-TEO-TE pathway. But it is unknown whether V4 neurons provide bifurcating afferent projections terminating in TEO and TE. In the present study, we injected nonreplicating viruses that are transported retrogradely from axon terminals throughout the neuron. We injected viruses expressing a colored fluorescent reporter into area TEO and a reporter with another color into TE. From these viral injections we can judge 1) the relative strengths of V4 projections to TEO and TE, 2) the general distribution of TEO-projecting and TE-projecting neurons in V4, and 3) the presence or absence of V4 neurons with bifurcated projections to both TEO and TE. To cover V4 axon terminals across large areas of TEO and TE, we used custom multichannel microinjector arrays. The high density of fluorescently labeled neurons in the targeted areas TEO and TE show that the viral delivery method worked well. We found populations of TEO-projecting neurons and TE-projecting neurons in V4, V4t and V4v, with intermixing of colored neurons in V4, and separation of colored neurons in V4v. In V4v, TEO-projecting neurons are in the more medial aspect, and TE-projecting

neurons are in the more lateral aspect. In addition, there was sparse population of neurons projecting to both TEO and TE in V4, V4t and V4v (shown by co-localization of two colors).

Disclosures: B. Richmond: None. **N. Miyazaki:** None. **B. Li:** None. **M.A. Eldridge:** None. **W. Lerchner:** None.

Poster

P484. Representation of Objects and Scenes III

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Program #/Poster #: P484.09

Topic: D.07. Vision

Support: NIH/NIMH/IRP

Title: Different roles for area TE and rhinal cortex in visual categorization in rhesus monkeys

Authors: *B. LI, M. A. ELDRIDGE, K. A. LOWE, S. CHANDRA, B. J. RICHMOND;
Lab. of Neuropsychology, NIMH, Bethesda, MD

Abstract: Visual perceptual categorization groups objects based on shared features, hence this process requires both visual perception and visual memory. Area TE and rhinal cortex are two candidate regions for the neural substrates serving visual categorization processing. Area TE is considered to be involved in the late stages of visual perception and object recognition. Rhinal cortex is an important node of visual memory, and its role in visual perception is heavily debated. A previous selective lesion study from our lab showed that bilateral rhinal cortex lesions did not impair visual categorization, and that bilateral TE lesions mildly impaired visual categorization. Here we investigated the role of TE and rhinal cortex in visual categorization further by making selective lesions of each area and then testing the monkeys under conditions of increased task difficulty. We presume the monkeys need to accumulate perceptual evidence to respond correctly. To vary task difficulty, we manipulated the presentation duration of visual stimuli. Monkeys were trained to perform a two-interval-forced-choice (2-IFC) task, i.e., release the bar in one of two different intervals based on the identity of a cue image (morphed between dogs and cats at in at one of 11 levels). The set of possible cue image durations was 25, 50, 100, 250 or 500ms, selected randomly trial-by-trial. Compared to unoperated controls, monkeys with bilateral TE lesions showed impaired categorization performance at all stimulus durations, but information processing time was not significantly different between these groups. Bilateral rhinal cortex lesions did not impair monkeys' categorization performance but was followed by longer information processing time. For all groups, processing time increased with longer cue image durations and with increasing ambiguity of morph level. We also adopted a failure rate analysis to study the decision-making process. The results suggest that it takes more time for monkeys to make decisions after rhinal cortex lesions but not after TE lesions. On the other hand, results from simulations with a wide range of decision-making models suggest that there is no consistent difference in decision-making strategy between TE lesion, rhinal cortex lesion and unoperated control groups. Overall, our results support the idea that TE might play a more perceptual role and rhinal cortex might play a more cognitive role in categorization-based decision making. One possibility is that rhinal cortex facilitates perceptual evidence accumulation via memory-guided attention.

Disclosures: B. Li: None. **M.A. Eldridge:** None. **K.A. Lowe:** None. **S. Chandra:** None. **B.J. Richmond:** None.

Poster

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Topic: D.07. Vision

Support: NRF-2017M3C7A1029659

Title: Art expertise and aesthetic preference for visual properties

Authors: *J. SONG, C.-Y. KIM;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract: Accumulating evidence suggests that aesthetic appreciation for visual properties is influenced by art expertise. However, the scattered evidence has not been integrated into a coherent explanation. The recent psychological models of aesthetic appreciation also did not point to the interaction between expertise and aesthetic preference for visual properties at the perceptual processing stage. The present study aimed to examine the interaction between expertise and aesthetic judgment for visual properties including curvature, complexity and symmetry. By analyzing published research findings, we specifically examined which side experts prefer among two competing dimensions of the properties (i.e. curvature-angularity, complexity-simplicity, symmetry-asymmetry) and how aesthetically sensitive they are to the dimension of the properties compared to non-experts. This study also aimed at investigating whether the interaction varies according to the processing level of visual properties. More information and later processes are expected to be involved in appreciation as you move from curvature, complexity, to symmetry. It was found that aesthetic preference for visual properties differs depending on the extent of expertise, and both preference and aesthetic sensitivity of experts are more influenced by higher level properties. We proposed that the results of experts' preference are mainly derived from their enhanced perceptual fluency and cognitive pursuit of atypicality. The study suggests that art expertise affects aesthetic appreciation from the perceptual processing stage, the first stage of the aesthetic appreciation process.

Disclosures: J. Song: None. **C. Kim:** None.

Poster

P488. Visual Learning, Memory, and Categorization

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Topic: D.07. Vision

Support: NIH R01EY019466
NIH R01EY027841

Title: Similarities and differences between the outcomes of a neural network model of contrast discrimination and human visual perceptual learning

Authors: *T. BARNES-DIANA, Y. SASAKI, T. WATANABE;
Cognitive, Linguistic, and Psychological Sci., Brown Univ., Providence, RI

Abstract: Neural Networks have been used to replicate a variety of phenomena in Visual Perceptual Learning, or VPL. These replicated phenomena include learning in orientation discrimination, task difficulty effects, and location specificity (Cohen & Weinshal 2017). Neural network models have been adapted, with a twin network modification, to perform 2-AFC (alternating force choice) tasks (Wenliang & Seitz 2018). This twin network methodology uses two parallel networks whose outputs are compared. Here, to examine similar and different aspects of a twin network model from human VPL, we use a twin network instantiation of a deep neural network (5 convolutional layers, 3 pooling layers, and one fully connected layer) to model VPL of contrast discrimination. This model provides each trail an estimate of which of two images has higher contrast. In the present study, we tested this model in a classic behavioral contrast discrimination protocol inspired by Yu et al 2004. Specifically, we examined whether the model can replicate important characteristics of human VPL such as 1) location specificity, 2) feature specificity (i.e., reference contrast), and 3) roving, whereby random interleaving of different reference contrasts annihilates the learning that would happen in the same amount of training in a blocked design. Similarly to human VPL, partial location specificity was observed. However, in contrast to human learning, no specificity to the reference contrast was obtained. In addition, learning did occur in the roving condition, though the amount of VPL was smaller than in the blocked condition. The failure of the feedforward network model to replicate the feature specificity and roving effect observed in human VPL could be because the model does not have a temporal chunking system, whereby temporarily adjacent similar trials are grouped together into meaningful categories.

Disclosures: T. Barnes-Diana: None. **Y. Sasaki:** None. **T. Watanabe:** None.

Poster

P488. Visual Learning, Memory, and Categorization

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Wellcome Grant 108726

Title: Learning orthogonalizes visual cortical population codes

Authors: *S. W. FAILOR, M. CARANDINI, K. D. HARRIS;
Univ. Col. London, London, United Kingdom

Abstract: When an animal sees a stimulus, this triggers a pattern of activity across a multitude of neurons in its visual cortex. These neurons' firing rates together define a representation of the stimulus in a high-dimensional space, similar to the representations constructed by machine learning algorithms. The similarity of the representations of two stimuli can be quantified by the angle or dot product between the corresponding vectors. In machine learning this similarity measure, known as the "kernel function", determines the generalizability of stimuli: stimuli evoking identical representations will generalize perfectly, while stimuli evoking orthogonal representations will not generalize at all. Allowing the representations to themselves change with learning is the heart of flexible learning algorithms such as neural networks.

In the brain, stimuli that evoke similar neural representations are likely to evoke similar behavioral responses. Furthermore, stimulus representations evolve as animals learn, even in primary sensory cortices. One might expect that after learning, the number of neurons selective for behaviorally-important stimuli increases, as has been observed in auditory, somatosensory, and visual cortex. Other studies, however, have found a paradoxical decrease in the number of cortical neurons responding optimally to learned stimuli, and in primary visual cortex (V1), neurons increase their slope at the task stimulus in a manner dependent on orientation preference. It is not yet clear whether these complex and apparently contradictory findings result from a single principle governing plasticity of cortical representations at a population level.

Here, we use two-photon calcium imaging to show how the tuning of 4,000-neuron populations in V1 change after mice learn an orientation discrimination task. At a single-cell level, the results appear complex: neuronal tuning curves evolve according to a lawful but complicated dependence on their prior orientation preference and tuning strength. At the population level, a simple principle emerges: learning transforms response vectors by a nonlinear function, whose convexity is largest for task-informative stimuli and small for the task-distractive stimulus. This transformation sparsens the population representations of the task-informative stimuli and orthogonalizes them from each other. A model of F-I curve modulation, requiring no synaptic plasticity, quantitatively predicted the learning effect. Lastly, the degree of sparsening varied across the population on a trial-by-trial basis, suggesting it emerges from rapid circuit dynamics, rather than slower plasticity mechanisms.

Disclosures: S.W. Failor: None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

P488. Visual Learning, Memory, and Categorization

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Title: Reward-associated images elicit enhanced responses and resist surround suppression in macaque area V2

Authors: *M. M. CARR[1], N. P. WILLIAMS[2], C. R. OLSON[3];
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Abstract: Previous studies exploring if reward associated images elicit enhanced visual responses in early primate visual cortex are inconclusive. We set out to resolve this issue by monitoring the activity of neurons in V2 of a rhesus macaque trained to associate some natural images with large rewards and others with small rewards. Each image subtended 3° visual angle and was positioned in the lower visual quadrant contralateral to the hemisphere destined for recording. On each training trial, while the monkey maintained central fixation, a single image was presented for 320 ms and, following a 320 ms delay, the associated reward was delivered. “High value” images received three times the volume of liquid reward as “low value” images. Training involved over 600 exposures to each image-reward pair over 18 weeks. After training, we measured the visual responses of V2 neurons to high and low value images presented within the classical receptive field (RF). The timing of each trial was the same as in training, except that stimulus duration was 620 ms. On average, high value images elicited stronger visual responses than low value images. This effect was of moderate strength (20% increase in response) and significant ($p < 0.01$; $n = 80$; sign test). Under natural viewing conditions, images are invariably embedded in clutter. It is conceivable that association with large reward would benefit the image representation in V2 by also conferring enhanced resistance to interference from clutter. To explore this possibility, we presented high and low value images in the RF along with a high contrast, reward-neutral display in the surround. The surround stimulus was an annulus centered on the RF with an inner diameter of 4° and outer diameter of 8°. Surround suppression, measured as a reduction in response strength when the annulus was present compared to when it was absent, was robust for low value images (9% reduction in response; $p <0.01$; $n = 80$; sign test) but was minimal for high value images (2% increase in response; $p = 0.43$ $n = 80$; sign test). This effect emerged 17 ms following visual response onset, a latency shorter than that commonly associated with top-down effects. It was not simply a secondary consequence of the difference in response strength, as surround suppression scaled with response strength over a wide range of firing rates for low value images but not for high value images. It persisted during sessions in which the reward was fixed and thus did not predict the size of the impending reward. We conclude that repeated pairing of an image with large reward produces a long-term effect whereby the image elicits stronger responses in V2 and independently exhibits immunity to surround suppression.

Disclosures: M.M. Carr: None. **N.P. Williams:** None. **C.R. Olson:** None.

Poster

P488. Visual Learning, Memory, and Categorization

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Topic: D.07. Vision

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NIH R01EY019466

Title: Transfer of high-level learning rules in visual perceptual learning

Authors: *A. MARZOLL, T. WATANABE;
Dept. of Cognitive, Linguistic, and Psychological Sci., Brown Univ., Providence, RI

Abstract: Visual perceptual learning (VPL) refers to long-term performance enhancement as a result of visual experience (Watanabe & Sasaki, 2015). Under classical VPL training conditions, improvement has been found to be highly specific to stimulus features such as retinal location and orientation (e.g., Karni & Sagi, 1992; Schoups, Vogels & Orban, 1995). However, recent research has revealed that transfer can take place under some circumstances (e.g., Harris, Gliksberg & Sagi, 2012; Tan et al., 2019). Additionally, some studies have emphasized the role of higher-level decision areas in VPL (Kahnt et al., 2011; Dosher et al., 2013). In the current study, we investigated if transfer of VPL to new stimulus features can be aided by previously established, complex decision rules. Human subjects (n=12 in total) first learned a category boundary in a categorization task with four relevant stimulus feature dimensions, with the boundary being diagonal to all axes of the stimulus parameter space. This arrangement forces subjects to integrate all stimulus features at once to improve their performance, preventing simple decision strategies. Difficulty in terms of boundary distance was adapted by a staircase procedure with feedback. After subjects learned this first categorization task for 7 sessions, they learned a second task with a set of new stimulus parameters (7 sessions). One group of subjects (n=5) categorized the stimuli across a boundary parallel to that of the first task, while the other group categorized across an orthogonal boundary (n=7). We hypothesized that the brain may be able to repurpose the previously learned decision boundary in the parallel condition—leading to transfer—while no such transfer should occur in the orthogonal condition. Preliminary results, however, paint a different picture: The difference between final performance in the first task and initial performance thresholds in the second task was +12.1% in the parallel condition and +4.8% in the orthogonal condition. Final performance in the second task was similar in both conditions (.158±.006 vs .159±.006 [a.u.]). Pending further investigation, this suggests that contrary to our prediction, established complex decision rules may be a hindrance to transfer if too similar. Alternatively, sufficiently dissimilar decision rules may enhance such transfer.

Disclosures: A. Marzoll: None. **T. Watanabe:** None.

Poster

P488. Visual Learning, Memory, and Categorization

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P488.05

Topic: D.07. Vision

Support: Simons Collaboration on the Global Brain award 543033
National Eye Institute of the National Institutes of Health R01EY020851

Title: The remarkable visual specificity of visual recognition memory behavior is shaped by representational sharpening, reflected in inferotemporal cortex

Authors: *B. G. L. JANNUZI, T. MEYER, M. HAY, C. M. HACKER, N. C. RUST;
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Abstract: We can remember the images that we have seen, even after seeing thousands, and we remember those images with considerable visual detail. How our brains manage to store visually detailed image memories at vast capacity is not well understood. 'Representational sharpening' proposals suggest that the visual representations of images that are reflected in high-level visual cortex are too overlapping to support the visual specificity of visual memory, and that downstream computations in the medial temporal lobe (including hippocampal pattern separation) act to sharpen them before visual memory storage. To investigate the assumptions and predictions of these proposals, we focused on the degree to which visual and visual memory representations in inferotemoporal cortex (IT) are more broadly tuned than visual memory behavior. To quantify behavior, subjects performed a Mnemonic Similarity task in which they were asked to judge whether images were novel or repeated in the presence of visually similar lure images. We found behavioral evidence for representational sharpening in humans as well as one rhesus monkey, reflected as sharpening relative to the benchmark of visual representations in the IT-analogous layer of a deep artificial neural network. To investigate the neural correlates of these behavioral effects, we recorded IT neural data as the monkey performed the task. We quantified the specificity of IT visual representations as the representational similarity of novel images and their lures, and we quantified the specificity of IT visual memory representations using a linear decoder optimized to extract IT visual memory information. Consistent with predictions of representational sharpening proposals, IT visual representations were more broadly tuned than visual memory behavior. However, at odds with predictions that representational sharpening is only reflected downstream of IT, we found that the visual specificity of IT visual memory behavior was well-aligned with IT visual memory representations. These results suggest that that the visual specificity of visual recognition memory behavior is shaped by representational sharpening, and that both the inputs to this process (visual representations) as well as the outputs (visual memory representations) are reflected in IT.

Disclosures: B.G.L. Jannuzi: None. **T. Meyer:** None. **M. Hay:** None. **C.M. Hacker:** None. **N.C. Rust:** None.

Poster

P488. Visual Learning, Memory, and Categorization

Location: Virtual Only

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Program #/Poster #: P488.06

Topic: D.07. Vision

Support: NIH Grant 1632738

Title: Increased pupil dilations are associated with unexpected false familiarity for faces

Authors: *K. ZIMAN, J. R. MANNING;
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Abstract: Our subjective sense that something we encounter is familiar to us is reflected by changes in pupil size. Although pupil dilation effects of familiarity have been well documented, familiarity is not the

only, or even the strongest, contributing factor to pupil dilation. Changes in pupil dilation also reflect changes in brightness, affective or emotional responses, hormonal release, expected value or utility, and surprise, among others. Because many factors can affect pupil dilation, important questions remain about how pupil dilation changes reflect high-order cognitive processes, like attention and memory. For example, because surprise and familiarity are often difficult to fully distinguish (since new experiences can be surprising or unexpected), it can be difficult to tease apart pupil dilation effects of surprise versus familiarity. To better understand the effects of surprise and familiarity on pupil dilation, we examined pupil responses during a recognition memory task involving photographs of faces and scenes. When participants rated novel face images as "familiar," we observed a robust pupil dilation response.

Disclosures: K. Ziman: None. **J.R. Manning:** None.

Poster

P488. Visual Learning, Memory, and Categorization

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P488.07

Topic: D.07. Vision

Title: A comparison of abstract categorical encoding in the primate superior colliculus and lateral intraparietal area

Authors: *B. PEYSAKHOVICH[1], S. TETRICK[1], O. ZHU[1], G. IBOS[2], W. J. JOHNSTON[1], D. J. FREEDMAN[1];
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Abstract: Primates have a remarkable ability to recognize the abstract categorical significance of sensory stimuli to guide decisions. Investigations of visual categorization in primates have focused on a hierarchy of neocortical areas for transforming sensory encoding in early visual cortex into abstract categorical encoding in higher-order areas. However, flexible categorical behaviors are evident throughout the animal kingdom, including in species with very different brain architectures and even those lacking a neocortex, such as birds and reptiles. Furthermore, recent work from multiple groups has shown that the primate superior colliculus (SC), a midbrain sensory-motor region that is evolutionarily conserved across all vertebrates, is engaged in complex behavioral functions such as decision-making and attention, going beyond its widely studied role in reflexive orienting movements. However, those studies of SC either used tasks in which the animals reported their choice with a saccadic eye movement, or tasks that involved modulation of spatial attention by directing animals to covertly orient to stimuli at particular locations. This raises a question about whether the cognitive or behavioral roles of primate SC are restricted to contexts involving orienting, whether overt (through saccadic eye movements) or covert (through modulation of spatial attention).
To determine whether SC is more generally involved in abstract cognition, we trained two monkeys to perform a novel abstract visual categorization task and compared activity in SC and the lateral intraparietal area (LIP), a cortical region shown to be causally involved in categorical decisions. In the task, monkeys grouped motion stimuli into two categories based on two orthogonal boundaries, such that directions that are 180° apart belong to the same category. Monkeys compared the category membership

of two stimuli (presented peripherally and separated by a 1200-ms delay) and indicated their choice by releasing a manual touch-bar while maintaining gaze fixation throughout the trial. We analyzed neuronal spiking activity in LIP (n = 189 neurons) and SC (n = 121 neurons) from one monkey during performance of the categorization task. SC exhibits robust abstract categorical encoding that is stronger and arises with a shorter latency than LIP, is evident during both stimulus viewing and short-term memory, and is independent of the actions subjects used to report their decisions. This suggests that primate SC is engaged in abstract cognition, even in tasks involving neither saccadic eye movements nor explicit manipulation of spatial attention, thus extending the role of SC beyond orienting behaviors.

Disclosures: B. Peysakhovich: None. **S. Tetrick:** None. **O. Zhu:** None. **G. Ibos:** None. **W.J. Johnston:** None. **D.J. Freedman:** None.

Poster

P488. Visual Learning, Memory, and Categorization

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Program #/Poster #: P488.08

Topic: D.07. Vision

Support: National Research Foundation of Korea BRL Program (2018R1A4A1025891)

Title: Disentangling neural signatures of sensory and decisional biases in visual working memory

Authors: *H. GU, S. KIM, D.-G. YOO, J. LEE, H.-J. LEE, H. LEE, J. LIM, M. CHOE, S.-H. LEE; Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: We guide our behavior based on visual working memory (VWM), a workspace that holds visual information when it is no longer present. The recall of such information is known to be biased by both external and internal drives: it can be attracted to intervening visual input (‘sensory bias’) or shifted in the direction consistent with our own decision (‘decisional bias’). Recently, a computational-level account has been provided for these biases. However, it remains unknown at which time points over the time course of VWM the biases occur; specification of their dynamics will provide clues about how VWM is maintained amidst the confluence of feedforward and feedback neural information flows. To this end, we tracked the neural signatures of sensory and decisional biases of VWM in the human visual cortex. Inside an fMRI scanner (Siemens 3T Tim Trio), human subjects (n=48) viewed an oriented grating (‘target’) and estimated its orientation following a substantive (16.5s) delay. To elicit sensory and decisional drives, we presented an oriented bar (‘reference’) during the delay (4.5s or 10.5s after the stimulus offset) and asked subjects to decide whether the target was tilted clockwise or counter-clockwise against the reference. We found that subjects’ recall of target orientation was attracted toward the reference and shifted in the decision-consistent direction as predicted by the previously proposed computational account. On top of that, we reconstructed the target orientations from the multivariate blood-oxygenation-level-dependent signals localized in the visual cortex using the inverted encoding model and inspected how the reconstructed orientation drifted over the course of the trial. We found that the reconstructed orientations drifted in a way consistent with the behavioral biases. Importantly, however, the neural signatures of the sensory and decisional biases markedly differed in temporal

dynamics: the drifts toward the sensory drive were short-lived, appearing abruptly at reference onset and dying quickly thereafter, whereas the decision-consistent drifts persisted throughout the post-decisional epoch, peaking at the moment of target recall. Our findings suggest that the cortical system of VWM disentangles the influences from the external and internal drives by incorporating them into neural memoranda in the visual cortex over different time windows.

Disclosures: H. Gu: None. **S. Kim:** None. **D. Yoo:** None. **J. Lee:** None. **H. Lee:** None. **H. Lee:** None. **J. Lim:** None. **M. Choe:** None. **S. Lee:** None.

Poster

P490. Visual Cognition: Decision Making

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P490.01

Topic: D.07. Vision

Title: Amygdala contributions to motivational biases in perceptual decision-making

Authors: *Y. LEONG, R. PATERSON, Y. LYU;
Dept. of Psychology, Univ. of Chicago, Chicago, IL

Abstract: People are biased towards seeing outcomes that they are motivated to see. For example, sports fans of opposing teams often perceive the same ambiguous foul in favor of the team they support. Why are people more likely to see what they are motivated to see? Here, we test the hypothesis that amygdala-dependent allocation of visual attention mediates motivational biases in perceptual decision-making by enhancing sensory evidence accumulation in favor of desirable perceptual outcomes. We had human participants (N=30) perform a visual categorization task for reward while undergoing functional magnetic resonance imaging. On each trial, we used financial incentives to motivate participants to see one category over another. Even though the reward maximizing strategy was to perform the categorization task accurately, participants were biased towards categorizing the images as the category we motivated them to see. Participants with higher amygdala activation exhibited stronger motivational biases in their perceptual decisions, and performed worse on the task. Trial-by-trial amygdala activation was also associated with participants categorizing an image as the desirable category. Amygdala activation preceded image onset, suggesting that it was not in response to having seen the desirable category. Instead, the results suggest that heightened amygdala activity predisposed participants towards motivationally biased categorizations. To examine how amygdala activity was associated with biased sensory processing, we used a multivariate classifier to decode the neural representation of the presented image in the visual cortex. Trial-by-trial fluctuations in pre-stimulus amygdala activity tracked increased neural activity encoding desirable percepts, suggesting that amygdala activity biased attention towards perceptual features associated with desirable outcomes. Analyses using drift diffusion models indicated that amygdala activity was specifically associated with biases in evidence accumulation - on trials with higher pre-stimulus amygdala activity, sensory evidence accumulates more quickly in favor of desirable percepts. Prior work examining biases in perceptual decision-making have focused on the role of frontoparietal regions. Our work highlights an important contribution of the amygdala to perceptual

decision-making. When people are motivated to see one outcome over another, the amygdala biases perceptual decisions towards those outcomes.

Disclosures: Y. Leong: None. **R. Paterson:** None. **Y. Lyu:** None.

Poster

P490. Visual Cognition: Decision Making

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P490.02

Topic: D.07. Vision

Support: France-Merrick Foundation
JHU MBI & KSAS

Title: A common mechanism for choice, reaction time, and confidence in a multisensory heading discrimination task

Authors: D. HARSCH, *S. J. JERJIAN, C. R. FETSCH;
Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Successful decision-making requires accurate inference of the state of the world from available sensory information. This information is often noisy or ambiguous and arises from multiple sources. For perception of self-motion, previous studies have suggested that optic flow and inertial motion cues are optimally weighted on a trial-to-trial basis according to their reliability. However, conventional cue-combination models do not explain the speed of multisensory decisions (i.e., response time, RT), and it is unclear whether and how decision confidence emerges from the same decision process that accounts for cue weighting. We adapted a psychophysical task where subjects report their perceived heading direction (left or right of straight ahead) based on inertial motion, optic flow, or a combination of both. Cue weighting was assessed by varying the coherence of optic flow and spatial congruency of the two cues. Human subjects reported choice and continuous confidence ratings simultaneously via a saccade to one of two graded color bars. One male macaque monkey performed the same task but reported choice via saccades to a left or right target, followed by a second saccade to indicate high or low confidence (post-decision wager). In most sessions, subjects made their decision as soon as they were ready, allowing for the measurement of choice, confidence, and RT on the same trials. Choice behavior revealed trial-by-trial reweighting of the cues based on relative reliability, as shown previously. We found that, conditioned on a particular stimulus, confidence was inversely related to RT and predictive of choice accuracy. Importantly, the trial-by-trial reweighting process was also evident in subjects' RT and confidence judgements, quantitatively matching the effect of reliability on choices for a given cue-conflict condition. To account for these observations, we built a race model comprising two anti-correlated accumulators, which combined momentary evidence in a weighted fashion, with parameters determining stimulus sensitivity, diffusion noise, decision bounds, and sensorimotor delays. Confidence depended on the value of the losing accumulator and elapsed decision time. Model fits to empirical data suggest that choice and confidence in multisensory environments arise from a common mechanism of bounded accumulation of

reliability-weighted evidence, furnishing a quantitative framework for linking belief states to perceptual inference.

Disclosures: D. Harsch: None. **S.J. Jerjian:** None. **C.R. Fetsch:** None.

Poster

P490. Visual Cognition: Decision Making

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Program #/Poster #: P490.03

Topic: D.07. Vision

Support: NIH R01 MH118929
NIH R01 EY029250
NSF Graduate Fellowship Grant 1747452

Title: Locus coeruleus neurons track variability in neural and behavioral signatures of perceptual decision making

Authors: *K. ACAR[1], M. A. SMITH[2];
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Abstract: In a complex and dynamic environment, our brains repeatedly make decisions about sensory inputs (perceptual decision making), wherein the available sensory information is evaluated and used to form an appropriate behavioral response. The accuracy of perceptual decisions fluctuates, in part because the brain drifts between higher and lower levels of arousal, attention and motivation throughout the day. Previous work indicates that changes in activity of locus coeruleus (LC) neurons, along with corresponding changes in brain-wide norepinephrine (NE) release, contribute to transitions in arousal state. These shifts in arousal in turn correlate with changes in performance of simple decision tasks. However, it is still unknown what aspects of the decision process LC may influence, and how its influence manifests in the population activity of cortical neurons.
We examined the role of LC in perceptual decision making by testing the hypothesis that changes in LC activity influence a specific component of the perceptual decision process, namely the animal's criterion as defined by signal detection theory. We simultaneously recorded from single LC units and a population of prefrontal cortex (PFC) neurons in area 8Ar, using a 100-electrode "Utah" array. These recordings were performed in rhesus macaques performing a visual 2-AFC change detection task with sinusoidal gratings. The trials were structured such that the stimuli containing the sensory evidence for a decision were temporally distinct from the saccade target stimuli for reporting choices. We found that on a trial-to-trial time scale, LC responses were not modulated during sensory evidence presentation, but rather increased substantially when aligned to choice period onset, peaking at ~100ms before a saccade. This suggests that LC phasic responses may be closely linked to the transformation of perceived sensory information into a behavioral response. We also found that slow (tens of minutes) fluctuations in LC activity were related to slow changes in pupil diameter, criterion, and a slow-varying, arousal-related signal in the population of neurons in PFC, a brain region previously linked to criterion changes during

decision making. Together these results provide novel insights into the role of the Locus Coeruleus-Norepinephrine system in decision making.

Disclosures: K. Acar: None. **M.A. Smith:** None.

Poster

P490. Visual Cognition: Decision Making

Location: Virtual Only

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Program #/Poster #: P490.04

Topic: D.07. Vision

Support: Whitehall Foundation
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NSF GRFP

Title: Isolating metacognitive sensitivity with a process model for confidence

Authors: *C. M. ZIEMBA, Z. M. BOUNDY-SINGER, R. L. T. GORIS;
Ctr. for Perceptual Systems, Univ. of Texas at Austin, Austin, TX

Abstract: Perceptual systems interpret the environment on the basis of sensory information that is often impoverished and noisy, making perceptual errors inevitable. Observers are aware of the fallibility of perception and can introspect about the correctness of a perceptual decision. Which computations underlie this metacognitive ability? One prominent proposal is that confidence judgments reflect the observer's estimated probability that a decision is correct. While this hypothesis identifies a theoretical objective, by itself, it does not specify the operations that underlie confidence, nor does it clarify the factors that determine the quality of the confidence computation. Here, we develop a doubly stochastic process model that offers exactly such insight. In our model, confidence reflects the magnitude of a normalized perceptual distance estimate. The perceptual distance estimate is subject to noise, and so is the normalization term, which is an imperfect estimate of the magnitude of the perceptual noise. Our model naturally separates bias and sensitivity for confidence reports, just as signal detection theory does for perceptual decisions. We fit the model to a large set of previously published perceptual confidence judgments, and found that it captures a variety of confidence phenomena exceptionally well. In doing so, our analysis provides a new perspective on metacognitive ability — how good observers are at evaluating perceptual decisions. We show that the model parameter expressing precision of the perceptual uncertainty estimate, or "metanoise", provides a better metric for metacognitive ability than the non-process-model based alternatives that currently prevail in the literature. Specifically, metanoise has higher test-retest reliability, is less affected by task difficulty and confidence reporting strategy (i.e., the tendency to declare "high confidence" in one's judgments), and has higher cross-domain stability. These findings illuminate the computations that give rise to our sense of confidence, and they suggest that the quality of perceptual introspection is fundamentally limited by observers' imperfect knowledge of their perceptual uncertainty.

Disclosures: C.M. Ziemba: None. **Z.M. Boundy-Singer:** None. **R.L.T. Goris:** None.

Poster

P490. Visual Cognition: Decision Making

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Topic: D.07. Vision

Support: Wellcome Trust Grant 219572/Z/19/Z

Title: Neural correlates of static and dynamic decision-criterion adjustments based on expected evidence strength and advance warning cues in continuous sensory detection.

Authors: *A. GEUZEBROEK, L. PIRET, H. CRADDOCK, S. KELLY;
Sch. of Electrical and Electronic Engin., Univ. Col. Dublin, Dublin, Ireland

Abstract: To accurately detect unpredictable targets within a noisy environment, a beneficial mechanism is to accumulate perceptual evidence over time until it reaches a decision bound - a criterion amount of evidence. Such decisions are highly dependent on top-down processes to adapt this bound to suit environmental conditions. Bound adaptations made to regulate the speed-accuracy tradeoff are much investigated, but there are other factors arising in continuous monitoring contexts that call for strategic bound adjustments. Here, we examine the neural processes underlying static and dynamic bound adjustments based on knowledge of prevailing evidence strength and on external warning cues. In Experiment 1, participants detected intermittent 1-second periods of coherent upward motion within an otherwise incoherent, continuously playing motion stimulus, in blocks with all weak (25% coherence), all strong (70% coherence) or randomly mixed targets. Participants made far more false alarms in the Weak than Strong context, and exhibited a baseline motor preparation (beta-band EEG amplitude) closer to the response "threshold" level, together indicating a static bound lowering to facilitate weak target detection. In line, a motor-independent signature of evidence accumulation, centro-parietal positivity (CPP), reached lower amplitudes for Weak targets. However, the mixed context further revealed that a portion of this effect arose from random fluctuations in motor preparation associating the successful detection of weak targets with a pre-target preparation level that happened to be high. These fluctuations also resulted in increasing CPP amplitude as a function of RT.In experiment 2, participants indicated the direction (left/right) of intermittent coherent motion targets of two interleaved coherences, this time with a warning beep sound played 1-second before half of the target. Not surprisingly, participants missed fewer targets and were faster when given a warning signal. They were however less accurate, consistent with a lowered decision bound. Participants' motor preparation signals dynamically shifted closer to the pre-response threshold level after warning signals. This indicates that the bound dynamically lowers to facilitate detection and faster responses. In line, the CPP reached lower amplitudes for the targets that were introduced by a warning signal. Thus, behavioral data and neural dynamics of both accumulation and motor preparation converge to indicate that bounds are statically lowered in contexts with weak target strength, and dynamically lowered on shorter timescales when an auditory warning signal heralds an upcoming target.

Disclosures: A. Geuzebroek: None. **L. Piret:** None. **H. craddock:** None. **S. Kelly:** None.

Poster

P490. Visual Cognition: Decision Making

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Program #/Poster #: P490.06

Topic: D.07. Vision

Support: NRF Grant 2021R1F1A105202011
NRF Grant 2018R1A4A1025891

Title: Autocorrelation of errors in visual estimation tasks

Authors: *J. LIM, H. GU, S.-H. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: A primary goal of vision is to estimate the visual feature of a target object in an unbiased and stable manner. However, a mounting volume of evidence indicates that our visual estimates are systematically biased by the stimuli encountered in previous estimation episodes, dubbed 'serial bias in estimation (SB)'. Here, we report another important kind of serial dependence: estimation errors are correlated between adjacent trials. Compared to SB, this phenomenon is not well studied but substantially contributes to the variance of visual estimation errors. We will refer to this intriguing phenomenon as 'autocorrelation of errors in estimation (AE)', to distinguish it from SB. To examine how AE differs from SB in basic properties, we collected two data sets from human subjects (n=28 and 33, respectively), who viewed oriented gratings and estimated their orientation after a short (1 s) delay by reproducing it with nonius dots. On each trial, a single grating was shown in the first set whereas two gratings were shown in different hemifields, only one of which was post-cued for estimation, in the second set. AE was consistently observed in both data sets: orientation estimation errors were significantly correlated between neighboring trials, especially between those in which the target orientations were similar to one another. We also found that, compared to SB, AE was spatially narrow-tuned, but temporally broad-tuned. We further validated the presence of AE and its tuning properties in other publicly available data sets in which different visual features (e.g., color) were estimated with different parameters. In principle, current estimation errors can be attributed to previous stimuli or previous estimation errors. In this regard, the previous work on SB showed that the previous-stimulus-conditioned expectation of current estimation errors is biased. By contrast, AE indicates that a considerable portion of the remaining estimation errors is related to previous errors, not stimulus. Further, the sharp contrast between SB and AE in spatial and temporal tuning properties suggests that the two phenomena, although both fall under the umbrella concept of 'serial dependence', are likely to be mediated by different cognitive and neural mechanisms.

Disclosures: J. Lim: None. **H. Gu:** None. **S. Lee:** None.

Poster

P490. Visual Cognition: Decision Making

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P490.07

Topic: D.07. Vision

Support: Hermann and Lilly Schilling Foundation
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CNMPB Primate Platform

Title: Effects of dorsal pulvinar perturbations during perceptual decision-making

Authors: *K. KADUK[1,2], L. GIBSON[1], M. WILKE[2,1], I. KAGAN[1];
[1]Decision and Awareness Group, Cognitive Neurosci. Lab., German Primate Ctr., Goettingen, Germany;
[2]Univ. Med. Goettingen, Goettingen, Germany

Abstract: Studies of visuospatial decision-making emphasize the interactions in the frontoparietal networks. These direct cortical connections are paralleled by indirect routes through the higher-order thalamic nuclei such as the pulvinar, raising the question how does pulvinar contribute to the selection of behaviorally relevant stimuli. Perturbations of the dorsal pulvinar (dPul) induce an overt spatial selection bias during free choices (Wilke et al., 2010, 2013; Dominguez-Vargas et al., 2017). Pulvinar has also been implicated in attentional and confidence processing (Petersen et al., 1987; Desimone et al., 1990; Komura et al., 2013; Fiebelkorn et al., 2019), suggesting a role in perceptual discrimination. It remains unclear whether the spatial selection bias is caused by contralateral perceptual deficit or a more general motor / orienting deficit. To address this question, we assessed changes in perceptual sensitivity (dprime) and response criterion after unilateral pharmacological inactivation and time-resolved electrical microstimulation of dPul. Two macaques performed a color discrimination task where the perceptual difficulty was determined by the color similarity of target vs. easy or difficult distractor. Target or distractor was either presented alone or with a second stimulus (either distractor or target) in the opposite hemifield. Monkeys had to saccade to the target or to continue fixating when only distractor(s) were presented. The dPul was either reversibly inactivated by the GABA-A agonist THIP or stimulated before or after stimuli onset in multiple sessions. After inactivation, we observed criterion shifts away from contralateral selection, especially when two competing peripheral stimuli were present. Criterion shifts manifested as reluctance to select stimuli in the contralateral hemifield for both difficulty levels. The reaction times for the contralateral selection increased for all conditions. Importantly, the dprime and the overall accuracy remained largely unaffected. The accuracy decreased substantially only in the target-difficult distractor condition in which one animal avoided contralateral hemifield and did not utilize the information from this hemifield for target selection. Early microstimulation matched the inactivation results showing an ipsilateral choice bias. Late microstimulation induced an opposite, contralateral choice bias for the double stimuli. Together, our results emphasize the role of dorsal pulvinar in facilitation of contralateral orienting and motor decision signals during spatial competition, rather than the specific role in perceptual discrimination.

Disclosures: K. Kaduk: None. **L. Gibson:** None. **M. Wilke:** None. **I. Kagan:** None.

Poster

P490. Visual Cognition: Decision Making

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Program #/Poster #: P490.08

Topic: D.07. Vision

Support: Whitehall Foundation
France-Merrick Foundation

Title: Dynamics of momentary decision evidence and its leverage on choice and confidence in a peri-decision wagering task

Authors: M. VIVAR-LAZO, *C. R. FETSCH;
Neurosci. & Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Previous work has shown that a common process of bounded evidence accumulation can jointly explain decision speed, accuracy, and confidence. However, standard models of this process assume a simple and static pooling mechanism for converting sensory cortical activity into momentary evidence for the decision. In contrast, recent studies have emphasized the complexity of sensory representations, exemplified by the dizzying interplay between correlated variability, choice-related signals, and readout weights. This work motivates a more nuanced investigation into the nature of sensory evidence, including whether and how these population-level descriptions change during decision formation, and how they shape response time (RT) and confidence.
To address these questions, we devised a 'peri-decision wagering' task which isolates the temporal window in which momentary evidence could be constructed to support choice and confidence. Monkeys discriminated the direction of motion in a random-dot display, and whenever they were ready, indicated their choice (left or right) and confidence (high or low bet) with a single saccade to one of four targets: left-high, right-high, left-low, right-low. Relative to low-bet trials, a high bet yielded a larger juice reward if the direction choice was correct, but a longer penalty timeout if the choice was incorrect. Behavioral results validated the peri-decision wager as a measure of confidence: accuracy for a given stimulus strength was greater for high versus low bets. RTs were inversely related to confidence, conditioned on the stimulus, as shown previously in humans.
Using linear arrays and 128-ch high-density probes, we recorded population spiking activity in visual area MT during the task. We quantified the relationship between spike rates and behavior using conventional choice probability (CP) and an analogous metric for confidence (ConfP), computed in sliding windows aligned to the motion onset and to the saccade. We then used these metrics to compute the spatiotemporal weighting profile, separately for choice and confidence, guided by a dynamic estimate of the correlation structure. Preliminary results suggest that, compared to choice, confidence is more heavily influenced by MT activity later in the decision epoch, and shows a broader spatial weighting profile across preferred directions. This may indicate distinct readout mechanisms for choice and confidence, contrary to earlier conclusions, at least when both are reported simultaneously. Our approach furnishes new constraints on the construction of momentary decision evidence, and poses challenges for how the readout is implemented downstream.

Disclosures: M. Vivar-Lazo: None. **C.R. Fetsch:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

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Title: Blind source separation using ICA reveals event-specific components of primate motor cortex LFPs

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Abstract: The cortical local field potential (LFP) is a composite signal derived from multiple, complex neural sources. What are the individual neural sources that make up the LFP, how are these sources distributed throughout the cerebral cortex? Here, we used a blind source separation approach to isolate the statistically independent signals that contribute to the LFP recorded from neural ensembles in primary motor (MI) and two premotor (PMv, PMd) regions in two nonhuman primates (NHP) during an object grasping task where the object, grasp type, and go cues were presented independently across separate task stages. We analyzed 5 recording sessions for each monkey, each containing approximately 80 correctly performed trials. We used Independent Component Analysis (ICA) in the 0.1-4Hz band to separate the LFP components. To explore the relationship of the extracted components to the seven stages of the movement task, we performed an analysis of the shape and latency of the independent components (IC). To estimate the contribution of the cortical areas studied in the context of the extracted ICs, we performed a statistical analysis of the spatial distribution of the unmixing matrix. We found that the independent components of the low-frequency(lf) LFP are strongly linked to task stages. We were able to isolate seven independent components, where each task stage was associated with a distinct and reliable component and characteristic latency distribution. We observed that the LFP ICs typically arise from electrodes distributed across multiple cortical areas - rather than originating from adjacent electrodes confined to a specific cortical area. Furthermore, the spatial distribution of the components is consistent across the five sessions studied, with higher correlations observed between sessions recorded on consecutive days. Altogether our results show that it is possible to isolate lf-LFP ICs associated with specific behaviorally relevant events. These signals potentially represent internal markers of changes in the network's computational state. Additionally, the distributed nature of the components suggests that specific computations engage sub-networks distributed across multiple cortical areas, instead of being localized to anatomically defined subregions of the motor cortex. The temporal consistency observed in the components suggests their potential utility for the development of BCI systems to align and scale computational epochs.

Disclosures: D. Orellana: None. **J.B. Hynes:** None. **J. Donoghue:** None. **C. Vargas-Irwin:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.02

Topic: E.04. Voluntary Movements

Support: French National Research Agency under Grant Agreement No. ANR- 16-CE19-0005-01 (Neuromeddle)
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SNSF National Center of Competence in Research (NCCR) in Robotics

Title: Cortical dynamics underlying vocal production in freely moving minipigs

Authors: *M. LION[1], M. PALMA[1], M. KHOSH-NEVIS[1], C. ZENGA[1], F. BOCQUELET[1], M. AUBERT[1], S. KEFS[2], F. FALLEGGER[3], G. SCHIAVONE[3], I. GABELLE-FLANDIN[2], S. P. LACOUR[3], B. YVERT[1];
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Abstract: Vocal production pathways of non-human primates show strong similarities with those of speech in humans (Hage & Nieder, 2016; Loh et al.,2017). However, the extent to which they can generalize to non-primate mammals still remains an open question. We developed a paradigm to investigate this question in miniature pigs, which are social and domestic animals easy to handle and producing spontaneously different vocalizations (Garcia et al., 2016; Kiley, 1972; Marino & Colvin, 2015). One Yucatan and two Aachner minipigs were chronically implanted with surface ECoG grids over their left hemisphere, one using a soft implant over the motor and premotor region, and two with a larger grid covering more extensively their left hemisphere including part of the inferior frontal area. The two Aachner minipigs were implanted between 3 and 5 months of age, a period when their frontal sinuses were not yet developed thus allowing to proceed with conventional craniotomy to access motor and frontal brain areas without further risks of infection. Cortical activity and vocalizations of these animals were recorded synchronously in a freely moving environment with a wireless system. We observed vocal-evoked cortical potentials over the motor and premotor regions initiating 45 ms before vocal onset and lasting beyond vocal offset. Moreover, in the two animals implanted with larger grids, we observed activity in the inferior frontal cortex starting about 400 ms before vocal onset and ending more than 1 second after the start of the vocalization. These preliminary results suggest that a complex cortical dynamics underly vocal production in minipigs, making this animal an interesting model to study vocal production networks in non-primate mammals.

Disclosures: M. Lion: None. **M. Palma:** None. **M. Khosh-Nevis:** None. **C. Zenga:** None. **F. Bocquelet:** None. **M. Aubert:** None. **S. Kefs:** None. **F. Fallegger:** E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stocks/patents. **G. Schiavone:** None. **I. Gabelle-Flandin:** None. **S.P. Lacour:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stocks/patents. **B. Yvert:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.03

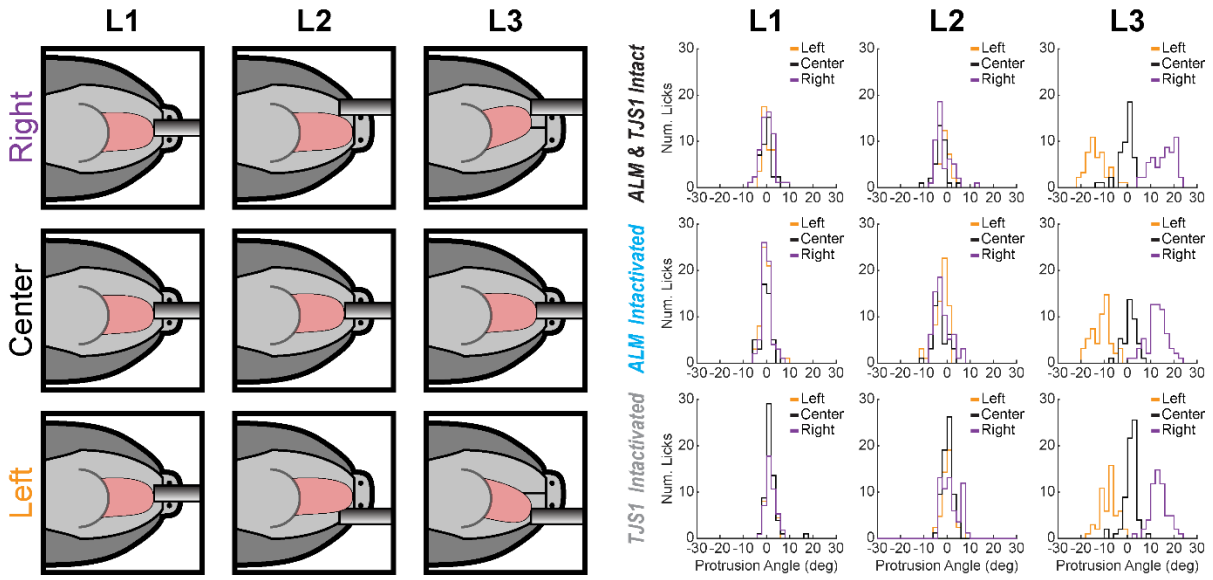
Topic: E.04. Voluntary Movements

Support: Jean Sheng
NSF Graduate Research Fellowship

Title: Subtle contact events guide ongoing movements during licking

Authors: *B. S. ITO[1], J. H. GOLDBERG[2];
[2]Dept. of Neurobio. and Behavior, [1]Cornell Univ., Ithaca, NY

Abstract: During non-visually guided grasping, subtle contact events guide ongoing movements. For example, when holding a cup of coffee, we readjust our grip in response to fine details of a slip - an upward slip on the index finger may recruit a different response than a downward one on the pinky. To study how fine tactile information is used to guide ongoing movements, we created a novel lick paradigm in head-fixed mice. First, we use kilohertz frame-rate imaging and a deep neural network to track tongue kinematics in 3D as mice retrieve water from a spout. Next, we detected the offset of tongue-spout contact on the first lick (L1) within a lick bout and randomly displaced the spout left or the right before the onset of the second lick (L2). Spout displacement magnitude was calibrated so that mice would nick the displaced spout with either the left or right side of the tongue during L2. We find that mice use this nick event to guide the immediately ensuing lick to the new target: left nicks guided the third lick (L3) left, and right nicks guided L3 right. Across-lick adjustments were not only aimed in the correct direction, but the magnitudes of these corrective responses were scaled appropriately depending on the tongue tip position at L2 contact: mice made larger corrections to the left or right on L3 if the tongue tip was farther away from the spout at L2 contact, and smaller corrections on L3 if the tongue tip was closer to the spout. Populations of neurons in anterolateral motor cortex (ALM) encoded nick position and lick direction fast enough to implement tactile feedback-guided corrections but, surprisingly, bilateral photoinhibition of ALM or tongue-jaw primary somatosensory cortex (TJS1) did not impair nick-guided corrections. Together, these data implicate yet-to-be identified subcortical circuits in implementing directionally specific contact-driven corrections.



Disclosures: B.S. Ito: None. **J.H. Goldberg:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.04

Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS111148
Pennsylvania HRFG

Title: Dynamics and directionality in the motor cortex during reaching

Authors: *H. MAO[1], A. B. SCHWARTZ[2];
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Abstract: As neural recording technology advances, scientists are recording activity of ever larger populations of neurons. Many computational tools have been employed to model neural population activity. Among them, the dynamical systems approach has gained interest in recent years. This approach treats firing rates of all simultaneously recorded neurons as the state of a dynamical system. With this perspective, the time-varying state of neural population activity is determined by the initial condition, internal dynamics (interaction between neurons), and external inputs to the recorded neurons. The dynamical systems approach has been used to model motor cortical neural activity during a delayed reaching task. In that experiment, the animal held its hand at a starting position during a delay period after a reach target was presented and waited for a go signal to start the reach. Neural activity during the delay period was assumed to set the initial condition. The neural population response during reaching was

modeled to be governed by internal dynamics alone, as no external input was explicitly included after movement onset. Further analysis revealed rotational patterns in neural trajectories, which have been used to support the hypothesis of an oscillatory pattern generator in the motor cortex for creating muscle activity during movement. However, these findings can be reconsidered to include external input to the neural population. Here, using simulation and empirical data, we studied the relation between movement direction and the dynamics of neural population activity. Two rhesus monkeys were trained to perform a standard center-out reaching task. We found that individual motor cortical neurons changed firing rate patterns during single reaches and the correlational structure between these patterns went through several robust phases. We then performed simulation to produce multiphasic activity patterns induced by directional input. In simulated data, neural activity in an earlier phase was well predicted by population activity in later phases, although there was no deterministic mechanism between them. Rotational neural trajectories were observed in neural subspaces defined by dimensions from two temporally overlapping phases. Results found in neural recordings from behaving monkeys matched these findings from simulation data. Our results suggest that instead of modeling neural population activity during movement as generated merely from interaction of recorded neurons, it is also subject to influence of external input carrying movement-related information.

Disclosures: H. Mao: None. **A.B. Schwartz:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.05

Topic: E.04. Voluntary Movements

Support: NS115975-01

Title: Myelin loss disrupts the neural representation of dextrous reaching in primary motor cortex

Authors: *D. NETTLES[1], K. G. GAGNON[6], R. WILLIAMSON[2], D. J. DENMAN[3], E. G. HUGHES[4], C. G. WELLE[5];
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Abstract: Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS) and patients with MS display impaired motor function. Previous work shows that demyelination slows action potential propagation and drives hyperexcitability in cortical neurons. Recently, we showed that demyelination leads to increased primary motor cortex (M1) neuronal hyperexcitability *in vivo,* which recovers concurrently with oligodendrogenesis and remyelination. This aberrant neuronal activity was associated with deficits in dextrous reaching, a skilled motor behavior. However, how demyelination-induced M1 hyperexcitability leads to impairments in motor performance remains unclear. This work aims to understand the cell-type specific consequences of myelin loss on M1

circuit function and resulting motor deficits.To explore the effects of myelin loss and repair on changes in motor circuit activity during skilled motor performance, we chronically implanted NeuroNexus arrays in M1 of mice to track longitudinal dynamics of motor representation. Demyelination was induced through dietary administration of 0.2% cuprizone for three weeks. Recordings were performed at multiple timepoints before, during and following cuprizone administration. Single units were clustered from extracellular activity and classified based on putative cell type (fast vs regular spiking), cortical depth, and movement-related activity. In demyelinated mice, we found increased neuronal hyperexcitability in both excitatory and inhibitory populations, but hyperexcitable excitatory neurons were specific to cortical layers 5 and 6, while inhibitory neurons were excitable throughout the cortex. During the reach, movement-related neurons had a decreased signal to noise ratio during reach representation and increased latency of peak firing with respect to the reach movement. To explore the neural population dynamics in greater detail, we performed acute recordings with Neuropixels arrays at three key timepoints (one week before, 0, and 3 weeks following cuprizone treatment). Acute Neuropixels experiments confirmed findings from chronically implanted NeuroNexus arrays and will allow for analysis of latent factors in the neural population. Together, these findings demonstrate that demyelination alters neural representation of dexterous reaching in M1 resulting in motor deficits characteristic of movement impairments of MS patients.

Disclosures: D. Nettles: None. **K.G. Gagnon:** None. **R. Williamson:** None. **D.J. Denman:** None. **E.G. Hughes:** None. **C.G. Welle:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

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Program #/Poster #: P536.06

Topic: E.04. Voluntary Movements

Support: KU Leuven grant C14/18/100
Odysseus grant G.0007.12

Title: Neural responses in ventral premotor cortex during action execution and action observation

Authors: *S. DE SCHRIJVER, T. DECRAMER, P. JANSSEN;
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Abstract: Mirror neurons that respond both to action execution and action observation were discovered in area F5c of the ventral premotor cortex. Recent studies have shown that these neurons also respond to videos of actions, and even, to videos of abstract shapes that causally interact with other shapes. To investigate the visual selectivity and motor properties of mirror neurons in F5c, we implanted 96-channel Utah arrays in area F5c in two macaque monkeys that were trained to grasp objects and to fixate videos of actions. We tested mirror activity during passive fixation of videos of a human or a monkey hand grasping the same object, together with control videos in which an ellipse either moved towards the object or moved on a scrambled background in the absence of the object. In 9 sessions, we recorded the activity of 96 mirror neurons and 198 MUA sites with mirror activity. The majority of the cells did not respond

during the entire video, but rather during a specific epoch of the action video, with a peak in the activity that occurred when the hand made contact with the object in 70% of the neurons. Furthermore, the large majority of mirror neurons (71%) also responded to the ellipse moving towards the object, indicating that meaningful actions are not required for mirror activity. Moreover, we measured very high correlations between the responses to the ellipse videos on a normal background and on a scrambled background (0.74 for SUA and 0.82 for MUA), indicating that the presence of the object was not necessary for the large majority of the mirror neurons. To test the motor properties of F5c neurons, we microstimulated F5c sites for 1s at 100Hz. We could evoke simple and complex movements with currents ranging from 60 to 130µA. Furthermore, subthreshold microstimulation of F5c sites while the monkey performed a visually guided delayed grasping task significantly increased the grasping time (i.e. the time necessary to reach towards, grasp and pull an object). This effect was observed both when stimulating mirror (65%) and non-mirror (33%) sites. Finally, we stimulated mirror sites in F5c during the delay period of the grasping task (for 700ms at 16Hz) while recording activity in primary motor cortex (M1) with another Utah array. Subthreshold stimulation of F5c mirror sites evoked extensive activations in M1. Thus, mirror neurons in F5c respond to surprisingly simple visual stimuli without any interaction with the object, and their output is highly directed towards the motor system. Together, these results have important implications for the interpretation of mirror neuron activity in the ventral premotor cortex.

Disclosures: S. De Schrijver: None. **T. Decramer:** None. **P. Janssen:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

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Program #/Poster #: P536.07

Topic: E.04. Voluntary Movements

Support: NIH NINDS K99/R00-NS101127

Title: Wavelimit: a spike-sorting algorithm that includes interspike interval information to improve performance

Authors: *X. SCHERSCHLIGT, A. ROUSE;
Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: Spike sorting algorithms have continued to improve, especially for large channel count, high-density recordings. However, these improvements are largely based on models with arrays that experience substantial crosstalk, such as dense silicon CMOS probes; which depend on evaluating cross correlograms that are less informative in larger microwire multielectrode arrays. Here, we propose a novel spike sorting algorithm, WaveLimit (WL), which incorporates information about interspike interval violations to improve performance, especially for channels with less crosstalk, and rivals other state-of-the-art sorters.
WL, like most sorting algorithms, first performs principal component analysis on all the waveshapes of spike events for every channel in a recording individually and putative units are subsequently assigned by cluster centers. The ideal threshold for assigning individual waveshapes (or spikes) to those putative units

is then made using the optimal trade-off between the estimated fraction of included true spikes and fraction of false spikes, which is derived from the identifying interspike time interval violations using idealized Poisson process statistics.
WL, along with three other state-of-the-art sorting algorithms, SpykingCircus (SC), IronClust (IC), and Tridesclous (TC), was used to sort three recording sessions from two different monkeys. The performance of each algorithm was further evaluated by comparing the number of units found as well as the number of spikes, ISI violations, and Signal-to-Noise ratio (SNR). Additionally, since the recordings were gathered while the monkeys performed a center-out-task, we compared the linear regression R2 of the rate of firing for each putative unit.
Our algorithm, on average, found more behaviorally tuned units per recording than the other algorithms. Our algorithm also found more spikes per unit for each unit found than both IC and TC and found a comparable number of spikes to that of SC. WL found not only more units per recording and more spikes per unit, the units had fewer ISI violations and better SNRs per unit. Interestingly, we found that the regression R2 mostly improved with the number of spikes included in the unit even as SNR worsened, suggesting R2 may be a poor measure of sorting quality.
Using ISI violation information, our WL sorting algorithm significantly improves the number of well isolated, single units from chronic multielectrode arrays in non-human primates.

Disclosures: X. Scherschligt: None. **A. Rouse:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.08

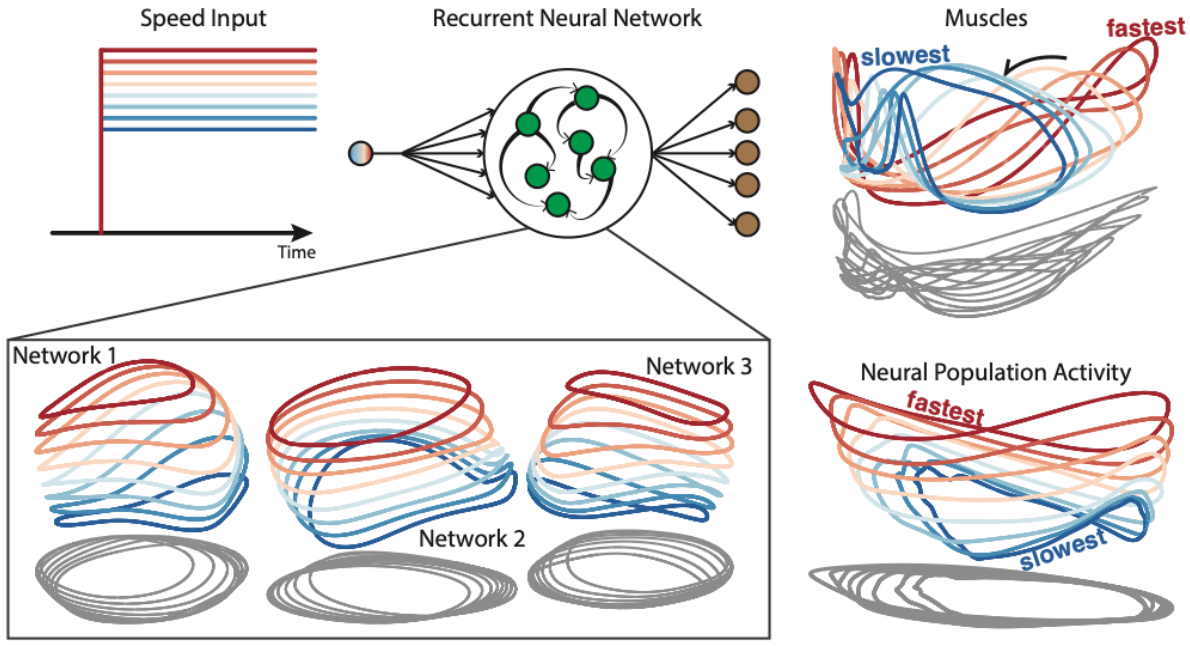
Topic: E.04. Voluntary Movements

Title: Motor cortex activity across movement speeds is predicted by network-level strategies for generating muscle activity

Authors: *S. SAXENA[1], A. A. RUSSO[2], J. CUNNINGHAM[2], M. M. CHURCHLAND[3];
[1]Univ. of Florida, Gainesville, FL; [3]Neurosci., [2]Columbia Univ., New York, NY

Abstract: Learned movements can be skillfully performed at different paces. What neural strategies produce this flexibility? Can they be predicted and understood by network modeling? We trained monkeys to perform a cycling task at different speeds, and trained artificial recurrent networks to generate the empirical muscle-activity patterns. Network solutions reflected the principle that smooth well-behaved dynamics require low trajectory tangling, and yielded quantitative and qualitative predictions. For a rhythmic trajectory, the lowest-tangled geometry is a circle. This yields the first prediction: regardless of the trajectory of muscle activity, the neural trajectory should - across all speeds - be dominated by two-dimensional circular structure. A second prediction arises from the observation that traversing a trajectory at different speeds would increase tangling. Thus, the near-circular trajectories (one per speed) should be separated by a translation and/or tilt into new dimensions. To evaluate predictions, we recorded motor cortex population activity during the same task. Responses supported the hypothesis that the dominant neural signals reflect not muscle activity, but network-level strategies for generating muscle activity.

Single-neuron responses were better accounted for by network activity than by muscle activity. Similarly, neural population trajectories shared their organization not with muscle trajectories, but with network solutions. We first analyzed the data for each speed separately. In the top two principal components, muscle trajectories varied greatly across speeds. Neural trajectories did not, but instead remained consistently circular. Analyzing all speeds together revealed that these circular trajectories were separated by a translation and tilted modestly into new dimensions. As a result, neural trajectory tangling remained low despite high muscle trajectory tangling. Thus, cortical activity could be understood based on the need to generate muscle activity via dynamics that allow smooth, robust control over movement speed.



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Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.09

Topic: E.04. Voluntary Movements

Support: NIH Grant NS102259

Title: Preparatory neural states in monkey premotor cortex differ for reaches to visual and predicted targets

Authors: T. J. ARAKERI, C. E. LARKIN, K. M. GOTHARD, *A. J. FUGLEVAND;
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Abstract: To reach to an object, motor areas of the brain need to efficiently plan the path of the hand to the object (based on information about object location and limb configuration) and then execute the command. The neural basis of such fundamental processes as planning and execution of voluntary commands remains relatively obscure. Recent findings, however, based on neural recordings in non-human primates, suggest that population activity in motor and premotor cortices exists in two orthogonal neural subspaces during movement preparation and movement execution. Furthermore, studies have also shown that population activity must reach a unique preparatory state, regardless of context, to subsequently generate appropriate population dynamics during movement execution (e.g., Lara et al. *eLife* 2018). Yet most of that work involved reaching toward overt visual targets. In many circumstances (e.g., hitting a baseball), however, visual input by itself is too slow to appropriately plan for such movements. Instead, there is increasing reliance on predictions based on internal models of the situation. Therefore, we asked whether motor-cortical population dynamics representing preparatory states were the same for reaches to visual targets versus those whose locations were predicted. In visually guided condition, a monkey was trained to make center out reaches to targets displayed on a computer screen. In the predicted condition (recorded in the same sessions), the monkey had to reach to the predicted location of a target using a "pre-target" visual cue that flashed momentarily. The actual target location was offset by a fixed angle from the pre-target. Our preliminary data recorded from dorsal pre-motor cortex indicates that there is a significant reduction in preparatory subspace occupancy when preparation was driven by a predicted target compared to a visual target. Subsequent neural dynamics in the movement subspace, however, were essentially the same. These results suggest that the sources of planning information (i.e., visual or internally generated) conveyed to the premotor cortex can differentially shape preparatory dynamics, and that different preparatory states can give rise to the same movement.

Disclosures: T.J. Arakeri: None. **C.E. Larkin:** None. **K.M. Gothard:** None. **A.J. Fuglevand:** None.

Poster

P536. Cortical Planning and Execution: Premotor and Motor Cortex: Neurophysiology: Animal I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P536.10

Topic: E.04. Voluntary Movements

Support: DARPA TNT

Title: Vagus nerve stimulation modifies the neural representation of a skilled reach in motor cortex

Authors: *X. PENG, R. HUANG, K. GAGNON, S. BOWLES, J. HICKMAN, C. WELLE;
Dept. of Neurosurgery, Dept. of Physiol. & Biophysics, Univ. of Colorado, Anschutz Med. Campus, AURORA, CO

Abstract: Vagus nerve stimulation (VNS) technology has broad therapeutic applications for a range of neurologic conditions including epilepsy, depression and stroke. However, the mechanism of action underlying VNS is unclear, hindering optimization of this therapeutic tool. Preclinical work suggests that while VNS drives cortical map plasticity in injured and healthy animals, cortical plasticity does not necessarily correlate with behavioral improvements. Thus, questions remain regarding if VNS can be

used to drive behavioral improvement in healthy nervous system, and if so, by what mechanism. Recently, we have shown that in a skilled reach-to-grasp task, VNS paired with a successful reach (Success VNS) can enhance motor learning in healthy mice. To understand how paired VNS can influence motor outcomes, we examined the effects of VNS on neurons in primary motor cortex (M1), which is required for learning and performance of the skilled reach task. We monitored neural activity in freely-moving mice expressing a calcium indicator (GCaMP6m) in L2/3 of M1 using a head-mounted miniature microscope. To measure VNS-driven neural modulation, animals were implanted with a cuff electrode on the left cervical vagus (Microleads), and neural activity was monitored during VNS delivery (30 Hz, 15 pulses, 0.1 ms pulse width). Approximately 10 ~ 30% of L2/3 neurons are modulated by VNS, with neurons showing either firing suppression or activation, but not both. Interestingly, the average peak timing of the suppression precedes the peak timing of activation by ~ 1.2 seconds, and both responses depend on acetylcholine receptor (AChR) mediated signaling. To measure VNS-driven modulation in skilled reach learning, neural activity during successful reaches was measured in two training sessions; one with and one without VNS. When applied following a successful reach, Success VNS modulates 80% of neurons that are activated by a successful reach, but does not influence the activity of neurons that are suppressed or non-modulated by reach success. Moreover, the effects of Success VNS on this population are not temporally limited to the acute window following VNS application. Instead, these neurons also show differential activity in the reach phase that precedes VNS during the VNS session. Together, these data suggest that Success VNS not only modulates success outcome representation in M1, but also modifies the neural representation of movement throughout the reach duration.

Disclosures: X. Peng: None. **R. Huang:** None. **K. Gagnon:** None. **S. Bowles:** None. **J. Hickman:** None. **C. Welle:** None.

Poster

P635. Sleep: Perturbations and Rhythms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P635.01

Topic: F.08. Biological Rhythms and Sleep

Support: World Premier International Research Center Initiative from MEXT
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JSPS KAKENHI 17H04023
JSPS KAKENHI 17H05583
JSPS KAKENHI 20H00567
JSPS KAKENHI 26507003

Title: Where does Sleepy mutation of SIK3 increase non-REM sleep?

Authors: *K. IWASAKI[1], T. FUJIYAMA[1], S. NAKATA[1], M. PARK[1], C. MIYOSHI[1], N. HOTTA-HIRASHIMA[1], A. IKKYU[1], M. KAKIZAKI[1], Y. ISHIKAWA[1], F. SUGIYAMA[2], S. MIZUNO[2], M. ABE[3], K. SAKIMURA[3], S. TAKAHASHI[2], H. FUNATO[1,4], M. YANAGISAWA[1,5,6];
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Abstract: The salt-inducible kinase (SIK) is a family of the AMP-activated protein kinase (AMPK) related kinases. SIK3 is expressed in various tissues and required for the proper development of the skeletal system, adipose tissues, and glucose/lipid metabolism, macrophage differentiation, and interleukin production. Recently, we found a gain-of-function *Sleepy* (*Slp*) mutation in the *Sik3* gene, which produces the mutant SIK3(SLP) protein, increases sleep amount and non-REM sleep (NREMS) EEG delta density, an index of sleep need. Since sleep is affected by peripheral organs and tissues, it remains to be elucidated whether neurons or other types of cells are responsible for the increased NREMS in *Sleepy* mutant mice.Here, we investigated whether SIK3(SLP) in mature neurons is sufficient for increasing sleep amounts and NREMS EEG delta density. Newly developed *Synapsin1*^{CreERT2}*;Sik3*$^{Sleepy\text{-}flox}$ mice enabled us to induce *Sik3(Slp)* in mature neurons upon tamoxifen injections. *Synapsin1*^{CreERT2}*;Sik3*$^{Sleepy\text{-}flox}$ mice administrated tamoxifen at late infancy exhibited increased NREMS time and NREMS EEG delta density. In addition, simulated sleep-homeostatic Process S of *Sik3*^{Slp} and *Synapsin1*^{CreERT2}*;Sik3*$^{Sleepy\text{-}flox}$ mice showed that increased ratio between the rates of sleep-need accumulation and dissipation. These results suggested that SIK3 plays important role regulating sleep amounts and sleep need in mature neurons.Furthermore, we explored neural populations which are responsible for the sleep phenotype of *Sleepy* mutant mice with SIK3(SLP) expressing AAV vectors. We found that mid-anterior medial parts of hypothalamus increased NREMS amounts upon SIK3(SLP) expression. However, no increase in NREMS EEG delta density was observed. These results imply that neural populations that increase NREMS and NREMS EEG delta power in *Sleepy* mutant mice are not identical. Now, we try to narrow down and characterize these NREMS-promoting neurons in *Sleepy* mutant mice.

Disclosures: K. Iwasaki: None. **T. Fujiyama:** None. **S. Nakata:** None. **M. Park:** None. **C. Miyoshi:** None. **N. Hotta-Hirashima:** None. **A. Ikkyu:** None. **M. Kakizaki:** None. **Y. Ishikawa:** None. **F. Sugiyama:** None. **S. Mizuno:** None. **M. Abe:** None. **K. Sakimura:** None. **S. Takahashi:** None. **H. Funato:** None. **M. Yanagisawa:** None.

Poster

P635. Sleep: Perturbations and Rhythms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P635.02

Topic: F.08. Biological Rhythms and Sleep

Title: Beneficial Effects of a Plasma Fraction on Normalizing Sleep Disturbances Associated with Aging

Authors: I. GALLAGER, E. PICKUP, S. LEE, V. KHEIFETS, *E. CZIRR;
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Abstract: RBD (REM sleep behavioral disorder) occurs 6-15 years prior to the onset of neurodegenerative disorders and is present in 90% of patients with Parkinson's disease, dementia or Lewy Body disease and MCI (mild cognitive impairment) commonly resulting in accelerated institutionalization. The process of aging is multifactorial, therefore single agent interventions would be unlikely to attenuate the myriad pathologies associated with advancing age including sleep disruptions. Plasma contains many beneficial factors which have been shown in animal models to ameliorate multiple age-related deficits across varied organ systems, including the brain. We focused on age-related hippocampus-dependent cognitive deficits, as the hippocampus is well accessed by the vascular system, especially within the subgranular zone. This makes it an attractive target for evaluation of plasma and plasma-derived factors. We confirmed that human plasma from young (18-22-year-old) donors reverses age-related cognitive decline and enhances hippocampal neurogenesis and cell survival in aged immunocompromised mice, while plasma from aged individuals (62-68 years old) has detrimental effects in young mice. We have extended these findings to show the benefits of a fractionated plasma product (PF) with enhanced properties. In addition, we examined PF in an α-synuclein mouse model of Parkinson's disease, where treatment significantly reversed functional, inflammatory, and neuronal deficits. Here we demonstrate in 22mo old C57BL/6J mice that additional to modifying CNS histological endpoints, PF normalizes sleep disruptions: Increasing REM sleep time, nREM time and length and decrease waking bouts and time. These results suggest direct physiological impact from plasma fraction treatment and provide a direct translatable endpoint for monitoring within future PF neurodegenerative clinical trials.

Disclosures: I. Gallager: A. Employment/Salary (full or part-time):; Alkahest Inc., a subsidiary of Grifols. **E. Pickup:** A. Employment/Salary (full or part-time):; Alkahest Inc., a subsidiary of Grifols. **S. Lee:** A. Employment/Salary (full or part-time):; Alkahest Inc., a subsidiary of Grifols. **V. Kheifets:** A. Employment/Salary (full or part-time):; Alkahest Inc., a subsidiary of Grifols. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest Inc., a subsidiary of Grifols.

Poster

P635. Sleep: Perturbations and Rhythms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P635.03

Topic: F.08. Biological Rhythms and Sleep

Support: NSF GRFP 2020294366
Simmons Foundation SFARI grant #385188
NIH R01 #1RF1AG068063-01A1

Title: The impact of acute sleep deprivation on the synaptic proteme is distinctly different between juvenile and adolescent mice

Authors: *S. GAY[1], N. K. BARKER[2], A. PREVATTE[2], J. M. SIMON[2], L. E. HERRING[2], G. H. DIERING[3];
[1]Neurosci., [2]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [3]Cell Biol. and Physiol., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: Sleep is essential for proper cognitive function and brain maturation. Even a single night of disrupted sleep can have immediate measurable deficits on cognitive functions. The importance of sleep during development is suggested by the comorbidity of sleep disruptions and numerous neurodevelopmental disorders. We hypothesize that sleep loss is not just a symptom of these disorders but also contributes to the cognitive and social deficits observed. Thus, making sleep a promising therapeutic target. There is little understanding of the restorative mechanisms of sleep and how sleep loss impacts the developing brain, leading to a lack of sleep therapies for children. Recent studies have shown that the synapse is remodeled during sleep and greatly impacted by sleep deprivation. As such, the synapse has emerged as a primary benefactor of the restorative functions of sleep, making it a locality of interest. Our present study aimed to understand how sleep deprivation impacts juvenile (postnatal, p21) and adolescent (p42-45) synapse biochemistry in mice. To analyze synapse biochemistry, we used mass spectrometry proteomics. We observed that acute gentle handling sleep deprivation significantly changed the expression of hundreds of proteins in both the juvenile and adolescent cortex and hippocampal synaptic proteome. Few proteins were similarly changed, due to sleep deprivation, at the juvenile and adolescent synapse. Interestingly, many proteins that increased in the juvenile synapse during sleep deprivation were found to decrease in the adolescent synapse during sleep deprivation. This data suggests that sleep, and consequentially loss of sleep, has a unique impact on synapse biochemistry in juvenile and adolescent mice. It further suggests that the impact of sleep loss is distinct at different developmental time periods, supporting a role of sleep loss in neurodevelopmental disorders.

Disclosures: S. Gay: None. **N.K. Barker:** None. **A. Prevatte:** None. **J.M. Simon:** None. **L.E. Herring:** None. **G.H. Diering:** None.

Poster

P635. Sleep: Perturbations and Rhythms II

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Program #/Poster #: P635.04

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit I01 BX004673
VA Merit I01 BX001356
VA Merit I01 BX004500
NIH R01 NS069777

Title: Characterization of Basal Forebrain Npas1+ Neurons In The Mouse

Authors: *R. E. BROWN[1], C. YANG[1], F. KATSUKI[1], D. D. AGUILAR[1], I. E. LIN[2], L. K. RADZIK[1], J. M. MCNALLY[1], C. S. CHAN[3], J. T. MCKENNA[1];
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Abstract: The basal forebrain (BF) is an important brain region for regulating sleep-wake behavior, cortical electrical activity, attention and reward processing. Furthermore, degeneration or dysfunction of BF neurons is implicated in cognitive deficits in neurodevelopmental disorders and in dementia.

Therefore, it is important to decipher the composition, connections and functional role of BF neurons. Here we report preliminary findings concerning a novel population of BF neurons which express the transcription factor neuronal PAS domain 1 (Npas1), a master regulator of neuropsychiatric risk genes. Npas1-cre-TdTomato mice were used for experiments. Immunohistochemical staining showed that BF Npas1+ neurons were distinct from parvalbumin (PV) or cholinergic projection neurons. Crossing Npas1-cre-tdTomato mice with GAD67-GFP knock-in mice revealed that the vast majority of Npas1+ neurons expressed GFP, suggesting they are a novel GABAergic population. Transduction of BF NPAS1 neurons with channelrhodopsin2-enhanced yellow fluorescent fusion proteins was used to identify projections. Initial examination suggested prominent projections of BF Npas1+ neurons to frontal association cortices, perifornical hypothalamus, amygdala, ventral tegmental area (VTA), supramammillary nucleus (SuM) and ventrolateral periaqueductal gray (vlPAG). Fibers were sparse or absent in the lateral habenula, a prominent target of BF vesicular glutamate transporter 2 (vGluT2) neurons and in the thalamic reticular nucleus, a notable target of BF PV and cholinergic neurons. Chemogenetic activation of BF Npas1+ neurons strongly increased wakefulness in three mice. However, there was no change in gamma band power during wakefulness, locomotor activity or sleep spindle density. Clozapine-N-oxide (0.3 mg/kg) alone had no significant effect on sleep-wake behavior or cortical EEG in mice without transduction of BF neurons, when compared to vehicle (saline) injections (N=4) Our experiments suggest that BF Npas1+ neurons represent a novel subtype of BF wakefulness-promoting neurons, distinct from previously characterized PV, cholinergic and vGluT2 neurons. Wake-promoting actions of Npas1+ neurons may be mediated by projections to perifornical hypothalamus, VTA and SuM.

Disclosures: R.E. Brown: None. **C. Yang:** None. **F. Katsuki:** None. **D.D. Aguilar:** None. **I.E. Lin:** None. **L.K. Radzik:** None. **J.M. McNally:** None. **C.S. Chan:** None. **J.T. McKenna:** A. Employment/Salary (full or part-time):; Merck MISP. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Merck MISP.

Poster

P635. Sleep: Perturbations and Rhythms II

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Program #/Poster #: P635.05

Topic: F.08. Biological Rhythms and Sleep

Support: VA grant IK2 BX004905 (DSU)
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Title: Testing the role of alpha-1 and alpha-3 containing GABAARs in thalamic neurons in sleep delta wave activity using CRISPR-Cas9 gene editing

Authors: *D. S. UYGUN, R. E. BROWN, R. BASHEER;
VA Boston Healthcare Syst. & Harvard Med. Sch., West Roxbury, MA

Abstract: High power of electroencephalographic (EEG) delta (0.5-4 Hz) waves is associated with restful non-rapid-eye-movement sleep (NREM) and is linked to longevity and good overall health, including psychiatric health. Problematically, sleep medicines which potentiate the activity of synaptic GABA-A receptors containing alpha1 and alpha3 subunits suppress these healthy delta waves, but it is unknown how. Though delta waves are recorded cortically, they are generated in large part by the thalamus, by self-oscillating "pacemaker" cells called thalamocortical (TC) relay neurons. TC neurons generate delta waves when they are in "burst firing" mode, which occurs when they are hyperpolarized. TC relay neurons receive their main source of inhibition from the neighboring GABAergic thalamic reticular nucleus (TRN) neurons. TRN neurons express synaptic receptors containing the alpha3 subunit whereas TC neurons express the α1 subunit. Here we use innovative *in vivo* CRISPR-Cas9 technology to dissect the role of α1 and α3 containing $GABA_A$ receptors in the thalamus. For experiments targeting TC neurons, we crossed lox-stop-lox-Cas9 mice with VGlut2-cre mice to generate VGlut2-Cas9 mice, introducing Cas9 in glutamatergic cells such as TC neurons, whereas for experiments targeting TRN neurons we used PV-Cas9 mice, targeting the large majority of TRN neurons which contain parvalbumin (PV). KD of α3 subunits in TRN increased the power of NREM delta waves (n=6). More fine-grained analysis revealed that there was no effect on the slower component (0.5-1.5 Hz) but a strong effect on a faster delta-band (2-4.5 Hz) which was recently shown to be homeostatically regulated (Hubbard et al., 2020). Effects were pronounced at NREM-REM transitions. In contrast, α1KD in the TRN caused no effect on delta waves [Mean (SEM): BL 50±2.5 vs KD 52.83±3.8; two-tailed paired t-test: $t(6) = -0.86$, $p = 0.4209$]. In ongoing analyses (N=3), we predict α1KD in TC neurons will reduce hyperpolarization in TC neurons and thereby attenuate NREM delta power, i.e. the opposite effect observed with α3KD in TRN. Our work suggests differential actions of α3 and α1 subunits in regulating NREM delta activity. This work could improve our understanding of the mechanisms of widely used sleep medicines.

Disclosures: D.S. Uygun: None. **R.E. Brown:** None. **R. Basheer:** None.

Poster

P635. Sleep: Perturbations and Rhythms II

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Program #/Poster #: P635.06

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R15GM122058
NIH Grant NR01AG062398
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SJU Summer Scholars Program
John P. McNulty Fellows Program

Title: Sleepless in C. elegans: Sleep duration affects the formation and clearance of stress granules

Authors: *L. CARMAN, M. DOUGHERTY, C. SAUL, J. C. TUDOR, M. NELSON;
St. Joseph's Univ., Philadelphia, PA

Abstract: Sleepless in *C. elegans*: Sleep duration affects the formation and clearance of stress granulesLynly Carman, Mary K. Dougherty, Christopher Saul, Matthew Nelson, Jennifer C. TudorSleep is conserved across the animal kingdom, and lack of sleep results in numerous detriments to an organism's health and wellbeing, including memory impairment. Memory formation requires protein synthesis, which is attenuated after sleep deprivation. We have previously shown that sleep deprivation impairs protein synthesis through suppression of the mammalian target of rapamycin (mTOR) pathway. Downregulation of the mTOR pathway has separately been linked to the formation of RNA aggregates called stress granules. Taken together, these observations suggest a possible relationship between sleep and stress granule production. This study uses the nematode *Caenorhabditis elegans* to observe how stress granule formation and clearance are modified by sleep duration. *C. elegans* exhibit two major forms of sleep: developmentally-timed sleep (DTS), which occurs during the lethargus phase of its lifecycle, and stress-induced sleep (SIS), occurring after exposure to noxious stimuli. By performing genetic crosses, we developed novel strains of *C. elegans* to model deprivation and enhancement of DTS and SIS. Stress granules were visualized in each strain through RFP-labeling of the poly-A binding protein (PAB-1) protein. We found that lack of SIS causes physiological changes within cells resulting in increased stress granule formation, and these changes are reversible concomitant with enhanced SIS. Manual deprivation of DTS increased stress granule count during sleep. Interestingly, stress granule count was reduced during DTS regardless of genotype or condition. These data suggest that sleep duration has an active role in altering stress granule dynamics. This has implications concerning how gene regulation is affected by sleep, providing a key contribution in the ongoing effort to understand the functions of sleep.

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Poster

P635. Sleep: Perturbations and Rhythms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P635.07

Topic: F.07. Autonomic Regulation

Support: NIH Grant UH2AT009145
NIH Grant UH3AT009145

Title: Effects of a mindfulness-based hypertension intervention on neural structural connectivity

Authors: *B. NEPHEW[1], J. POLCARI[1], R. CALI[4], S. LU[5], M. RASHKOVSKII[2], J. WU[1], F. SAADEH[6], E. LOUCKS[6], J. A. KING[3];
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Abstract: Hypertension related illnesses are a leading cause of disability and death in the United States. Due to the high prevalence of adverse effects of pharmacological interventions for hypertension, there is increased interest in the development of nonpharmacological interventions. A Mindfulness-based blood

pressure reduction program (MB-BP) is effective in attenuating hypertension, but the neural correlates of this intervention are unknown. The objectives of the present study were to identify structural neural correlates of MB-BP using diffusion tensor magnetic resonance imaging (DTI) and assess potential correlations with key clinical outcomes. In subset of participants from a larger randomized controlled trial, MB-BP participants exhibited increased mindfulness and decreased depression compared to controls. Analyses of DTI data revealed significant group differences in several white matter neural tracts in the limbic system and/or associated with hypertension. Specific changes in neural structural connectivity were significantly associated with clinical measures of blood pressure, depression, anxiety, mindfulness, and emotional regulation. It is concluded that MB-BP has extensive and substantial effects on brain structural connectivity which could mediate beneficial changes in mindfulness, depression and related clinical measures in individuals with hypertension.

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Poster

P643. Energy Metabolism I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P643.01

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Department of Defense Grant W911NF2010275
NIH Grant 1R15NS112920-01A1

Title: Running on fumes: Glycogenolysis transforms a circuit to operate without oxygen and glucose delivery

Authors: *N. BUESCHKE[1], J. M. SANTIN[2];
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Abstract: The central nervous system has a high energy demand for proper function which will result in permanent neuronal damage when not adequately fueled. We describe a series of experiments that show a 20-30 fold increase in time until metabolic failure during anoxic and ischemic conditions in the American bullfrog, the largest documented in a vertebrate species. Although several hypoxia-tolerant species exist, American bullfrogs are not considered highly resistant to energetic stress, and the brainstem network that produces breathing provides an example of this “lack” of hypoxia tolerance. Brainstems from control bullfrogs (n=6) produce rhythmic output for 11±5 minutes in hypoxia (0% O_2) and 4±0.5 minutes during simulated ischemia (O_2 and glucose deprivation; OGD; n=8). In contrast, hibernation (i.e., 1 month of cold-acclimation to simulate the overwintering environment) resulted in transformation that allowed for activity to persist for 230±13 minutes in hypoxia (n=8) and >120 minutes in OGD (n=6). Despite bubbling with 0% O_2, we controlled for the possibility that O_2 might not be 0% within the tissue and that aerobic metabolism may still operate at low levels in hibernation preparations. To do this, we applied OGD+ 1 mM sodium cyanine for 1 hour. All preparations (n=5) produced rhythmic activity at 1 hr. We

then applied 1 mM iodoacetate in the presence of OGD+ 1 mM cyanine to confirm that glycolysis fuels the network after hibernation. All 5 preparations stopped within 5±1 minutes following exposure to iodoacetate. Finally, to understand which energy substrate fuels glycolysis in the absence of oxygen and glucose delivery, we tested the hypothesis that brain glycogen breakdown can support network activity after hibernation. To test this, we applied OGD in the presence of an inhibitor of glycogen phosphorylase (250 µM DAB) in hibernation preparations. In the presence of DAB, hibernation preparations produced rhythmic output for 25±1 min, significantly less 120 minutes typical of hibernation preparations ($p<0.0001$), but still significantly greater than the ~4 minutes observed in controls ($p<0.0001$). Thus, a large fraction of hibernation-induced OGD tolerance stems from a shift to glycolysis supported by glycogen breakdown; however, additional physiological or biochemical mechanisms likely play a role. Future work will address additional possibilities, as well as the source of brain glycogen that maintains activity. Given the unprecedented shift to function during energetic stress, understanding the underlying mechanisms will provide insight to neuronal energetics and novel strategies for neuroprotection.

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Poster

P643. Energy Metabolism I

Location: Virtual Only

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Program #/Poster #: P643.02

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Council for Scientific and Technological Development (CNPq) Grant 141700/2017-3

Title: Maternal hyperglycemia and snack intake effects on offspring behavior and metabolism in adulthood and senescence

Authors: *M. G. MARTINS[1,2], B. WOODSIDE[3], A. C. I. KISS[1,2];
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Abstract: Maternal metabolism and nutritional status are key to a healthy offspring's intrauterine and postnatal development, with previous studies showing that snack intake during pregnancy and lactation further impairs glucose tolerance in hyperglycemic female rats. However, their long-term consequences to offspring behavior and metabolism are unknown. To investigate those effects, newborn female Wistar rats were divided into Control (citrate buffer, s.c.) or STZ (streptozotocin, 100 mg/kg, s.c.) groups. On postnatal (PND) 90, rats from both groups were mated and subdivided into four groups: females fed with standard chow (Control, n = 22; STZ, n = 23); and females fed with standard chow plus potato chips and 1.5% sucrose solution from pregnancy day 0 to lactation day 14 (Control-snack, n = 23; STZ-snack, n = 23). Dams gave birth naturally and, on PND 1, litters were culled to 6 pups (3 males, 3 females). On PND 90 and 360, male and female offspring behavior was evaluated in the marble-burying test, the open field arena, and the elevated plus-maze, followed by a glucose tolerance test and a sucrose preference test. All

experimental procedures were approved by the local ethics committee (Protocol number 919). Maternal hyperglycemia and snack intake association did not affect burying and exploratory in adulthood and senescence. Although there were no changes in anxiety-like behavior in adult offspring, maternal hyperglycemia and snack intake association led to an increase in anxiety in 360-days-old offspring. Sucrose preference in adulthood was reduced due to maternal snack intake. Offspring glucose tolerance was not affected by either maternal manipulation, still, offspring from hyperglycemic dams showed an impaired return to glucose baseline levels in adulthood. In sum, while no differences related to maternal metabolism and diet were observed in adulthood, senescent offspring had increased anxiety-like behavior, showing that the effects of a disrupted maternal metabolism may manifest only in the long term. Since both maternal diabetes and inappropriate nutrition have been linked to offspring cognitive impairments, future studies should evaluate deficits in learning and memory. Despite aggravating maternal hyperglycemia, snack intake leads to glucose levels within the mild hyperglycemic range in pregnant females, which may explain why there were no major behavioral impairments in the offspring. Nonetheless, changes in offspring behavior reinforce the importance of women sustaining target glucose levels and a healthy diet during pregnancy and lactation.

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Poster

P643. Energy Metabolism I

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Program #/Poster #: P643.03

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: DOD Grant W911NF2010275
NIH Grant 1R15NS112920-01A1

Title: Action potential firing ability is preserved in motoneurons during network collapse due to anoxia

Authors: *L. DO AMARAL-SILVA[1], J. M. SANTIN[2];
[1]Biol., Univ. of North Carolina, Greensboro, NC; [2]Biol., Univ. of North Carolina at Greensboro, Greensboro, NC

Abstract: Neural circuits activity is costly for vertebrates requiring ongoing ATP production through aerobic metabolism. Work in our lab shows that rhythmic network activity in the AmericanBullfrogs brainstem (*Lithobates catesbeianus*) stops within few minutes of anoxia. However, after hibernation, this network transforms to maintain activity up to 4h in anoxia and more than 2h in oxygen and glucose deprivation (OGD), the largest improvement among vertebrates. We aim to understand the mechanisms that underlie this remarkable response. As the first step, we characterized network components and cellular processes responsible for failure during energy deprivation in control frogs. We used whole-cell patch-clamp electrophysiology to assess function of labeled motoneurons isolated from the network (transverse slices) or within the intact rhythmic network by using a novel preparation. This preparation allowed us to monitor the firing of single motor neurons and whole network output simultaneously. Neural function was recorded under baseline conditions (1.5%, CO2 and 98.5% O2) followed by anoxia

exposure (1.5% CO2 and 98.5%N2) or OGD (sucrose substituted glucose in the aCSF bubbled with 1.5%, CO2 and 98.5%N2). When the rhythmic preparation was exposed to anoxia, activity stopped in 14±3 min(n=3). Motoneurons fired in phase with the network 100% of the time and fired spontaneously for 5±1 min after coordinated network activity stopped because anoxia, which shows they can generate action potentials despite loss of phasic synaptic input. Indeed, motoneurons isolated from the network could fire undisturbedly in anoxia for up to one hour under a rhythmic current injection protocol that mimics physiological synaptic inputs (19±4 Hz before / 20±3 Hz after 1h, n=3). Surprisingly, firing rate also did not change during OGD exposure for up to 1h (31±5 Hz before / 34±5 Hz after 1h, n=8). Glycolysis was inhibited by iodoacetic acid in 3 slices under OGD, and firing stopped in 8±2 min, indicating that action potential generation can be supported exclusively by local fuel sources for glycolysis. Given that control cells had the striking capacity to fire without oxygen and glucose, our data suggest that network collapse in anoxia derives from the loss of synaptic input to motoneurons. Thus, network failure seems to be caused by greater energetic demands of either action potential firing of upstream rhythm generating neurons or synaptic communication between the rhythm generator and motor pools. Subsequent work will address these possibilities and seek to understand how these large physiological costs are overcome to function for hours without energy delivery following hibernation.

Disclosures: L. do Amaral-Silva: None. **J.M. Santin:** None.

Poster

P643. Energy Metabolism I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P643.04

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Obesity Initiative Seed Grant (UGA)

Title: Sexually dimorphic effects of Western Diet on brain mitochondrial bioenergetics and neurocognitive function

Authors: *M. LORD, J. HOFFMAN, K. DONOHUE, M. SPAULDING, A. SCHIFINO, J.-W. HEO, J. CALL, E. NOBLE;
Univ. of Georgia, Athens, GA

Abstract: Western Diets (WD), high in added sugars and saturated fats, have been shown to impair learning and memory function and contribute to weight gain in both human and animal models, however, neural mechanisms mediating these effects are not completely understood. Mitochondria in the brain provide essential energy for neural plasticity and have been suggested to play a role in whole body energy metabolism. Our objective was to determine whether a WD consisting of sugar-sweetened beverages and high-fat food impacts brain mitochondrial bioenergetics, behavior, and metabolic outcomes. Male and female Sprague Dawley rats were singly housed and randomized to receive a WD consisting of high-fat pellets (60% kcal from fat), an 11% high fructose corn syrup beverage, and water (WD; n=10 males, n=12 females) or standard laboratory chow with access to two bottles of water as the control diet (CTL; n=10 males, n=12 females). Behavioral outcomes tested were anxiety-like behavior (Elevated Plus Maze)

and hippocampal-dependent learning and memory (Novel Location Recognition). Food intake and body weight were monitored daily, and glucose metabolism, body fat, and liver fat were measured. Whole hypothalamus (HYP) and hippocampi (HPC) were collected for analyses of mitochondrial oxygen consumption, membrane potential, and redox status of NAD(P)H. Results revealed a sexually dimorphic macronutrient preference between male and female rats, where females on the WD consumed a greater percentage of calories from sugar compared to males, who consumed a greater percentage of calories from fat. Both males and females on WD gained significantly more fat and showed impaired glucose tolerance when compared to same-sex CTLs. Males on WD demonstrated impaired HPC-dependent learning and memory functioning, whereas females did not. Comprehensive bioenergetics analysis of WD effects on HPC and HYP brain revealed a tissue-specific adaption to WD in the HYP, where males on the WD oxidized more fat, and females oxidized more fat and sugar at peak energy demand compared to same sex CTLs. In the HPC of males, analyses showed an elevated tendency toward a high membrane potential, which has been linked with oxidative stress. Taken together, these results suggest that adult male rats show a susceptibility toward HPC dysfunction on a WD, and that HYP mitochondrial bioenergetics are altered by WD in a sex-specific manner.

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Poster

P643. Energy Metabolism I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P643.05

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH BRAIN Initiative R01MH111359
NIH BRAIN Initiative R01DA050159
NIH BRAIN Initiative R01NS108472
Swiss National Science Foundation (P2ZHP3_181568)

Title: Two-photon microscopy of oxygen consumption in different layers of the mouse cerebral cortex

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Abstract: The cerebral cortex is organized in cortical layers that differ in their cellular density, composition, and wiring. Cortical laminar architecture is also readily revealed by staining for cytochrome

oxidase - the last enzyme in the respiratory electron transport chain located in the inner mitochondrial membrane. It has been hypothesized that a high-density band of cytochrome oxidase in cortical layer IV reflects higher oxygen consumption under baseline (unstimulated) conditions. Here, we test the hypothesis using direct measurements of the partial pressure of O_2 (pO_2) around diving arterioles in cortical tissue obtained with 2-photon phosphorescence lifetime microscopy (2PLM) in awake mice. For that, we injected the new red-shifted oxygen sensing probe Oxyphor-2P through a port in the window into the brain. From 6 arteriole of 4 subjects more than 20 planes were analyzed. Previously, we introduced a method for extraction of $CMRO_2$ based on 2PLM that relies on the Krogh-Erlang model of O_2 diffusion from a cylinder and applied this method to estimate $CMRO_2$ in the rat cerebral cortex. However, periarteriolar spaces void of capillaries in the mouse cortex are narrower than those in the rat. Therefore, the basic Krogh-Erlang assumption of the center arteriole serving as the sole O_2 source is challenged. We revisited the model to account for contribution of the capillary bed and then applied the revised model to estimate baseline $CMRO_2$ in awake mice across cortical layers. Our results show that, in contrary to the common notion, baseline $CMRO_2$ in layer IV is lower than that in upper layers. In agreement, there was a significant increase in the low tail (the lower 35%) of the pO_2 distribution with depth indicating an increase in oxygenation of tissue in between capillaries in layer IV compared to layer I. Our results imply that capillary, cytochrome oxidase, and mitochondrial densities cannot serve as a proxy for oxidative energy metabolism under baseline conditions. We speculate that the cytochrome oxidase band in layer IV may fulfill higher metabolic demands during transient surges in neuronal activity. These findings are important for interpretation of cortical-layer-resolved Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) studies.

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Poster

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Program #/Poster #: P643.06

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: PICT2017-3196

Title: Calorie-restricted mice display activation of the reward-related brain centers and saccharine overconsumption, in a growth hormone secretagogue receptor-dependent manner

Authors: *D. CASSANO, C. SAENZ, N. DE FRANSCESCO, G. FERNÁNDEZ, M. CORNEJO, G. GARCÍA ROMERO, M. PERELLÓ;
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Abstract: Several evidences indicate that calorie restricted (CR) animals display short and long-term changes in their reward-related behaviors towards palatable stimuli, but the molecular basis underlying

such adaptations remain uncertain. Ghrelin is a stomach-derived hormone that acts via growth hormone secretagogue receptor (GHSR) and enhances reward-related behaviors. GHSR is expressed in the ventral tegmental area (VTA), which is a hub of the so-called mesolimbic pathway that innervates the ventral striatum (i.g, the nucleus accumbens (Acb)) in order to control reward-related behaviors. Since plasma ghrelin levels increase under calorie restriction, GHSR signaling could act in the mesolimbic pathway and affect the short- and long-term behavioral adaptations toward rewarding stimuli observed in CR animals. Here, we investigated the induction of the marker of neuronal activation cFos in the mesolimbic pathway as well as the saccharine consumption in wild-type (WT) mice and GHSR-deficient mice during a 5-day 60% calorie restriction protocol. We observed that GHSR-deficient mice showed: 1) a more severe weight loss and hypoglycemia, 2) a similar increase of cFos in the VTA but a smaller increase of cFos in the Acb, and 3) a reduced overconsumption of saccharin, than WT mice during the calorie restriction protocol. When CR mice where refed, we found that GHSR-deficient and WT mice did not show different hyperphagia, glycaemia or saccharine consumption, in a similar fashion as seen before the calorie restriction. Thus, we conclude that GHSR plays a main role during, but not after, a calorie restriction condition. In particular, we found GHSR seems to be required for the maintenance of energy balance and glucose homeostasis during calorie restriction as well as for the full calorie restriction-induced activation of the reward-related brain centers and saccharine overconsumption.

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Poster

P643. Energy Metabolism I

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P643.07

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Brain mechanisms in cancer associated cachexia

Authors: *D. KALTENECKER[1,2,3], M. TODOROV[2,3], S. ZHAO[4], P. MORIGNY[1], J. ZUBER[1], S. HERZIG[1], M. BERRIEL DIAZ[1], A. ERTURK[2,3];
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Abstract: Cancer alters diverse metabolic activities in the body. Cancer-associated cachexia (CAC) is a prominent one characterized by loss of body weight via muscle and adipose tissue wasting. It negatively affects cancer treatments and is responsible for up to 40% of cancer deaths, highlighting the urgent need for novel treatment options. While the brain contributes to cachexia development by promoting anorexia, the neuronal circuits that govern CAC establishment and progression remain poorly understood. Here, we studied changes in neuronal activity in brains of tumor-bearing mice (weight-stable vs. CAC). To this end, we performed whole-brain cFos labeling using a modified SHANEL protocol (Zhao⋯Ertürk, Cell, 2020). After light-sheet imaging of whole mouse brains, we used ClearMAP (Renier et al., Cell, 2016) to identify cFos+ cells automatically. Subsequent registration to the Allen brain atlas yielded in the

identification of brain regions with significant alterations. We observed increased neuronal activity in multiple brain areas in mice transplanted with a cancer cell line that does not induce weight loss (weight-stable mice). These include the lateral hypothalamic nucleus involved in regulating feeding behavior and cortical regions, which were not implicated in metabolic activities before. Interestingly, increased cFos expression in these brain regions disappeared in cachectic animals, suggesting that their over-activation is involved in blocking CAC in weight-stale mice. Thus, our findings highlight novel brain regions that can be targeted to ameliorate weight loss in cancer as novel CAC treatment options.

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Poster

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Program #/Poster #: P643.08

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: A*STAR Investigatorship (1530700142) to Dr. Fu Yu

Title: Neural ensemble encoding context-dependent food consumption

Authors: *H. MOHAMMAD[1], E. SENOL[1], M. GRAF[2], C.-Y. LEE[3], G. AUGUSTINE[2], Y. FU[1]; [1]Inst. of Mol. and Cell Biol. , Agency for Science, Technol. and Res., Singapore, Singapore; [2]Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore; [3]Singapore bioimaging consortium, Singapore, Singapore

Abstract: Feeding is not only controlled by metabolic needs, however there are number of external cues associated with food that can elicit excessive consumption in sated animals. The availability of palatable food along with environmental context promotes excessive food intake which is one of the major contributor to obesity. However the neural mechanisms that drive contextual feeding are not well understood. Here, we designed a novel paradigm for studying contextual feeding using chemogenetic approach, and identified a novel subset of neurons in the hypothalamus of the brain that are capable of driving robust contextual feeding in mice. Using modern tracing tools available, we show here that these neurons are connected to hippocampus, and, this hippocampus to hypothalamus connection is critical for the establishment of context dependent food intake. Altogether our data reveal a novel circuit that enables an environmental context to promote excessive food intake.

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Poster

P643. Energy Metabolism I

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Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH P01 NS097197
NIH R35 NS116824

Title: Brain glycogen serves as a critical sugar cache required for protein glycosylation

Authors: *M. GENTRY[1], R. C. SUN[2];
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Abstract: Glycosylation defects are a hallmark of many nervous system diseases. However, the molecular and metabolic basis for this pathology is not fully understood. In this study, we demonstrate that N-linked protein glycosylation in the brain is critically and directly connected to glycogenolysis. The primary function of glycogenolysis is to liberate glucose-1-phosphate from glycogen. We demonstrate that in addition to glucose, glucosamine is an abundant covalent constituent of brain glycogen. We define the biosynthetic incorporation of glucosamine into glycogen by glycogen synthase and glucosamine release by glycogen phosphorylase *in vitro* by biochemical and structural methodologies, *in situ* in primary astrocytes, and *in vivo* by isotopic tracing and mass spectrometry imaging. We establish that glycogen-derived glucosamine is a significant source of amino sugars required for protein glycosylation in the brain. Further, we demonstrate that disruption of cerebral glycogen metabolism causes global decreases in free UDP-N-acetyl-glucosamine and N-linked protein glycosylation using two glycogen storage disease models. These findings reveal a previously unknown yet key fundamental biological role for brain glycogen in protein glycosylation that has direct relevance to multiple human diseases of the central nervous system.

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Poster

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Program #/Poster #: P643.10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Develoment of Non-Human Primate Multi-phase Feeding Behavior Assessment Method and Quantitative Analysis and Palatability Effect

Authors: *L. J. HA[1], M. KIM[1], H. YEO[2], K. KIM[2], M. LEE[1];
[1]Col. of Med., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Korea Res. Inst. of Biosci. and Biotech. (KRIBB), Natl. Primate Res. Ctr., Seoul, Korea, Republic of

Abstract: <META NAME="author" CONTENT="하재선">Background: Despite feeding behavior assessment method using rodent model is long been used, no study reported the specific feeding behavior assessment method of Non-Human Primate(NHP). The aim of the present study is to provide feeding behavior assessment method of NHP, which could dissect multi-phase component of feeding behavior and quantify the effect of palatability and hunger.Methods: Three Rhesus macaques (Macaque mulatta) was used. To assess the approach and consumption phase of feeding behavior, specialized cage and tray were designed. Fourteen different behavioral indices (e.g. approach to the food, pushing the cheek, etc) were developed for approach and consumption phases. Additionally, two food test indices were developed to compare behaviors for two different food items. The feeding behavior of NHP is video recorded and is viewed in slow motion to identify the feeding behavior index of approach and consumption phase. Further, to reflect the temporal dynamics, every 5min bins during total 15-20mins were analyzed. To validate the application efficacy for palatability assessment, different level of palatability foods was used. And, for hunger effect assessment, both sated and fasted NHP were studied. Results: As designed, among fourteen behavior indices, most of the indices showed robust efficacy of quantifying palatability and hunger effect. For several indices, hungry NHP showed significantly higher index score compared with sated NPH. Two-dimensional analysis of two indices showed that the internal hunger state and calculated palatability value of NHP could be plotted in 2D plots. Conclusion: For the first time, multiple behavioral indices for feeding behavior assessment methods for NHP were developed. The validation results showed that these methods could be applied for hunger effect and palatability effect assessment. These novel feeding behavior assessment methods could open new research platform for multiple areas of NHP research.

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Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P683.01

Topic: H.06. Social Cognition

Support: P50MH100023

Title: Social status regulates looking behavior indicative of theory of mind

Authors: *T. M. CHAMP[1], S. LEE[1,2], E. A. HILLIER[1], D. O'NEILL[1], T. GANAPATHY[3], N. R. LINGENFELTER[1], S. MARX[1], K. M. GOTHARD[1];

[1]Dept. of Physiol., [2]Dept. of Electrical and Computer Engin., Univ. of Arizona, Tucson, AZ; [3]St. Louis Univ., St. Louis, MO

Abstract: Theory of mind is necessary for human and non-human primates to successfully function in a complex hierarchical society. An elemental manifestation of theory of mind is the production of gaze-following saccades. Shared attention is a version of gaze following that occurs when both partners fixate on the same target. The goal of the study was to determine whether gaze following and shared attention are influenced by social status. We generated artificial hierarchies by juxtaposing videos of threatening and appeasing behaviors to simulate that a subordinate monkey responds submissively to the threats of a dominant monkey. Each artificial hierarchy had four members of the same sex, which resulted in six pairwise hierarchical interactions. All individuals shown in the videos were unfamiliar to our male and female viewer monkeys. We recorded the scanpaths of the viewer monkeys as they watched these hierarchical interactions, and identified the saccades that met criteria for gaze following or shared attention: gaze following saccades that ended in a fixation on the social partner in the video were classified as shared attention saccades. We confirmed previous findings that higher ranking individuals command longer viewing times. Increased viewing time was expected to also increase the likelihood of following the gaze of the dominant animal. Our preliminary data from two viewer monkeys, however, show that subordinate monkeys elicited a higher frequency of both gaze following and shared attention saccades (ANOVA $p<0.001$, N = 3 hierarchies, 1500 saccades). This effect was more prominent for hierarchies of the same sex as the viewer. Furthermore, when viewing the subordinate monkey, the subjects generated a higher proportion of shared attention vs. gaze following saccades suggesting that they were more closely tracking the gaze interactions from the subordinate to the dominant. We then compared the temporal distribution of gaze following and shared attention saccades between viewer monkeys and found that videos that generated the highest correlation values depicted interactions of the lowest ranking animal in each hierarchy (Hierarchy 1, Pearson rho = 0.5596, $p<0.001$; Hierarchy 2, rho = 0.3823, $p<0.001$). Taken together, these findings suggest that although the dominant animals receive most of the viewer's attention, the subordinate triggers behaviors more suggestive of theory of mind.

Disclosures: T.M. Champ: None. **S. Lee:** None. **E.A. Hillier:** None. **D. O'Neill:** None. **T. Ganapathy:** None. **N.R. Lingenfelter:** None. **S. Marx:** None. **K.M. Gothard:** None.

Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

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Topic: H.06. Social Cognition

Support: P50MH100023

Title: Quantitative assessment of information content and learning extracted from the scanpaths of macaques viewing videos of social interactions

Authors: *S. LEE[1,2], T. M. CHAMP[1], E. A. HILLIER[1], B. T. SEATON[3], D. O'NEILL[1], N. N. JACOBSON[4], B. R. DENNIS[1], J. W. ROZENBLIT[2], K. M. GOTHARD[1];

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Abstract: Videos of social interactions contain rich information about the protagonists including their social status. The content of the video often determines the scanpath of the viewer. The scanpath also contains information about the viewer, specifically the amount of information the viewer extracted and learned from the video. The goal of our study was to quantify the information in videos of macaque interactions and determine whether the social status of interacting macaques can be identified from the scanpaths of conspecific viewers. We generated multiple virtual social hierarchies, each consisting of four individuals of the same sex strictly organized by linear dominance. In these hierarchies, the highest and lowest ranking individuals show only threatening or appeasing expressions, but the mid-ranking individuals show both dominant and submissive expressions. By watching the pairwise interaction videos, the viewer learns about the hierarchical position of everyone. Each male and female macaque learned each two sets of male and female hierarchies. From their scanpaths we generated a map of fixation density in each region of interest. These became terms in an equation that generated descriptors for each video type. We also generated a ground truth model quantifying the ratio of the number of the pixels corresponding to the face, body, and background in videos. Then, we used the ground truth model to generate a second set of descriptors. A support vector machine (SVM) classified the descriptors for the ground truth model and the experimental data. The SVM performance was assessed by cross validation, and we used the generalized classification error (GCE) as a performance indicator. As previously shown, the viewing time of the subject was proportional with the rank of each individual, showing a rank-related staircase pattern of viewing time. We then explored whether there was a relationship between GCE and the emergence of the rank-related staircase viewing pattern. This pattern emerged when GCE was low (approx. 20%) and its cumulative trend followed the cumulative trend of GCE in the ground truth model. When we compared the classification performance across male and female hierarchies and male and female viewers, we found a learning advantage for hierarchies of the same sex as the viewer. Taken together these findings suggest that this approach is adequate to quantify the information relevant for social hierarchy in videos of interacting macaques. Moreover, this approach can also evaluate the viewer's knowledge about social hierarchy and highlights sex-related differences in social learning. Lastly, this approach can be generalized and applied to related studies.

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Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

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Program #/Poster #: P683.03

Topic: H.06. Social Cognition

Support: P50MH100023

Title: Does social rank subvert attention allocation to novelty?

Authors: *N. N. JACOBSON[1], S. LEE[2,3], B. R. DENNIS[2], C. M. BOLLES[1], S. KIM[2], B. T. SEATON[4,5], T. M. CHAMP[2], D. O'NEILL[2], K. M. GOTHARD[1,2];
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Abstract: All human and non-human primates who live in hierarchical societies, use knowledge about the status of others for social decision making. Dominant individuals command visual attention. Novelty also captures visual attention. The goal of this study was to determine whether Rhesus macaques prioritize social rank over novelty when they perform a Visual Paired Comparison (VPC) task. We hypothesized a conflict between the natural inclination to look at novel faces and the drive to view dominant faces changes accuracy and reaction time in a VPC task. We generated artificial social hierarchies and independently assessed that the viewer monkeys learned the position of each individual in the hierarchy. During the VPC task, the viewer was first familiarized with a video of a conspecific selected from the learned hierarchy. This was followed the presentation of two images: a static frame from the prior familiarization video (familiar image) next to a static image of another monkey chosen from the rest of the same hierarchy set (novel image). Both the familiar and novel images contained only neutral facial expressions. To successfully complete a trial and receive a juice reward, the viewer monkey was required to fixate on the novel image. We measured the choice accuracy of one viewer monkey, and compared the proportion of errors when choosing a dominant familiar vs. a subordinate familiar monkey. We found a higher probability (ANOVA $p < 0.05$, $N = 34$ sessions) of errors when the familiar individual was dominant. The probability of incorrectly choosing the highest ranking animal when paired with the second highest was even higher ($p < 0.01$). Thus, we confirmed that preference for dominance can influence the preference for novelty in a VPC task. These errors in novelty selection may be related to the viewer's certainty of rank, because the effects were strongest for both the highest and lowest ranking individuals ($p < 0.01$). Furthermore, preliminary data indicate that this dominance effect is temporary and depends on social context, as the effect was not present when the stimulus monkeys were not engaged in hierarchical interactions ($p = 0.5$). The interference between preference for novelty and for high social status suggests that the VPC task can be used to probe the perception or knowledge of social status.

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Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

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Program #/Poster #: P683.04

Topic: H.06. Social Cognition

Support: 5P50MH100023
R01 MH121706

Title: Autonomic state predicts engagement of macaques with videos of conspecific social interactions.

Authors: *M. A. CARDENAS[1], S. LEE[2,3], T. M. CHAMP[3], N. N. JACOBSON[4], E. A. HILLIER[3], C. M. BOLLES[3], S. KIM[3], D. O'NEILL[3], A. B. MARTIN[3], K. M. GOTHARD[3];

[1]GIDP in Neurosci., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Physiol., [4]Univ. of Arizona, Tucson, AZ

Abstract: Video playback studies in both humans and non-human primates typically report the effect of video content on looking behavior and autonomic responses. The inverse causality, where the autonomic state of the viewer determines the looking behavior, has been rarely explored. The justification for this approach rests on the assumption that interoceptive states, signaled by autonomic afferents, influence the processing of external stimuli. We quantified the relationship between the moment-to-moment autonomic state of macaques (indexed by heart rate and heart rate variability) and their interactive looking pattern with unfamiliar conspecifics. Videos depicting conspecifics engaged in aggressive and appeasing displays were juxtaposed to simulate dominant-subordinate interactions. Previous studies have shown that such videos capture the attention of viewer monkeys and trigger gaze-following saccades, or saccades of shared attention. We found an inverse correlation (rho: -0.23) between heart rate and total looking time ($p<.001$). Related to looking time duration, the probability of a gaze following/shared attention saccade also increased during trials with lower heart rates ($p<.05$). No change in heart rate was found in response to events in the videos, suggesting these trends are not the result of a response to video content, but instead due to the state of the animal. This is reinforced by the observation of similar correlation power in the pre-stimulus period. To determine whether lower heart rate indicated a decrease in sympathetic arousal or an increase in parasympathetic drive (vagal tone), the high frequency band (~0.2-0.35 Hz) in the R-R interval power spectrum was used as an index of vagal tone. Periods of enhanced vagal tone were positively correlated ($p<.05$) with an increased number of shared attention saccades, but not with looking time. We then determined whether during periods of low and high vagal tone, gaze following/shared attention saccades originated mainly from the dominant or the subordinate monkey. Typically, these saccades started when the viewer's gaze was on the subordinate video monkey. However, with low heart rate and high vagal tone, the viewers were more likely to follow the gaze of the dominant monkey ($p<.001$). These results suggest the viewer monkey is more likely to engage in observing dominant-subordinate social interactions and more inclined to engage with the dominant monkey when the vagal tone is higher. These observations reinforce the viewpoint that vagal tone is correlated with increased social openness and suggest that interoceptive states influence the extraction of relevant information from socio-emotional stimuli.

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Poster

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Topic: H.06. Social Cognition

Support: R01 MH121009

Title: Neurons in the primate amygdala signal social context through sustained changes in baseline firing rates

Authors: *A. BOWMAN[1], K. R. ANDERSEN[2], M. A. CARDENAS[1], A. B. MARTIN[3], E. A. HILLIER[3], K. M. GOTHARD[1,2,3];
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Abstract: Typical neurophysiological experiments used to explore the role of the amygdala in affective and social behavior involve rapid presentation of stimuli that induce an emotional reaction or require a behavioral response. These studies bring to light the cellular basis of immediate emotional reactivity and its impact on decision-making. However, this approach leaves the cellular underpinning of long-term changes in mood unexplored. Natural social behavior also unfolds on a larger time scale. To explore the representation of social context in the amygdala, we designed an experiment where the subjects experienced alternating blocks of non-social and social touch. During the delivery of non-social tactile stimuli (directed gentle airflow), the animal was alone in a closed booth. Social touch, akin to grooming, was delivered by a trusted social partner who sat in front of the animal. Both types of touch were delivered to the same area of the skin. Under these experimental conditions, a subset of neurons in the amygdala (98 neurons from 624 recorded from 2 monkeys) showed sustained elevations of baseline firing rate in either social or non-social touch blocks. To identify these neurons, baseline activity in each condition was concatenated and smoothed with a wide window (Gaussian $\sigma = 2$ minutes). To determine whether activity in one condition was sustained relative to the other condition, we measured a proportion value defined as the proportion of time that the baseline activity in one condition was greater than the mean baseline firing rate of the other condition. Neurons were classified as "context-responsive" if the proportion value of one condition was at least 1.5 times higher than the other condition. A fraction of these context-responsive neurons (62%) also responded to the instantaneous presentation of airflow, grooming, or both. These neurons were found throughout the amygdala, with 44% recorded in the basal nucleus. Their characteristics mirror previously reported neuronal properties seen in the primate amygdala - multidimensional responses, distribution across multiple nuclei, and encoding through temporal patterns of firing. In addition, each monkey's heart rate varied across sessions and conditions, and these cells indicated context regardless of changes in the heart rate. These results suggest that the amygdala is involved in orchestrating temporally protracted affective states which transcend moment-to-moment emotional reactions elicited by external stimuli. As such, changes in the baseline firing of neurons in the amygdala may represent the neural substrate for sustained affective states.

Disclosures: A. Bowman: None. **K.R. Andersen:** None. **M.A. Cardenas:** None. **A.B. Martin:** None. **E.A. Hillier:** None. **K.M. Gothard:** None.

Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P683.06

Topic: H.06. Social Cognition

Support: NIH F30 MH122048

NIH DC004845
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University of Rochester Schmitt Program in Neuroscience

Title: Decoding of Expression and Identity from Neural Responses to Faces and Vocalizations in Primate Prefrontal Cortex

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Abstract: The ventrolateral prefrontal cortex (VLPFC) is a multisensory integrator that is highly responsive to social stimuli. In both humans and macaques, areas within the VLPFC exhibit robust and specific responses to faces that are modulated by the emotional or expressive qualities of the face. In macaques, the VLPFC contains neurons with selective firing for species-specific vocalizations, head-orientations, and faces. Furthermore, macaque VLPFC neurons exhibit non-linear multisensory integration of visual and auditory information suggesting a rich and complex population response. In light of the VLPFC's established multisensory integration and putative social function, we sought to investigate the relationship between VLPFC neuronal activity and the perception of socioemotional expressions. In this study, we recorded single and multi-unit neurons in VLPFC using multi-electrode arrays, while non-human primate subjects (*Macaca mulatta*) viewed movies of macaques vocalizing with accompanying facial gestures. Stimuli consisted of 400-1000msec movies of 3 different audiovisual expressions from 3 different conspecifics. Linear Discriminant Analysis of neural firing rates revealed neurons with greater than chance decoding accuracy for expression and identity within the VLPFC. Combined as a pseudo-population, these cells exhibited increasing decoding accuracy for both variables as a function of population size, with decoding accuracy of identity increasing faster than expression. Principle component analysis of pseudo-population mean responses to each stimulus revealed that, along the first two principle components, responses to the same identity occupy separable regions of the response space. Additionally, a two-way ANOVA analysis of single neuron firing rates revealed that the majority of VLPFC neurons with a significant main effect of expression or identity also had a significant interaction effect. Our data show that sufficient information for the classification of different expressions and identities is present at the population level in the VLPFC, with identity as the primary driver of the population response. At the single cell level, responses to natural stimuli are highly complex, mirroring non-linearities seen in multisensory integration. Our results encourage further investigation into the role of the VLPFC in social communication as well as the perception and interpretation of emotional expressions.

Disclosures: K.K. Sharma: None. **M. Diltz:** None. **L.M. Romanski:** None.

Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

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Topic: H.06. Social Cognition

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Canadian Institutes of Health Research FRN 353372
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Canada First Research Excellence Fund to BrainsCAN

Title: Understanding social cognition in the common marmoset using functional magnetic resonance imaging.

Authors: *J. CLERY[1], K. GILBERT[1,2], Y. HORI[1], D. SCHAEFFER[3], J. GATI[1,2], R. MENON[1,2], S. EVERLING[1,4];
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Abstract: Social cognition is a dynamic process that requires the perception and integration of a complex set of idiosyncratic features between interacting conspecifics or during the observation of these interactions. A promising nonhuman primate model for investigating the neural basis of social cognition, and in particularly social interaction, is the common marmoset (*Callithrix jacchus*), a small New World primate that shares a rich social repertoire with humans. Here we used functional magnetic resonance imaging (fMRI) in awake marmosets to investigate the neural basis of primate social cognition. First, we acquired fMRI at 9.4 Tesla to map brain areas activated by social interaction observation, i.e., while a marmoset was viewing a video of two other marmosets interacting with each other (grooming, playing, fighting). In the second study we simultaneously measured whole-brain activations of two socially interacting marmoset monkeys at 3 Tesla. We discovered a network of subcortical and cortical areas, predominately in the anterior lateral frontal and medial frontal cortex, that was specifically activated by social interaction observation. Interestingly, while two marmosets where facing each other in-person, we observed increased activation in these regions, compared to when the marmoset viewed a video of the other marmoset. These findings show similarities with a recent social interaction networks identified in Old World macaque monkeys and suggest that this network is largely conserved between New and Old World primates. Our findings support the use of marmosets for studying the neural basis of primate social cognition.

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Poster

P683. Animal Behavior: Social Behavior and Cognition in Non-Human Primates

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Program #/Poster #: P683.08

Topic: H.03. Decision Making

Support: MEXT KAKENHI JP16H06567

JST CREST JPMJCR1853

Title: Representations of actual and counterfactual choice outcomes in the primate orbitofrontal cortex, ventral striatum, and midbrain dopamine neurons

Authors: *M. YUN, M. NEJIME, T. KAWAI, H. YAMADA, M. MATSUMOTO;
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Abstract: Individuals evaluate their past decisions by assessing what was gained (the actual outcome) as compared to what would have been gained by making a different choice (the counterfactual outcome). A large body of studies have shown that actual outcome value processing is distributed in many cortical and subcortical areas. On the other hand, although some studies reported that the orbitofrontal cortex (OFC) is involved in counterfactual outcome value processing, the entire picture of neural mechanisms underlying this process remains unknown. To address this issue, we focused on the OFC and two core regions of the subcortical system signaling actual values: the ventral striatum (VS) and midbrain dopamine (DA) neurons, and investigated how and whether they process counterfactual values in monkeys. We developed a value-based decision-making task in which two options were sequentially presented. When the first option was presented, the monkey needed to decide whether to choose it though the animal did not yet see the second option at that time. If deciding to choose the first option, the monkey was unable to choose the second option even if the value of the second option was better than that of the first option, and then obtained the reward associated with the first option. If deciding not to choose the first option, the monkey obtained the reward associated with the second option. Thus, the value of the second option became counterfactual or actual depending on whether the monkey chose the first option or not. We observed that a substantial number of OFC, VS and DA neurons represented the actual value of the second option. By contrast, we found that a larger proportion of OFC neurons represented the counterfactual value of the second option than VS neurons, and DA neurons did not represent this type of value. The latency of the counterfactual value signal was shorter for OFC neurons than VS neurons. Notably, during the presentation of the second option, the OFC population represented not only the counterfactual value of the second option but also the actual value of the first option but in an opposite direction, suggesting that the OFC population compares the actual and counterfactual values. This opposite value representation was not observed in the VS population. Previous studies have shown that the OFC is involved in subjective feelings of decision outcome evaluation such as relief and regret, which are generated by the comparison between actual and counterfactual values. Taken together, our findings reveal a gradient in the capability of processing counterfactual value from the cortical to subcortical reward systems, and suggest the key role of the OFC in decision outcome evaluation.

Disclosures: M. Yun: None. **M. Nejime:** None. **T. Kawai:** None. **H. Yamada:** None. **M. Matsumoto:** None.

Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.01

Topic: H.03. Decision Making

Support: National Institutes of Health grant R01MH115557-01

Title: Suboptimal inference inverts the bias-variance trade-off in decisions with asymmetric evidence

Authors: *T. EISSA[1], J. I. GOLD[3], K. JOSIC[4], Z. P. KILPATRICK[2];
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Abstract: Solutions to challenging inference problems are often subject to a trade-off between bias (being wrong) that is minimized with complex strategies and variance (being noisy) that is minimized with simple strategies. However, when strategies are suboptimal but complex, the implications of the bias-variance trade-off are unclear. To better understand sources of errors in human suboptimal inference, we examined people's responses in a two-alternative forced choice task for which each choice had asymmetrically available evidence. Unlike most decision tasks, asymmetric evidence direct impacts evidence weights of the ideal Bayesian observer, resulting in choice asymmetries (i.e., a tendency to chose one alternative over the other across all trials), even when the alternatives are equally likely. Human choice strategies were individually variable and reflected both Bayesian-like as well as heuristic decision strategies. These suboptimal strategies displayed an inversion of the classic bias-variance trade-off: subjects who used more complex, but imperfect, Bayesian-like strategies tended to have lower response variance but excessive biases because of incorrect tuning to latent task features, whereas subjects who used simpler heuristic strategies tended to have higher variance but minimal biases. This inverted form of bias-variance trade-off followed from the differences in the two strategies: suboptimalites in Bayesian-like strategies involved mistuned estimates of task-relevant latent variables, which led to excess choice biases without adding choice variability. Suboptimalities in simple heuristic strategies that did not infer latent variables tended to add variability that also smoothed out choice asymmetries. Our results highlight how breaking the symmetry of standard decision tasks and considering the diversity of strategies used in large subject cohorts can reveal novel and unexplored relationships between strategy complexity, bias-variance balance, and the sources of human errors.

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Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.02

Topic: H.03. Decision Making

Support: NIH T32 Training Grant

Title: Rewards elicit choice reactivation for credit assignment

Authors: *C. D. CARRASCO, Y. ZHANG, S. LUCK, E. BOORMAN;
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Abstract: The process of identifying what set of choices leads to an outcome, known as credit assignment, can be formalized as occurring in a model-free or a model-based manner. In the model-free case, reward is thought to be tied back to the most recent choices through eligibility traces that weigh these actions with an exponential decay over time. In the model-based case, when the choice and outcome are separated by a sufficient delay, it is theorized that a reactivation of a causal choice's representation triggered by an outcome is needed for a given choice-outcome association to form through Hebbian plasticity. However, if and when this reactivation occurs during learning is still unknown.
In order to test for reactivation of neural representations associating outcomes with choices separated in time, we had participants perform a decision-making task where they had to gamble between two stimulus options (faces and houses) which predicted rewards with slowly drifting and independent probabilities. For each of these stimuli participants received feedback as to whether their choice led to reward and if the unchosen stimulus would have led to reward. Using electroencephalography, we generated event related potentials (ERPs) while participants performed this task that were time locked onto stimulus presentation, choice, and feedback portions of the task. We then used these ERPs to train a series of support vector machines to test if we could identify a reactivation of neural representations tied back to a specific stimulus choice.
Preliminary behavioral results (N = 16) as predicted by reinforcement learning theory, showed that subjects learned from both the experienced and counterfactual outcomes, with effects decaying over time when performing logistic regression analyses ($p < .05$). Neural results suggest a neural reactivation of the choice identity, specifically at the time its feedback is delivered (200 - 400 ms), to form associations between favorable outcomes and chosen stimuli. However, we did not find evidence that these representations were the same as sensory representations measured at stimulus presentation. There was no significant reactivation triggered by counterfactual feedback. Our results suggest that model-based credit assignment indeed elicits a reactivation of neural representations in order to form associations between choices and delayed outcomes at times of feedback, but that these neural representations may be distinct from purely perceptual representations of a given stimulus.

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Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.03

Topic: H.03. Decision Making

Title: Speed-accuracy tradeoffs in a disinhibition-based neural circuit model of decision-making

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Abstract: Objective: Speed-accuracy tradeoffs (SAT) in decision-making have long been a phenomenon of interest in psychology and neuroscience. As a signature of decision dynamics, the SAT has been considered a necessary benchmark for neural decision circuits but how such dynamics arise is unknown.

Sequential models of decision-making predict behavioral SAT on the assumption of the shifting of decision criteria. However, this assumption is contradicted by recent neurophysiological findings on neural decision thresholds and does not capture the empirical evidence for baseline elevation or gain tuning in neural dynamics. Here we examine how well a novel biologically-based circuit - the local disinhibition decision model (LDDM) - captures the behavioral and neural signatures of SAT across different datasets. Methods: The LDDM implements recurrent excitation and global gain-control inhibition drawn from existing models and incorporates a biologically plausible element of local disinhibition that governs "top-down" control of the network. The model was implemented as a dynamical system capturing firing rate responses. We tested this model in capturing the behavioral and neural dynamics in a range of empirical datasets: 1) behavior and neural dynamics of SAT in monkeys (Heitz and Schall, 2012; Hanks et al., 2014; Thura & Cisek, 2016, 2017), 2) SAT under individual differences in working memory (Heitz and Engle, 2007), and 3) causal manipulation of NMDA antagonism on the behavior of SAT (Shen et al., 2010). Results: We show that the LDDM captures the behavioral tradeoff between reaction time (RT) and choice accuracy by controlling the intensity of local disinhibition during the process of decision making. The best-fitting models to the behavior capture the neural dynamics of baseline elevation and increased gain across different datasets. Increasing the network recurrent excitation, a parameter related to working memory, steepens the slope of accuracy log-odds as a function of RT, consistent with the empirical findings on working memory. Reducing excitatory connectivity as an analog of NMDA antagonism predicts slower and more accurate performance, consistent with the empirical causal manipulation results. Conclusion: We find that local disinhibition in a biologically plausible decision circuit with recurrent excitation and global inhibition captures a broad range of behavioral and neural SAT dynamics. These findings show that different SAT characteristics such as baseline elevation and increased gain can arise from a single circuit mechanism, highlighting the critical role of disinhibition in biological decision-making.

Disclosures: B. Shen: None. **K. Louie:** None. **P. Glimcher:** None.

Poster

P776. Modeling and Behavior I

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P776.04

Topic: H.03. Decision Making

Support: NIH-R01MH111703 (VPF)

Title: Monkeys appear to detect abstract order in randomness

Authors: *Y. JIN[1], G. G. JENSEN[2], J. P. GOTTLIEB[4], V. P. FERRERA[3];
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Abstract: An animal's survival often depends on learning features of the environment that predict reward, and distinguishing those learnable features from others that are not predictive. However, subjects often mistake accidental patterns for learnable ones and phenomena like auto-shaping and past-trial biases

suggest that animals impose spurious structures onto objectively random events. Those phenomena of spurious learning are examples of innate approach behaviors that can be explained by model-free reinforcement learning (RL). However, it is unknown to what extent animals also impose model-based representational structures onto unstructured feedback when presented with more abstract cognitive tasks. Therefore, we tasked monkeys (N=3) with discovering the implicit ordering of sets comprising 5 pictorial stimuli. In the case of "learnable" lists (indicated here by the letter "L"), the stimuli were implicitly ordered in a way that could be inferred by trial and error. When presented pairs from the L list, a reward was given only if the monkey chose the image with the higher rank. In the "unlearnable" case (indicated by the letter "U"), feedback was delivered at random regardless of which image the monkey chose. Both L and U lists comprised 5 images. Each day, 2 lists of novel images were presented with L and U trials randomly interleaved. We replicated prior results that monkeys reliably learned the implicit order of L lists. Surprisingly, we also found that monkeys behaved as though some ordering existed among items from U lists even though the reward scheme did not incentivize subjective ordering. They showed consistent preferences that were stable over the course of an entire behavioral session. In simulations, we found that a model-free RL algorithm (Q-learning) also displayed a degree of consistent subjective ordering among U list items. Under a follow-up task designed to break subjective preferences by giving rewards more frequently to whichever item was selected less often, Q-learning failed to show spurious learning, but monkeys still showed preferences indicative of a subjective ordering. Our results suggest that the spurious learning extends beyond reward-driven conditional learning, a result that is best understood in terms of more cognitive model-based learning mechanisms.

Disclosures: Y. Jin: None. **G.G. Jensen:** None. **J.P. Gottlieb:** None. **V.P. Ferrera:** None.

Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.05

Topic: H.03. Decision Making

Support: SENSHIN Medical Research Foundation

Title: Assessment of risk aversion in depression and anxiety by computational modeling based on the Cumulative Prospect Theory

Authors: *K. HAGIWARA, C. CHEN, H. LEI, M. HIROTSU, T. MATSUBARA, S. NAKAGAWA; Div. of Neuropsychiatry, Dept. of Neurosci., Yamaguchi Univ., Ube-shi, Japan

Abstract: Both depression and anxiety have been associated with risk aversion in decision-making, but the underlying cognitive computational mechanisms remain uninvestigated. Furthermore, given the high comorbidity between depression and anxiety, their independent association with risk aversion is unclear and no study has evaluated them simultaneously. In the present study, we set out to investigate the underlying cognitive computational mechanisms of risk aversion in depression and anxiety using a value-based decision-making task and computational modeling based on the Cumulative Prospect Theory. We also aimed to specify the unique versus common mechanisms of risk aversion in depression and anxiety.

This study was conducted with the approval of the Ethics Review Committee of the Yamaguchi University Hospital. 56 healthy subjects conducted a decision-making task to maximize the amount of reward, considering both the amount of money won and the probability of winning. In model-based analysis, we estimated risk aversion due to a concave utility function (λ, a power function) and risk aversion due to nonlinear probability weighting (γ, the one-parameter Prelec weighting function) for each subject, respectively. Depression and anxiety were measured by BDI-II and STAI state anxiety subscale. Correlation analysis showed a significant positive correlation between depression/depression-pure (BDI-II without anxiety-related items) and γ, and no correlation between depression/depression-pure and λ, and anxiety and γ/λ. Partial correlation analysis showed that the significant correlation between depression/depression-pure and γ remained after controlling anxiety, and a positive correlation trend was observed between anxiety and λ after controlling depression. To our best knowledge, this is the first study to assess risk aversion due to a concave utility function and nonlinear probability weighting separately for depression and anxiety using a computational modeling approach. Depression is independently associated with underweighting of small probabilities and overweighting of large probabilities. We are currently recruiting clinical patients to confirm the above findings. By using computational models based on decision-making theories, the current study may improve our understanding of decision-making deficits in depression and anxiety.

Disclosures: K. Hagiwara: None. **C. Chen:** None. **H. Lei:** None. **M. Hirotsu:** None. **T. Matsubara:** None. **S. Nakagawa:** None.

Poster

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R01 (1R01MH125571-01)
NIH Grant (5T90DA043219)

Title: Rats infer hidden-states in a temporal wagering task

Authors: *A. MAH[1], S. SCHIERECK[1], V. BOSSIO[2], C. M. CONSTANTINOPLE[1];
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Abstract: A principle of modern decision theories is reference dependence, in which the subjective value of a reward is computed relative to an internal reference point that is thought to reflect outcome expectations. Previous work has often assumed that reference points are retrospective, deriving directly from past experiences. Here, we use behavioral modeling to show that rats use inference to compute and switch between multiple reference points. We have designed a behavioral paradigm with partially-

observable states - blocks of trials offering small (low blocks) or large rewards (high blocks). Rats must determine how long to wait for uncertain rewards, providing an explicit behavioral readout of a rat's subjective value of rewards. Rats' wait times are sensitive to the reward volumes and also the block structure: rats wait longer for the same volume of water reward in low blocks compared to high blocks. We developed computational models based on optimal foraging theory that instantiate retrospective or inferential strategies for computing the reference point. Our high-throughput, semi-automated training facility generates thousands of trials from dozens of rats per week, which allows for well-powered model fits across a large population of rats. Using model comparison, we found that inferential computational models better describe the rats' wait-time data (74 out of 74 rats). The inferential model outperforms the retrospective model most strongly at block transitions, consistent with a sudden change in the inferred block. We corroborated these results using complementary analyses of latency to start trials, which also covaries with blocks. Our models allow us to discriminate rats' behavioral strategies, and estimate latent cognitive variables underlying decision-making processes, such as an internal reference point that reflects the learned opportunity cost of time. We apply these models to a variety of problems in value-based decision making, including the role of lOFC in hidden-state inference and hormonal regulation of decision-making.

Disclosures: A. Mah: None. **S. Schiereck:** None. **V. Bossio:** None. **C.M. Constantinople:** None.

Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.07

Topic: H.03. Decision Making

Support: R01MH117323
R01MH114965

Title: Insight and compensation under distorted perception

Authors: *A. MIHALI[1], M. BROEKER[2], G. HORGA[3];
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Abstract: Insight is a complex form of metacognition that denotes an agent's ability to recognize the extent to which their subjective internal perceptual experiences track with the actual states of the external world. Insight can help discern which conscious experiences will be used to alter our existent beliefs and which will be discounted as "not real", for instance dreams, illusions or hallucinations. To induce strong perceptual distortions, we created a task based on a variant of the motion after-effect (MAE) illusion. To measure insight in a quantitative manner, we quantified participants' ability to report beliefs in which they demonstrate compensation for their perceptual distortions. Healthy participants compensated for the MAE illusion in the condition in which they were asked to infer the actual direction of motion ('Believe' condition) as opposed to reporting perceived motion ('See ' condition). In a second experiment, a parametric choice of the test stimuli allowed us to apply an optimal-observer model to the participants' responses and confidence reports which provided a good fit to the data. This model revealed that a

possible mechanism for belief compensation is updating the category prior in the 'Believe' condition. Furthermore, confidence reports, reaction times and pupil dilation patterns shifted in tandem with the psychometric curves, suggesting changes in perceptual uncertainty during belief compensation and supporting an interpretation in terms of adjustments at an intermediate perceptual-decision stage, consistent with the model. In sum, we show that healthy individuals may plausibly achieve effective insight – and compensate for distorted perception – through adjustments in perceptual-decision variables such as prior beliefs.

Disclosures: A. Mihali: None. **M. Broeker:** None. **G. Horga:** None.

Poster

P776. Modeling and Behavior I

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Program #/Poster #: P776.08

Topic: H.03. Decision Making

Support: NIH Grant ZIAMH002928-11

Title: Monkeys learn to maximize the accumulation of tokens associated with the preferred outcome in a reinforcement learning task

Authors: *D. BURK, B. AVERBECK;
NIH, Bethesda, MD

Abstract: Reinforcement learning (RL) is a theoretical framework that describes how agents learn to select options that maximize rewards and minimize punishments over time. In many RL tasks, reward size and/or probability are varied, and animals learn to make choices to maximize the total reward received. We often make choices to obtain secondary reinforcers that can later be exchanged for primary reinforcers. In the present study we have examined how monkeys learn, through secondary reinforcers defined by tokens, to make choices that maximize either juice or water rewards. At the beginning of each task block we introduce unfamiliar visual images, each associated with a fluid type and quantity. In each trial, after a baseline fixation period, we present two of the images to the monkeys. They make a saccade to one of the images to indicate their choice. We associate four different outcomes with the images such that the monkeys receive either 3 juice tokens (orange), 1 juice token (orange), 3 water tokens (blue) or 1 water token (blue) after choosing the corresponding image. The monkeys learn from the outcomes of their choices, represented by a change in the number of tokens on the screen. Tokens are accumulated across trials and cashed out after a variable number of correct trials. Preliminary data show that the monkey learned to primarily select images that delivered juice tokens, even when the offer pair included an option with more water tokens than juice tokens. Thus, they had a strong preference for juice tokens, that were later traded for primary juice rewards. Furthermore, trial abort frequency was higher for trials in which only water tokens were available, which suggests that those choices were relatively aversive. Together, these results show that monkeys can learn to associate differently colored tokens with different liquid reward outcomes, and they can learn to choose images that maximize accumulation of tokens for the preferred outcome. This task allows us to explore how traditional RL models do and do not capture

learning from secondary reinforcers when there is more than one, as is typical in a real-world environment.

Disclosures: D. Burk: None. **B. Averbeck:** None.

Poster

P804. Cellular Mechanisms in Working Memory

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Program #/Poster #: P804.01

Topic: H.05. Working Memory

Support: CIHR NGN-171423

Title: Inferring cross-region differences in mammalian interneuron physiology using single-cell transcriptomics

Authors: A. HOGGARTH[1], A. NIGAM[2], F. M. KRIENEN[5], Y. CHEN[3], S. MCCARROLL[6], S. I. HILL[4], ***S. TRIPATHY**[4];
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Abstract: Single-cell transcriptomics offers a potentially powerful way to bridge single cell gene expression with cellular phenotypes such as in vitro electrophysiology and morphology.
Here, we used data from the emerging Patch-seq method to infer electrophysiological features from single-cell transcriptomes using multi-modal datasets collected from publicly-available data from 3486 interneurons collected from the mouse visual cortex. Specifically, we identified over 500 genes strongly correlated with within-cell type heterogeneity in electrophysiological features such as action potential width, rheobase, and input resistance.
We applied these methods to infer cross-region gradients in cellular phenotypes using unimodal single-nucleus transcriptomics data collected from different cortical regions from mice, non-human primates, and humans. Based on region-specific patterns in gene expression, we inferred that interneurons in primary sensory areas are likely to be more electrically excitable, with greater maximum firing rates and more narrow action potential widths, relative to orthologous interneuronal cells types present in association cortices. These cross-region differences are inferred to arise based on the expression of key ion channel genes, such as KCNC1 and KCNC2 (Kv3.1 and Kv3.2), and calcium binding proteins, such as parvalbumin. In vitro experiments to confirm these cross-regional gradients in cellular physiology are ongoing.
In summary, this work suggests novel patterns of interneuron functional specialization in different areas of the neocortex.

Disclosures: A. Hoggarth: None. **A. Nigam:** None. **F.M. Krienen:** None. **Y. Chen:** None. **S. McCarroll:** None. **S.I. Hill:** None. **S. Tripathy:** None.

Poster

P804. Cellular Mechanisms in Working Memory

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P804.02

Topic: H.05. Working Memory

Support: CIHR
NSERC
DFG
NSF

Title: Characterizing neuronal diversity in intrinsic properties across non-human primate species and cortical areas

Authors: *M. FEYERABEND[1], E. S. KUEBLER[1], M. S. JIMENEZ-SOSA[1], J. K. SUNSTRUM[1], S. MESTERN[1], S. MATOVIC[1], M. WIEDERMAN[1], K. PRADEEPAN[1], S. EVERLING[1], A. NEEF[2], J. F. STAIGER[3], D. A. LEWIS[4], G. GONZALEZ-BURGOS[4], W. INOUE[1], J. C. MARTINEZ-TRUJILLO[1]; [1]Univ. of Western Ontario, London, ON, Canada; [2]MPI For Dynamics and Self-Organization, Göttingen, Germany; [3]Inst. für Neuroanatomie, Georg-August-Universität, Göttingen, Germany; [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Higher order mental representations underlying working memory function, are believed to arise in primates, with the development and expansion of the granular prefrontal cortex (PFC). For example, in vivo extracellular recordings from behaving non-human primates (NHPs) have shown that persistent firing representing the contents of working memory can be found in lateral PFC, but is absent in early sensory areas such as primary visual (V1) cortex. However, the mechanistic basis of potentially unique primate PFC circuitry remains speculative partly due to the lack of data on the biophysical and morphological features of diverse cell-types directly obtained from different brain areas of NHPs. Furthermore, potential differences in PFC single-neuron properties among different NHP species (e.g. New-world monkey Marmoset and old-world monkey Macaque) remain unknown. The latter is an important question, as marmosets are increasingly being used as models for human cognition, yet their neural correlates remain poorly documented. In the international consortium funded by NeuroNex, we aim to characterize the biophysical and microanatomical properties of cortical neurons from the dorsolateral (DL)PFC and V1 of multiple NHP species (*Macaca mulatta, Macaca fascicularis, Callithrix jacchus*) using patch clamp electrophysiology in acute brain slices. We systematically collect membrane voltage responses to different characterization protocols and analyzed intrinsic neural properties, similar to the Allen Institute Cell Type Database. To date, we accumulated about 300 electrophysiological recording. In addition, we examine morphological features including dendritic type and laminar location of reconstructed neurons. Some of these data can be browsed on the website 'PrimateDatabase.com', a collection of publicly available NHP intracellular recordings. In addition, the neuronal morphology of a proportion of recorded cells have been digitally reconstructed. The goal of our project is to provide data that will allow the search for differences in intrinsic properties across cortical areas and across NHP species and enable modelling studies of working memory using realistic single neurons simulations.

Disclosures: M. Feyerabend: None. **E.S. Kuebler:** None. **M.S. Jimenez-Sosa:** None. **J.K. Sunstrum:** None. **S. Mestern:** None. **S. Matovic:** None. **M. Wiederman:** None. **K. Pradeepan:** None. **S. Everling:**

None. **A. Neef:** None. **J.F. Staiger:** None. **D.A. Lewis:** None. **G. Gonzalez-Burgos:** None. **W. Inoue:** None. **J.C. Martinez-Trujillo:** None.

Poster

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Program #/Poster #: P804.03

Topic: H.05. Working Memory

Support: NIH grant R01 MH112746
NSF NeuroNex grant 2015276
NIH grant R01 EY017077

Title: Trial-to-trial variability of spiking delay activity in prefrontal cortex constrains burst-coding models of working memory

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Abstract: A hallmark neuronal correlate of working memory (WM) is stimulus-selective spiking activity of neurons in prefrontal cortex (PFC) during mnemonic delays. These observations have motivated an influential computational modeling framework in which WM is supported by persistent activity in stable attractor networks. Recently this framework has been challenged by arguments that observed persistent activity may be an artifact of trial-averaging, which potentially masks high variability of delay activity at the single-trial level. In an alternative scenario, WM delay activity could be encoded in bursts of selective neuronal firing which occur intermittently across trials. However, this alternative proposal has not been tested on single-neuron spike-train data. Here, we developed a framework for addressing this issue by characterizing the trial-to-trial variability of neuronal spiking quantified by Fano factor (FF). By building a doubly stochastic Poisson spiking model with biophysically constrained parameters, we first demonstrated that the burst-coding proposal implies a significant increase in FF positively correlated with firing rate, and thus loss of stability across trials during the delay. Simulation of the corresponding spiking cortical circuit WM models further confirmed that FF is a sensitive measure that can well dissociate distinct WM mechanisms. We then tested these predictions on datasets of single-neuron recordings from macaque prefrontal cortex during three WM tasks of different modalities. In sharp contrast to the burst-coding model predictions, in each one of these tasks, we only found a small fraction of neurons showing increased WM-dependent burstiness, and stability across trials during delay was actually strengthened in empirical data. Therefore, reduced trial-to-trial variability during delay provides strong constraints on the contribution of single-neuron intermittent bursting to WM maintenance. Our study provides a benchmark in terms of across-trial stability for future computational modeling studies of WM.

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Poster

P804. Cellular Mechanisms in Working Memory

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Program #/Poster #: P804.04

Topic: H.05. Working Memory

Support: NSERC
CIHR
NeuroNex

Title: Temporal structure of persistent activity in macaque lateral prefrontal cortex during a naturalistic working memory task

Authors: *M. ROUSSY[1], A. N. BUSCH[1], M. KHAKI[1], R. LUNA[1], A. J. SACHS[2], L. PALANIYAPPAN[1], L. E. MULLER[1], J. C. MARTINEZ-TRUJILLO[3];
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Abstract: Neural activity in the primate lateral prefrontal cortex (LPFC) has been causally linked to working memory (WM)—the maintenance and manipulation of task relevant information for short periods of time. Some researchers have described this pattern of activity as persistent firing. One issue that remains unclear, due to traditionally limited numbers of simultaneously recorded neurons, is whether persistent firing has a spatiotemporal structure within populations of LPFC neurons. Here, we hypothesize that precise temporal sequences of individually active neurons enable persistent firing and thus coding of WM in LPFC. We report precisely structured and behaviorally relevant temporal sequences of spiking activity in the LPFC of two macaque monkeys performing a naturalistic WM task in a virtual environment. We implanted two 96-channel Utah microelectrode arrays in each animal (areas 9/46 dorsal and ventral to the principal sulcus). During the task, a target was presented in 1 of 9 locations in a virtual circular arena. The target then disappeared and following a 2 second delay period, subjects navigated to the cued target location using a joystick.
We analyzed responses of 7116 isolated units (median 201 per session). Spiking activity showed clear temporal structure, with short bursts of action potentials occurring in individual units. When ordered by peak firing time, these short bursts formed clear “bands” spanning the duration of the trial. We next sought to understand whether these temporal sequences of bursts were related to memory content, so we developed a novel computational method to analyze spike sequences across trials. This method, which works by representing individual sequences as a complex-valued vector and performing dimensionality reduction on the resulting covariance matrix, allows efficient unsupervised discovery of consistent spike patterns across trials. With this new method, we find that sequence structure, independent from firing rate information, is related to target location in the WM task. Consistent with this, many individual neurons also fired at consistent times during the WM trial. The relation between temporal structure and WM content was less consistent on incorrect trials and following injections of ketamine at subanesthetic doses (0.25-0.8 mg/kg), which disrupts task performance. Taken together, these results reveal a striking spatiotemporal organization of spiking activity during WM in LPFC neuronal ensembles. They also suggest that persistent firing in LPFC has a precise temporal structure that allows neuronal ensembles to robustly maintain and manipulate task relevant information in the absence of sensory inputs.

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Poster

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Topic: H.05. Working Memory

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AARF-17-533294
American Federation for Aging Research/Diamond Postdoctoral Fellowship

Title: Role of calcium-related schizophrenia risk gene CACNA1C in primate dorsolateral prefrontal cortex layer III microcircuits

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[1]Yale Univ., New Haven, CT; [2]Genet., [3]Dept. of Genet., Harvard Med. Sch., Boston, MA; [4]Dept Neurobiol, [5]Yale Univ. Sch. Med., New Haven, CT; [6]Yale Univ. Sch. of Med., New Haven, CT

Abstract: Calcium dysregulation is increasingly linked to cognitive disorders, e.g. calbindin-containing pyramidal cells are most vulnerable to Alzheimer's degeneration, and calcium channels are a focus of genetic insults. Gain of function mutations in the *CACNA1C* gene encoding the l-type calcium channel, Cav1.2, are a risk factor for schizophrenia, and are associated with impaired working memory and reduced connectivity of the dorsolateral prefrontal cortex (dlPFC). However, it is not known why a gain of function mutation in Cav1.2 would impair dlPFC function. The current study examined the localization and function of Cav1.2 in the rhesus monkey dlPFC, and related findings to transcriptome signatures in human dlPFC neurons. Previous studies in monkeys showed that layer III dendritic spines contain the molecular machinery for cAMP to magnify internal calcium release near NMDAR-GluN2B synapses, where moderate levels sustain neuronal firing, but high levels weaken connectivity via opening of nearby K^+ channels. These pyramidal cells also express calbindin when young, but lose it with age. The current study used immunoEM and found extensive labeling of Cav1.2 on dlPFC layer III dendritic spines and shafts. Cav1.2 in spines were predominantly localized on the plasma membrane near glutamatergic synapses, often in association with the smooth endoplasmic reticulum spine apparatus where they may contribute to the magnification of calcium release. These findings were consistent with transcriptomic expression patterns in human dlPFC, where CACNA1C (Cav1.2) expression was highest in the subset of layer II/III pyramidal cells that also express very high levels of GRIN2B (NMDAR-GluN2B) and CALB1 (calbindin), likely needed to regulate high levels of cytosolic calcium. We also examined the physiological effects of Cav1.2 manipulation on dlPFC "Delay cells" in rhesus monkeys performing a working memory task. We found an inverted U dose-response, where either too little or too much Cav1.2 signaling reduced Delay cell firing, and a low dose of the Cav1.2 blocker, diltiazem, enhanced persistent firing, likely by reducing calcium-cAMP-K^+ channel signaling to strengthen connectivity. In sum, these data reveal a population of dlPFC pyramidal cells with extensive calcium signaling essential to persistent

neuronal firing during working memory, but where excessive signaling actually reduces firing. These data help to explain why gain-of-function mutations in *CACNA1C* would be linked to dlPFC cognitive deficits and increased risk of schizophrenia, and why loss of calbindin with age may be especially damaging to this subset of pyramidal cells with high levels of Cav1.2 signaling.

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Poster

P804. Cellular Mechanisms in Working Memory

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Program #/Poster #: P804.06

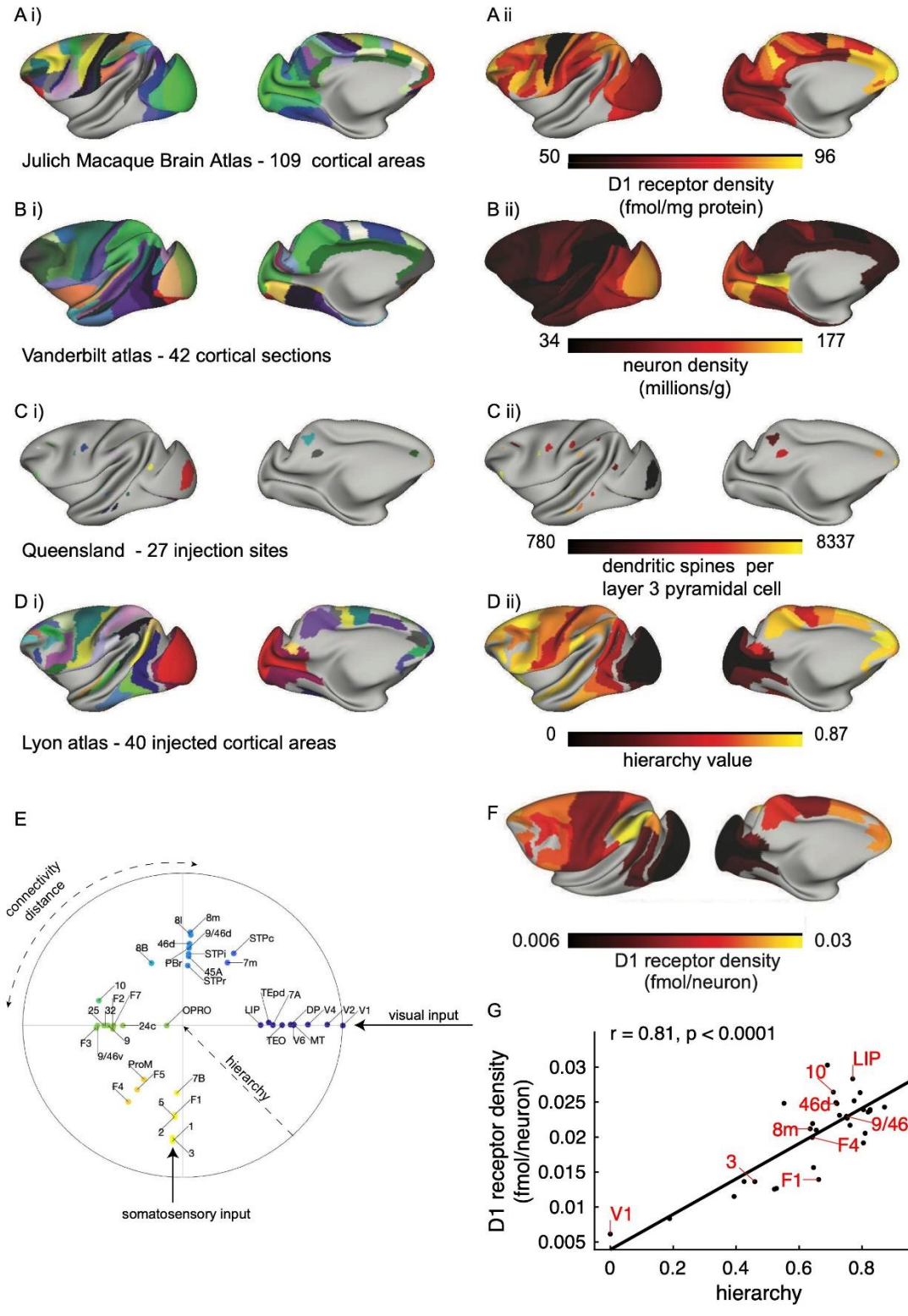
Topic: H.05. Working Memory

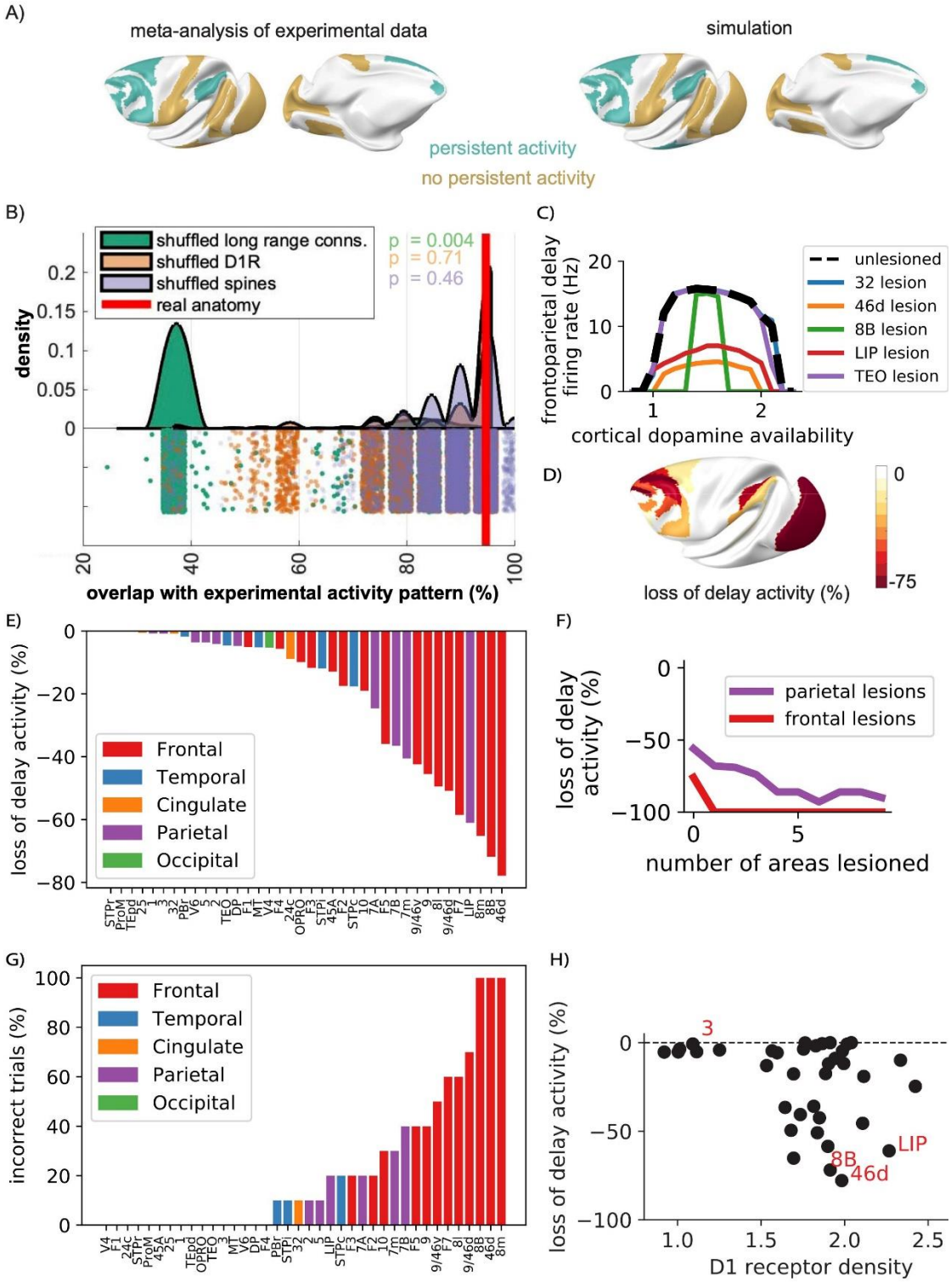
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BMBF Grant 01GQ1902
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EU HBP SGA2 785907
EU HBP SGA3 945539

Title: A dopamine gradient controls access to distributed working memory in large-scale monkey cortex

Authors: *S. FROUDIST-WALSH[1], D. P. BLISS[1], X. DING[1], L. RAPAN[2], M. NIU[2], K. KNOBLAUCH[3], H. KENNEDY[3], N. PALOMERO-GALLAGHER[2], X.-J. WANG[1];
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Abstract: Dopamine is required for working memory, but how it modulates large-scale cortical networks is less known. Here we report that dopamine D1 receptor density per neuron, measured by in-vitro receptor autoradiography, displays a macroscopic gradient that increases along the macaque monkey's cortical hierarchy. This gradient is incorporated in a connectome-based large-scale cortex model endowed with multiple neuron types. The model captures an inverted U-shaped dependence of working memory on cortical D1-receptor stimulation, and spatial patterns of persistent activity observed over 90 experimental studies. Moreover, we show that dopamine is crucial for filtering out irrelevant stimuli by enhancing inhibition from dendrite-targeting calbindin/somatostatin interneurons. Our model revealed that an activity-silent memory trace can be realized by short-term synaptic facilitation of long-range connections, and adjusting dopamine levels in the cortex could induce a switch from the activity-silent state to active persistent activity. Taken together, our work represents a cross-level understanding from molecules and cell types to recurrent circuit dynamics underlying a core cognitive function distributed across the primate cortex.


A i)
Julich Macaque Brain Atlas - 109 cortical areas
A ii
50
96
D1 receptor density
(fmol/mg protein)
B i)
Vanderbilt atlas - 42 cortical sections
B ii)
34
177
neuron density
(millions/g)
C i)
Queensland - 27 injection sites
C ii)
780
8337
dendritic spines per
layer 3 pyramidal cell
D i)
Lyon atlas - 40 injected cortical areas
D ii)
0
0.87
hierarchy value
E
connectivity
distance
visual input
hierarchy
somatosensory input
F
0.006
0.03
D1 receptor density
(fmol/neuron)
G
r = 0.81, p < 0.0001
D1 receptor density
(fmol/neuron)
hierarchy



Disclosures: S. Froudist-Walsh: None. **D.P. Bliss:** None. **X. Ding:** None. **L. Rapan:** None. **M. Niu:** None. **K. Knoblauch:** None. **H. Kennedy:** None. **N. Palomero-Gallagher:** None. **X. Wang:** None.

Poster

P804. Cellular Mechanisms in Working Memory

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Topic: H.05. Working Memory

Support: NIH Grant P50 MH103205
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Title: Interactions between synaptic inhibition and excitatory synaptic drive modulate gamma oscillation frequency in prefrontal and parietal cortex networks

Authors: *G. GONZALEZ-BURGOS[1], T. MIYAMAE[1], N. REDDY[1], S. DAWKINS[1], J. ENWRIGHT[1], C. CHEN[2], A. HILL[3], B. ERMENTROUT[1], D. LEWIS[1];
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Abstract: The primate dorsolateral prefrontal (DLPFC) and posterior parietal (PPC) cortices are high-order nodes in the network of cortical areas mediating working memory (WM). These regions interact functionally during WM tasks and are reciprocally connected by projections from layer 3 pyramidal cells (L3PCs). Functional interactions across the primate cortex depend on superficial layer gamma oscillations (γOs). Hence, L3PC properties that may contribute to γO production are crucial for DLPFC-PPC interactions during WM.
The peak frequency of γOs observed during WM tasks is higher in monkey DLPFC relative to PPC (J Cogn Neurosci 32:2024). Since γOs seem associated with information maintained in WM, and are correlated with spiking activity during various phases of WM tasks, the regional differences in γO frequency and the mechanisms generating these differences may be critical for information processing in WM.
γOs are thought to be generated via rhythmic $GABA_AR$-mediated synaptic inhibition, and γO frequency depends strongly on the properties of inhibitory post-synaptic currents ($GABA_AR$-IPSCs) on L3PCs (Cereb Cortex 25:4076). Moreover, L3PCs show ~2 times greater number of dendritic spines in monkey DLPFC than PPC (J Neurosci 39:7277), suggesting that stronger excitatory drive from local recurrent excitation may provide a substrate for higher γO frequency in DLPFC.
Here, we studied $GABA_AR$-IPSCs using patch clamp recordings from L3PCs in acute slices from macaque monkey DLPFC and PPC. No $GABA_AR$-IPSC properties differed between DLPFC and PPC L3PCs. Moreover, gene expression for $GABA_AR$ subunits known to be localized synaptically did not differ between DLPFC and PPC L3PCs, consistent with the lack of differences in synaptic physiology.
In a subset of the L3PCs in which $GABA_AR$-IPSCs were studied, we quantified dendritic spines in basal dendrites. DLPFC L3PCs exhibited higher dendritic spine numbers, suggesting that while $GABA_AR$-IPSC features are similar, excitatory synaptic drive is stronger in DLPFC.
Finally, using computational simulations, we assessed γO properties in a recurrent network of excitatory (E) and inhibitory neurons in which the strength of excitatory synaptic coupling between E cells was manipulated. Preliminary results suggest that increases in E-E synaptic coupling (primarily the NMDAR-mediated component) promote an increase in γO frequency as the $GABA_AR$-IPSC properties were kept

constant.
Our data suggest that whereas the mechanisms of $GABA_AR$-mediated inhibition are highly conserved between DLPFC and PPC, stronger drive from local recurrent excitation may produce inhibition-based rhythms with higher frequency in the DLPFC network.

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Poster

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Program #/Poster #: P804.08

Topic: H.05. Working Memory

Support: Startup Funds from Vassar College
Grant-in-aid of research from Sigma Xi
Vassar College URSI Program

Title: Chemogenetic manipulation of astrocytes in prelimbic cortex during spatial working memory.

Authors: *L. A. NEWMAN[1], J. BONANNO[3], **J. L. LIN**[2], J. A. D'ORAZIO[2], K. U. TANG[2], H. TANAKA[2], T. ZIMMER[2], S. KUKRETI[4];
[1]Psychological Sci., [2]Vassar Col., Poughkeepsie, NY; [3]Yale Univ., New Haven, CT; [4]Spackenkill High Sch., Poughkeepsie, NY

Abstract: Astrocytes are glial cells within the brain that modify blood flow, energy production, neurotransmitter levels and ionic balance. All of these functions influence synaptic plasticity, a critical component of memory. However the specific role of astrocytes in memory is still being characterized. Our study focuses on the relationship between astrocyte activity and spatial working memory. We employed a chemogenetic technique (Designer Receptors Exclusively Activated by Designer Drugs, or DREADDs) to activate astrocytes in the prelimbic cortex of rats during a delayed spontaneous alternation task. Bilateral injections of either hM3D(Gq)-mCherry with a GFAP promoter or an GFAP-eGFP control virus (AAV, serotype 5) were given into the prelimbic cortex of Long Evans male and female rats. After 2 weeks to allow for viral expression, rats underwent delayed spontaneous alternation testing in which they received intraperitoneal injections of either the corresponding hM3D(Gq) receptor agonist, Compound 21 (C21), or the vehicle 30 minutes before delayed spontaneous alternation testing in a counterbalanced order. Extra-maze cues were changed to provide novel stimuli for each testing session. Preliminary results unexpectedly showed 3 mg/kg of C21 significantly inhibited the number of arm entries made as compared to 1 mg/kg of C21. With the 1 mg/kg dose of C21 there is an interaction of sex and DREADDs activation on spatial working memory such that males showed improvements and females showed impairments when astrocytes are activated. Morphological characterization of the astrocytes and GFAP staining suggest possible astrocytic sex differences in this study. Our research indicates astrocytes play an integral role in memory processes in the prefrontal cortex and are a novel target for treatment in neurodegenerative diseases.

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Poster

P804. Cellular Mechanisms in Working Memory

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P804.09

Topic: H.05. Working Memory

Title: Synaptic correlates of working memory: spectral DCM study with MEG data

Authors: *A. SANTO-ANGLES, K. K. SREENIVASAN;
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Abstract: Working memory (WM) has been largely associated with persistent neural activity in prefrontal circuits. A key question is how different neural populations within these circuits contribute to meso- and macro-level WM activity and how changes in these populations drive behavior. Biophysical models and monkey single-unit studies continue to shed light on these questions, but it is unclear the degree to which these findings translate to humans. Here, we used dynamic causal modelling (DCM) of MEG data to infer prefrontal synaptic changes supporting WM in humans. Subjects (n = 26) performed a delayed continuous report task. Behavioral responses were fitted with a 3-component mixture model to classify individual responses into one of three trial types: accurate, inaccurate, and swap (i.e., transposition) error. We observed greater synchronization in theta and low alpha in accurate compared to inaccurate and swap trials. Source reconstruction of the MEG signal identified a prefrontal source in superior frontal gyrus whose 12-Hz activity significantly varied as a function of trial type; this source was subsequently used to fit a spectral DCM with a canonical microcircuit model. Subject- and trial-specific DCMs were inverted using the grand-averaged DCM parameters as priors. Model estimates were evaluated using Parametric Empirical Bayes (PEB). In accord with biophysical circuit models of WM as well as recent investigations into layer-dependent activity in humans and monkeys, we found that activity during the WM delay for accurate trials was associated with (i) increased excitability of superficial pyramidal cells and (ii) decreased excitability of inhibitory interneurons. Additionally, these trials also exhibited (iii) reduced coupling strength from inhibitory interneurons to spiny stellate cells, and (iv) reduced coupling from superficial to deep pyramidal cells. Critically, the DCMs differed for inaccurate and swap error trials. Although both types of error trials displayed increased excitability of superficial pyramidal cells, as in accurate trials, the reduction of excitability in inhibitory interneurons was notably weaker in inaccurate trials, while swap error trials exhibited increased, rather than reduced, coupling from superficial to deep pyramidal cells. These results indicate that, despite similar oscillatory profiles, inaccurate responses and swap errors arise from distinct neurobiological substrates. Importantly, this work also demonstrates the feasibility of DCM approaches to measure synaptic-level modulations in humans.

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Poster

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Program #/Poster #: P804.10

Topic: H.05. Working Memory

Support: Project F1051

Title: Complementary roles of AMPA and NMDA receptors in a connectome-based model of conscious access in monkey cortex

Authors: *U. KLATZMANN[1], S. FROUDIST-WALSH[2], D. BLISS[4], P. THEODONI[3], J. MEJIAS[5], M. NIU[6], L. RAPAN[6], N. PALOMERO-GALLAGHER[7], C. SERGENT[8], S. DEHAENE[9], X.-J. WANG[2]; [1]New York Univ., Paris, France; [3]Ctr. for Neural Sci., [2]New York Univ., New York, NY; [4]Ctr. for Neural Sci., NYU, New York, NY; [5]Univ. of Amsterdam, Amsterdam, Netherlands; [6]Res. Ctr. Jülich, Jülich, Germany; [7]Res. Ctr. Juelich, INM-1, Juelich, Germany; [8]Univ. de Paris, Paris, France; [9]INSERM-CEA, GIF/YVETTE, France

Abstract: When consciously perceived, a stimulus triggers a sudden non-linear bifurcation event across multiple cortex areas called 'ignition.' In contrast, the same stimulus might only drive transient linear activity largely restrained to sensory areas when not detected. Computational models of ignition have mainly focused on local cortical regions, neglecting the large-scale nature of the phenomenon. In contrast, large-scale models of the cortex have failed to produce critical aspects of ignition, such as its rapid non-linear increase in activity and strong, sustained stimulus-related activity throughout the cortex. Here, we develop a large-scale model of the macaque cortex and show how feedforward connections targeting excitatory populations with fast AMPA receptors and feedback connections targeting essentially inhibitory populations with slow NMDA receptors play an essential role in signal propagation from sensory to associative areas; while preventing sustained activity in sensory areas. Our model predicts, counterintuitively, that fast responding sensory areas contain a higher ratio of NMDA to AMPA receptors compared to higher cortical areas that show slow, sustained activity. We validate this prediction using in-vitro receptor autoradiography data. Finally, we show how this model can account for various behavioral and physiological effects linked to consciousness. Together, these findings help us understand how a large-scale network of the cortex can exhibit bifurcation ignition-like events and how gradients of receptor densities along the cortical hierarchy contribute to such higher cognitive functions.

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Poster

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Program #/Poster #: P804.11

Topic: H.05. Working Memory

Support: NIDA R00DA042934
NIA R00DA042934-03S1
NIGMS T34GM127154

Title: The effects of sex on working memory in Fischer F344 rats

Authors: *T. GOHAR[1], S. DUNN[2], E. A. WEST[3];
[1]Rowan Univ. Sch. of Osteo. Med., Stratford, NJ; [3]Cell Biol. and Neurosci., [2]Rowan Sch. of Osteo. Med., Stratford, NJ

Abstract: Working memory is the online retention of a small amount of information that helps to guide behavior during a cognitive task. Working memory depends on the hippocampus and its functional connection with the prefrontal cortex. Some studies have reported sex differences in working memory while others suggest no sex difference exists during working memory performance tasks. Patients with early-stage Alzheimer's disease (AD) show impaired working memory. Critically, sex differences have been observed in the prevalence of AD and the rate of cognitive decline. Specifically, women with AD experience a faster cognitive decline compared to men. Addressing underlying sex differences is therefore critical for the development of effective therapeutics. Here, we tested working memory in male (n=8) and female (n=8) Fischer F344 rats using a delayed nonmatch to position (DNMTP) task. The DNMTP task consisted of 3 phases; sample, delay, and choice phase. During the sample phase, the house light was illuminated and one of two levers (e.g. right) extended into the chamber. The rats were required to press the lever for a reward, which then initiated the delay phase. During the delay, all lights extinguished and the levers retracted. After the delay, the house light illuminated and the rats were required to nosepoke to initiate the choice phase. During the choice phase, both levers extended and the rats were required to press the opposite lever (i.e., nonmatch) from the sample phase (e.g., left) to obtain a reward. After training the rats, both the sexes were tested for 3 DNMTP sessions each employing 4 different delays (2-32 seconds) intermixed pseudorandomly with 15 trials/delay. Session 1 consisted of shorter delays, session 2 had relatively longer delays and session 3 had the longest delays. Any trial for which the rat did not press lever during the choice phase was recorded as an omission. The percent correct for each sex was calculated (i) for choice-only trials and (ii) for all trials including the omissions. A two-way repeated-measures ANOVA with sex and delay as factors showed no significant difference in percent correct between male and female rats during the choice-only trials for any of the three sessions. However, when percent correct was obtained from all the trials including the omissions, a significant difference was found during session 1 ($F(1, 14)=8.32$, $p=0.012$). Specifically, females performed better during session 1 but no sex difference was observed later during sessions 2 and 3. Our future aim is to investigate working memory impairments in transgenic rats (TgF344-AD) on this Fischer 344 background strain that is developed to recapitulate AD pathology in both sexes.

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Poster

P841. Place Cells IV

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P841.01

Topic: H.09. Spatial Navigation

Support: Biotechnology and Biological Sciences Research Council scholarship (BB/M009513/1)
European Research Council starter grant (CHIME)
Human Frontiers Science Program Young Investigator Award (RGY0067/2016)
Biotechnology and Biological Sciences Research Council Research grant (BB/T005475/1)
NVIDIA Corporation

Title: Replay detection methods- How can we tell which one is best without a ground truth?

Authors: M. TAKIGAWA[1], M. HUELIN GORRIZ[2], M. TIROLE[3], Y. QIAN[1], ***D. BENDOR**[1]; [1]Univ. Col. London, London, United Kingdom; [2]Inst. of Behavioural Neurosci., Univ. Col. of London, London, United Kingdom; [3]UCL, London, United Kingdom

Abstract: Since the discovery of hippocampal replay almost 30 years ago, replay detection methods have gradually become more advanced and sophisticated. All of these approaches measure the statistical significance of the match between a behaviourally-related template and a replayed sequence, however one important caveat is that these methods operate without a ground truth. For this reason, it is challenging to compare replay detection methods, as while one method may detect more statistically significant events, we do not know if it is "better" as the proportion of false positives may have also increased. Here we present a new framework for addressing this problem, relying on hippocampal recordings from rats exploring two different novel linear tracks. We propose that "true events" should have a match between sequence-based and sequenceless decoding methods (i.e. the track with the significant trajectory is also the track with the larger proportion of posterior probability). Using this framework we can quantitatively compare the detection performance of different replay analysis methods and determine if one approach is indeed better than the rest.

Disclosures: M. Takigawa: None. **M. Huelin Gorriz:** None. **M. Tirole:** None. **Y. Qian:** None. **D. Bendor:** None.

Poster

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Topic: H.09. Spatial Navigation

Support: Biotechnology and Biological Sciences Research Council scholarship (BB/M009513/1)
- European Research Council starter grant (CHIME)
Human Frontiers Science Program Young Investigator Award (RGY0067/2016)
Biotechnology and Biological Sciences Research Council Research grant (BB/T005475/1)
NVIDIA Corporation

Title: Experience-driven rate modulation is reinstated during hippocampal replay

Authors: *M. TIROLE[1], M. HUELIN GORRIZ[2], M. TAKIGAWA[3], L. S. KUKOVSKA[4], D. A. BENDOR[4];
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Abstract: Replay, the sequential reactivation of a neuronal ensemble, is thought to play a central role in the hippocampus during the consolidation of a recent experience into a long-term memory. Following a contextual change (e.g. entering a novel environment), hippocampal place cells typically modulate their in-field firing rate and shift the position of their place field, providing a rate and place representation for the behavioral episode, respectively. However, replay has been largely defined by only the latter- based on the fidelity of sequential activity across neighboring place fields. Here we show that dorsal CA1 place cells in rats can modulate their firing rate between the replay of two different contexts, mirroring the same pattern of rate modulation observed during behavior. This context-driven rate modulation within replay events was experience-dependent, observable during both behavioral episodes and throughout the subsequent rest period, but not prior to experience. Furthermore, we demonstrate that both the temporal order and firing rate of place cells can independently be used to decode contextual information within a replay event, revealing the existence of two separable but complementary neural representations available for memory consolidation processes.

Disclosures: M. Tirole: None. **M. Huelin Gorriz:** None. **M. Takigawa:** None. **L.S. Kukovska:** None. **D.A. Bendor:** None.

Poster

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Program #/Poster #: P841.03

Topic: H.09. Spatial Navigation

Support: NIH grant NS113557

Title: Replay fields -- single cell measures of tuning to imagined position during replay.

Authors: *J. WIDLOSKI, M. R. KLEINMAN, D. J. FOSTER;
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Abstract: Hippocampal cells show precise spatial tuning to the animal's position during behavior. During stopping periods, the hippocampus encodes spatially coherent trajectories through the environment called replays that resemble the animal's behavior. Replay has been proposed as a form of virtual experience that supplements real experience for the purposes of learning and planning. However, it is unknown whether the precise spatial tuning of place cells as a function of animal position is preserved as a function of encoded replay position, independent of the animal's location. This is far from obvious, given that replay unfolds at much higher speeds and is likely to involve different mechanisms and circuits. We show that in a 2D environment, spatial tuning is preserved as a function of the encoded position during replay (its

"replay field"), using a leave-one-out analysis that removes the cell's contribution to replay before evaluating its replay field. Replay fields are shown to match place fields on both coarse- and fine-grained measures, including spatial information, field shape and skewness, as well as in the relative positions and peak rates of the primary and secondary fields. Crucially, however, we show that replay fields do not exhibit the overdispersion or excess temporal variance of spiking that is characteristic of place fields, suggesting that firing patterns during replay are well predicted by a spatial, inhomogeneous Poisson process and therefore less subject to covert shifts in attention and context as during behavior. Lastly, we show that similarity between place fields and replay fields is increased if we relax the requirement that replays form smooth trajectories and instead include all spatially coherent activity during stopping periods (encompassing approximately half of all spikes emitted during such periods), demonstrating that tuning to encoded position is a persistent feature not just restricted to times during traditionally-defined replay.

Disclosures: J. Widloski: None. **M.R. Kleinman:** None. **D.J. Foster:** None.

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P841. Place Cells IV

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Program #/Poster #: P841.04

Topic: H.09. Spatial Navigation

Support: Charles H. Revson Senior Fellowship in Biomedical Science
NIH U19NS104590

Title: Offline Memory Reactivation Predicts the Consolidation Of Spatially Unbiased Long-Term Cognitive Maps

Authors: *A. GROSMARK[1], F. T. SPARKS[2], M. J. DAVIS[4], A. LOSONCZY[3];
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Abstract: Spatial memories which can last a lifetime are thought to be encoded during ‘online’ periods of exploration and subsequently consolidated into stable cognitive maps through their ‘offline’ reactivation. However, the mechanisms and computational principles by which offline reactivation stabilize long-lasting spatial representations remain poorly understood. Here we employed simultaneous fast calcium imaging and electrophysiology to track hippocampal place cells over two weeks of online spatial reward learning behavior and offline resting. Here, we describe that recruitment to persistent network-level offline reactivation of spatial experiences in mice predicts place cells’ future representational stability days in advance of their online reinstatement. Moreover, while representations of reward-adjacent locations are generally more stable across days, offline-reactivation related stability is, conversely, most prominent for reward-distal locations. Thus, while occurring on the tens-of-milliseconds time-scale, offline reactivation is uniquely associated with the stability of multi-day representations which counter-balance the overall reward-adjacency bias, thereby predicting the stabilization of cognitive maps which comprehensively reflect entire underlying spatial contexts. These findings suggest that post-learning

offline-related memory consolidation plays a complimentary and computationally distinct role in learning as compared to online encoding.

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Poster

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Program #/Poster #: P841.05

Topic: H.08. Learning and Memory

Support: KU Leuven C1 grant C14/17/042

Title: A dynamic shift in hippocampal replay length and focus follows spatial reversal learning in rats

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Abstract: Spatial reversal learning depends on the ability to select behavioral strategies, to learn which behavior is rewarding, and to flexibly change one's behavior as a response to changing reward contingencies. Both the hippocampal long-term memory system and the prefrontal executive system have been shown to contribute to spatial reversal learning.
Reactivation of task-specific neural activity patterns (replay) is thought to be an important neural mechanism to support such flexible behavior. In the hippocampus, reactivation of place cell sequences occurs predominantly during fast, transient "sharp-wave ripple" oscillations. Sharp-wave ripple associated replay is thought to be crucial for spatial navigation and planning when it occurs during awake exploration, and for memory consolidation when it occurs during sleep.
It is still unclear, however, in what way reactivation patterns during sharp-wave ripples differ between awake, rest and sleep periods; how replay properties change as a function of learning and how this affects the interaction between the hippocampus and the medial prefrontal cortex.
Adult Long Evans rats were trained on a plus-shaped maze to follow allocentric or cue-based rules to obtain food reward. An array of tetrodes was implanted in the hippocampus and medial prefrontal cortex to monitor cellular activity and field potentials while the rats were learning and executing the task, as well as during inter-trial intervals and post-task sleep.
Reactivation of spatial locations and trajectories was observed during sharp-wave ripple activity in the hippocampus. As the animals learned spatial rules on the maze, the replay trajectories in the hippocampus became shorter in length, and there was a stronger reactivation of the end platform where the animals found a reward. The medial prefrontal cortex field potential activity peaked following ripples that contain a strong reactivation of the end platform, especially when the rule had been learnt.
Together, these findings suggest that hippocampal activity and its interplay with the medial prefrontal cortex in spatial reversal learning depends strongly on behavioral performance and that memory consolidation may favor either the entire maze or rather focus on the reward sites, depending on the stage of learning.

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Poster

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Program #/Poster #: P841.06

Topic: H.08. Learning and Memory

Support: Restracomp award to AMPM
Research Institute Exceptional Trainee Award Fund Bursary to AMPM
CIHR Foundation grant to PWF

Title: Cumulative learning via the integration of related experiences

Authors: *A. M. P. MILLER[1], A. D. JACOB[2], A. I. RAMSARAN[4], T. ZHANG[1], M. L. DE SNOO[3], S. A. JOSSELYN[5], P. W. FRANKLAND[6];
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Abstract: Mice and other animals learn about their environments by integrating information across many experiences. Although the hippocampus supports many forms of learning, its role in memory integration is less understood, including how it determines which experiences to integrate. We hypothesized that mice selectively retrieve memories that facilitate learning, thereby promoting the integration of new information into the retrieved memory trace. To test this, we trained mice on a series of tone discrimination problems whereby mice learn to wait longer in response to a rewarded tone than to an unrewarded tone. The problems were interleaved with probe tests to observe how mice responded to tones across their entire auditory range, and to see how their responses changed after each problem. Mice undergoing 'integration' training, where similar frequencies were used for the rewarded tones in every problem, showed improved discrimination performance and more rapid learning on later problems, while mice undergoing 'non-integration' training showed no improvement. The responses on the probe tests supported the idea that the integration group formed a single memory combining information from all problems, while the non-integration group formed distinct memories of each problem. Additionally, probe responses predicted future performance on novel problems: if mice already preferred the soon-to-be rewarded tone during the preceding probe test, then they learned the problem faster during subsequent training. Furthermore, mice updated their memory less (i.e. similar probe responses before and after learning) if they already preferred the soon-to-be rewarded tone. Calcium imaging of hippocampal CA1 neurons throughout training revealed that memory integration was accompanied by the reactivation of ensembles and activity patterns associated with prior problems. In the integration group, the roster of active neurons changed from session to session early in learning before stabilizing with the repeated reactivation of overlapping ensembles, while no such shift was observed in the non-integration group. Similarly, we saw that individual hippocampal neurons were active at reliable times during individual trials, and that the pattern of activity across all neurons was stable between later training sessions in the integration group but not in the non-integration group. Together, these results suggest that memory

retrieval and the associated reactivation of hippocampal activity states during learning supports the integration of new information into pre-existing memories.

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Poster

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Topic: H.08. Learning and Memory

Support: U19NS104590
Lundbeck Foundation

Title: Hippocampal GABAergic cell type selectively controlling local and extra-hippocampal interneurons during sharp-wave ripples

Authors: *G. G. SZABO[1], B. DUDOK[1], W.-H. HOU[2], J. S. FARRELL[1], A. ORTIZ[1], C. VARGA[3], P. MOOLCHAND[1], C. I. GULSEVER[1], T. GSCHWIND[1], G. J. FISHELL[4], M. CAPOGNA[2], I. SOLTESZ[1]; [1]Dept. of Neurosurg., Stanford Univ., Stanford, CA; [2]Univ. of Aarhus, Aarhus, Denmark; [3]Univ. of Pecs, Pecs, Hungary; [4]Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Sharp wave-ripples (SPW-Rs) are short, synchronous population patterns critically involved in learning and memory. Distinct interneuron classes exhibit diverse behaviors during these events including interneurons becoming silent during SPW-Rs. Sources of inhibition silencing these neurons in a SPW-R-timed manner is unknown. Here we identify and characterize in behaving mice a GABAergic cell population that is dedicated to deliver inhibition shortly before and during SPW-Rs and provides selective control over certain hippocampal interneuron subtypes including parvalbumin- and cholecystokinin expressing cells. Unlike other GABAergic neurons, these cells reduce their firing frequency during running, likely due to a combination of septo-hippocampal GABAergic inputs and activation of inhibitory cholinergic receptors. The unique behavior of such cells (i.e. SPW-R entrainment and suppression during theta) remains unchanged across brain states. In addition, these cells broadcast inhibition beyond the hippocampus, forming a substantial fraction of long-range GABAergic projections originating from the CA1. Our findings suggest an important role of GABAergic disinhibition in shaping SPW-R related network functions. Funded by the NINDS (grant U19NS104590 to I.S.) and by the Lundbeck Foundation (to M.C. and I.S.).

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Poster

P841. Place Cells IV

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Program #/Poster #: P841.08

Topic: H.08. Learning and Memory

Title: Differential memory consolidation features of localized and global neocortical spindle oscillations in rats

Authors: *O. RAUHALA[1], ***O. RAUHALA**[1], P. DAHAL[1], J. GELINAS[3], D. KHODAGHOLY[2]; [2]Electrical Engin., [1]Columbia Univ., New York, NY; [3]Columbia Univ. Med. Ctr., New York, NY

Abstract: Memory consolidation depends on synaptic plasticity and changing strength between neuronal connections. Spatiotemporal memory encoding for example, is hippocampus-dependent. The mechanism involves local labile memory traces in the hippocampus being transferred to long-term neocortical storage in quiescence and non-REM sleep by hippocampal sharp-wave ripple (SWR) oscillations. However, many types of memories are also consolidated without the hippocampus playing a causal role such as object recognition and motor skills. The mechanisms for non-hippocampal memory encoding are more varied and less defined. However, sleep may play an important role in some aspects of non-hippocampal learning as well. In this work, we explore the neocortical activation patterns and SWR dynamics during non-REM sleep after spatial navigation, object recognition and spatially-cued object recognition in rats. We focus specifically on spindle oscillations, which have been implicated in memory processes and can occur both independently or exhibit strong coupling to SWRs. This feature makes the spindle a good target for investigating the dynamics in non-hippocampal and hippocampal-dependent memory. Each of our rats is trained on the three tasks in sequence to allow us intrasubject comparison between the modes of learning. We record from the whole dorsal surface of one cerebral hemisphere using a high-resolution multi-channel ECoG array (NeuroGrid), and from the medial prefrontal cortex and the hippocampus using silicon probes. We then detect spindles and SWRs from sleep recordings before and after learning and evaluate the spatial patterns of spindles, the dynamic coupling between SWRs and spindles and how these vary across our behavioral protocol. We find that a spindle event can occur simultaneously in all brain regions covered by our ECoG array (global spindle) or be restricted to a local region (local spindle) and that SWRs show stronger coupling to global spindles. Our investigation finally addresses how this phenomenon varies across behavioral tasks and how it is related to task performance.

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Poster

P843. Hippocampal Network Properties and Cognition

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Program #/Poster #: P843.01

Topic: H.08. Learning and Memory

Support: NIH Grant R01NS110806-01A1

NIH Grant R01MH106552
NIH Grant R01MH112523

Title: Hippocampal and cortical theta-oscillons in wake rats

Authors: *Y. DABAGHIAN[1], M. S. ZOBAER[2], D. JI[3], L. PEROTTI[4], C. DOMENICO[3];
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Abstract: Hippocampal and cortical θ-oscillons in wake rats
Zobaer, M. S[1]., Domenico, C. M. [2], Perotti, L. [3], Ji, D. [2], Dabaghian, Y.[1]
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Extracellular Local Field Potentials (LFP) play a key role in organizing and synchronizing neuronal activity across the brain. However, a detailed understanding of the LFPs functions depends on our interpretation and explication of their structure: it matters, e.g., whether the basic constituents of the signal are mathematically formal, indirect or whether they reflect the actual organization of the underlying circuit dynamics. We study the LFP oscillations using a recently developed adaptive technique that may capture the physical architecture of synchronous oscillations in neuronal ensembles. This approach reveals new level of organization of the brain rhythms—a small number of discrete, phase-modulated waves processes—the *oscillons*—embedded in a weak noise background. In this study, we focus on the lowest-frequency oscillons that correspond to the traditional hippocampal and cortical θ-waves, and analyze their dynamics during active and quiescent behaviors of male rats. We find that the dynamics of the θ-oscillons is characterized not only by the changes of their amplitudes but also by overt frequency modulations. In particular, we find that both the mean frequency and the embedded frequencies are coupled to the animals' speed and acceleration. These results expand and refine a number of previously observed relationships between the traditionally defined θ-wave and the animal's physiological state and provide a number of qualitatively novel observations that pertain specifically to θ-oscillons. Importantly, our results dovetail with several theoretical models that explain the emergence of θ-rhythms from neuronal synchronization, thus providing a direct link between modeling and experiment.
1

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Poster

P843. Hippocampal Network Properties and Cognition

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Topic: H.09. Spatial Navigation

Support: NIH 1U01MH115746

Jessamine K. Hilliard Neurobiology Graduate Student Award (UCLA)

Title: Rodent hippocampus encodes angle and distance of a simple visual cue.

Authors: *C. PURANDARE[1], S. DHINGRA[2], R. RIOS[3], C. VUONG[4], T. TO[2], A. HACHISUKA[3], K. CHOUDHARY[5], M. R. MEHTA[6];
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Abstract: Rodent hippocampus is believed to be critically involved in generating a cognitive map of allocentric space, using neurons firing in localized regions of space, a.k.a. place cells. Such abstract responses are thought to require both distal visual cues and self-motion cues and are prospective in nature. In primates, however, hippocampal neurons encode object-place association without any locomotion requirement, and such visual sensory responses are typically retrospective in nature. Previous studies have suggested that spatial selectivity depends crucially on self-motion while change in the visual cues causes remapping. The precise contribution of vision and locomotion to these processes are unknown. Hence, we manipulated these variables independently. To dissect the contributions of these different variables on hippocampal spatial selectivity, we have recently developed a virtual reality apparatus. Here, the rat runs on a spherical treadmill that floated freely on an acoustically quiet air cushion, to receive liquid rewards through a tube in front of the rat. Our VR system employs a hinged harness that gently body-fixes the rats but allows for head movements around body. In prior work, we have shown that the distal visual cues in the VR causally control direction selectivity in hippocampal neurons from region CA1 (1). Here, we investigated the selectivity of hippocampal neurons with respect to a simple bar of light in the VR apparatus. We find that nearly 40% of CA1 pyramidal neurons showed significant angular tuning to the position of the bar of light. The angular position of the bar could be decoded from only a few hundred neurons' activity. This selectivity was further invariant with respect to the pattern and color of the bar. Similar to the angular representation, hippocampal neurons also encoded the distance from the bar of light. These experiments further allowed us to compute the differential contribution of visual cues, different types of behaviors and experience on neural selectivity and stability. We posit that these responses would influence the cortico-hippocampal circuit and form the basis for generating place cells.
1. Acharya et al, (2016), Cell 164, 197-207

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Poster

P843. Hippocampal Network Properties and Cognition

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Program #/Poster #: P843.03

Topic: H.09. Spatial Navigation

Support: NIH/NINDS, R01 NS10110803

Title: Disrupted phase coding, remapping, and sharp-wave ripple generation in a rat model of traumatic brain injury

Authors: *C. ADAM[1], C. COTTONE[1], K. GAGNON[1], V. JOHNSON[1], J. WOLF[1,2];
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Abstract: Cognitive deficits, including learning and memory impairments, are commonly reported following TBI, and hippocampal dysfunction is often linked with these deficiencies. TBI-associated cognitive deficits can be present even in the absence of overt cell loss in the hippocampus, suggesting functional impairments of hippocampal circuits following even mild TBI. In order to investigate the physiological mechanisms underlying these functional impairments, we subjected rats to a lateral fluid percussion injury of 1.8 atmospheres (resulting in a mild impairment in the Morris Water Maze without overt hippocampal cell loss) then implanted them with high-density, laminar probes in the dorsal CA1 region of the hippocampus. Electrophysiological recordings were obtained one-week post-injury while rats explored a familiar and novel environment. In injured rats, we found that a greater percentage of cells were active in both the familiar and novel environment compared to sham-injured animals, and that cells active in both environments had firing rates that were strongly correlated between environments in injured but not sham animals. This suggests that TBI rats have a deficit in remapping, an important mechanism for pattern separation processes that allow the hippocampus to create and store distinct representations of different contexts. In addition to these population and rate coding deficits, we found that TBI rats had a decrease in theta and gamma power along the apical dendritic arbor of CA1 and a large decrease in theta-gamma phase-amplitude-coupling where CA3 and entorhinal inputs synapse. Reduced gamma power and coupling to theta was localized in a frequency-band specific manner with low gamma power and coupling losses localized to stratum radiatum where CA3 inputs synapse, and mid gamma power and coupling losses localized to stratum lacunosum moleculare where entorhinal inputs synapse. Additionally, there was a substantial decrease in the strength of entrainment of CA1 interneurons to theta in injured rats, which provides a potential mechanism for the decrease in power and coupling. Lastly, TBI rats had fewer and shorter sharp-wave ripples (SWRs) compared to sham rats which suggests a deficit in memory consolidation mechanisms. Sharp-wave amplitudes increased when rats were in the novel environment, but this increase was less pronounced in injured rats suggesting a loss of CA3 input. Ripples in TBI rats had a larger fast ripple index and entropy which is indicative of potential epileptogenic activity. Overall, TBI rats showed deficits in remapping, phase-coding, and SWR generation all of which are capable of impairing cognition post-TBI.

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Poster

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Title: Attractor network theories of mammal spatially-responsive neurons in one, two, and three dimensions

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Abstract: Attractors, and their use as a theoretical model of neuronal spatial encoding, have been one of the most influential ideas in the field of spatial cognition. Attractor-based theoretical models of spatially responsive cells have allowed researchers to explain a number of mysterious phenomena and make sense of behavioral semantics of neuronal activity. Yet, the theory of attractor brain dynamics is not generally accepted today as the mechanism of place cell (PC), grid cell, and head direction (HD) cell phenomena. Spatially responsive cells are known to model the environment geometry, but the question is whether this property follows from attractor dynamics or from learning in deep networks driven by perceived or imagined sensory input, without attractors involved. Moreover, the concept of an attractor seems incompatible with realistic brain conditions and is understood differently by different scholars. Here we use the definition of an attractor given by Strogatz (1994, p.324) for describing continuous attractors, in which every element is an irrelevant equilibrium. This mathematical abstraction applied to the mammal brain translates to a quasi-continuous attractor (Samsonovich & McNaughton, 1997). Because brain networks cannot be considered isolated from external inputs and noise and in addition are plastic, attractor dynamics in them are hard to prove. Nevertheless, we argue that it is possible, after a refinement of the notion of an attractor. Here we present our analysis of previously documented experimental data that support continuous attractor hypotheses for a number of brain systems, including HD cells and PCs. We argue for the cases of 1D and 2D attractors in rodents and bats and then consider their possible extension to three dimensions. The HD system has a 1D attractor, and the PC attractor is 2D; support of the attractor hypothesis includes the persistence of the internal state of the system at a time when sensory input is absent, such as during sleep. Extending the topology of these attractors during 3D navigation is nontrivial. The grid cell pattern becomes irregular in 3D (Grieves et al., Nat. Neurosci., 2021 in press). This is reportedly true not only for rodents, but also for bats. Furthermore, observations of angular correlates and "forbidden" states in cell pairs at a millisecond time scale suggest that the mechanism is intrinsic to the network. Observed 3D properties of the 1D and 2D attractors further support this conclusion. While there is no evidence for 3D attractors, we investigate the properties and constraints of such systems too, evaluate the consequences for spatial encoding, and suggest experimental paradigms for validation of our findings.

Disclosures: K.J. Jeffery: None. **A.V. Samsonovich:** None.

Poster

P843. Hippocampal Network Properties and Cognition

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P843.05

Topic: H.09. Spatial Navigation

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Title: Hippocampal encoding of positions of static visual objects

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Abstract: The hippocampus is a key structure for processing spatial information including the discrimination of the location of objects in space. We combined single-unit electrophysiological recordings in rats with an operant behavior task using visual stimuli presentation to decipher neural mechanisms involved in the encoding of positions of visual objects. Our unconventional experimental design provided us with the possibility to study the discrimination of positions of visual objects located in a part of an environment that is not accessible to the animal. This is a crucial advantage of the present behavioral task as it prevents the rats from associating their position with the object at that location. We trained rats to press a lever for food reward when an object displayed on a distant computer screen was at particular reward positions and not to press it when the object was at other positions. Once a rat reached asymptotic performance, we implanted an array of tetrodes and recorded the activity of dorsal hippocampal CA1 neurons during the task. For each individual principal cell, a general linear mixed model was calculated with the firing rate (spikes/100-ms bin) as the outcome variable. The fixed factors were behavioral and task-related variables (object's position, lever presses, time from the onset of the stimulus, etc.). Preliminary analysis showed that the firing rate of hippocampal neurons can be influenced by particular positions of a visual object in our discrimination task. These data suggest that hippocampal neurons encode the positions of visual objects.

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Poster

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Program #/Poster #: P843.06

Topic: H.09. Spatial Navigation

Support: 1R15 AG060461-(01)

Title: Novel application of nonlinear modeling algorithms on juvenile hippocampal local field potentials recorded during maze exploration

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Abstract: Juvenile and mature animals encode spatial memories differently. Prior to maturation of learning systems in the brain, young animals form memories, but they become rapidly irretrievable). Work from our laboratory implicates alterations in AMPA receptors in the switch from juvenile to mature memory formation. A shift in the AMPA receptor composition at hippocampal synapses facilitates the induction of activity-dependent synaptic plasticity in the older animals permitting mature behavior in spatial mazes. The observation that a positive modulator of AMPA receptors (such as CX614), promotes more mature synaptic plasticity and spatial behavior in younger animals reinforces the causal nature of AMPA receptor composition on hippocampal integrity. Recently, we addressed network operations and showed that peak frequency of slow gamma oscillations remained constant throughout the age range of P18-P24 while peak frequency decreased with age. CX614 application impacted slow (25-55 Hz) and fast gamma (65-100 Hz) differently at different ages, decreasing slow gamma event rate in older animals and increasing fast gamma power in younger animals. Both slow and fast gamma have been implicated in spatial memory retrieval and performance on spatial navigation tasks in adult animals. Our work begins to shed light on the function of gamma oscillations on network activity and spatial cognition in juveniles. However, due to the nature of frequency analyses, the exact underlying temporal dynamics of these oscillations are not well understood. To account for this, we analyzed the previously recorded local field potentials (LFPs) with a novel method, Diffusion Mapped Delay Coordinates (DMDC). DMDC operates under the assumption that each temporal measurement is a sample of a dynamic manifold, and attempts to analyze the overall minimum dimensionality and volume. DMDC is being used to model nonlinear and dynamic physical systems, but has yet to be applied to neurological signals. We will compare our results in DMDC to previous data on gamma rhythms during Y-maze navigation, with the prediction that differences in the temporal dynamics of gamma rhythms will be detected in DMDC. We expect differences to increase as our filters approach gamma ranges. Current results comparing alternation trials in the Y-maze show significant differences in the dimensionality of the signal between P17-18 and P23-24 animals as well as between control and drug conditions. Thus, we have shown that DMDC may be a valuable tool in relating dynamics of brain oscillations to cognitive states.

Disclosures: D.A. Gonzalez: None. **J.H. Peel:** None. **T. Pagadala:** None. **J. Leveret:** None. **J.R. Cressman:** None. **T.C. Dumas:** None.

Poster

P843. Hippocampal Network Properties and Cognition

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P843.07

Topic: H.08. Learning and Memory

Title: Anatomically plausible Hippocampome.org Hopfield spiking neural network

Authors: *D. J. HAMILTON, J. D. KOPSICK, D. W. WHEELER, G. A. ASCOLI;
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Abstract: The hippocampal CA3 subregion has been described as an autoassociative network [Marr, 1971], and computational models of CA3 have been constructed to demonstrate this property [Zhang et al., 2016; Zhao et al., 2009]. However, these models were only abstractions of the actual CA3 circuitry. In contrast, our research implements Hopfield Net [Hopfield, 1982] behavior in a neuroinformatic-sourced Spiking Neural Network (SNN), the circuitry of which is derived from Hippocampome.org [Wheeler et al., 2015]. The potential connectivity of the CA3 computational model, as defined by Hippocampome.org, is based on experimental evidence mined from peer-reviewed publications, making it anatomically plausible. The biological circuit is fundamentally distinct from classical Artificial Neural Networks (ANNs) by the facts that (i) its sparse connectivity depends on the axonal and dendritic patterns of the constituent neuron types (as opposed to feedforward or all-to-all), (ii) it communicates through spiking dynamics, and (iii) it contains a diversity of inhibitory and excitatory neurons. In particular, the inhibitory interneuron connections with principal excitatory neurons dampen oscillations and cancel noise. The excitatory/inhibitory circuitry may also form cell assemblies that can provide a latching mechanism for instant memory storage, without the need for Hebbian-style [Song et al., 2000] synaptic strengthening. The ability to substitute an ANN implementation of a Hopfield Net with an anatomically plausible Hippocampome.org Hopfield Spiking Neural Network (HHSNN) implementation, while still observing similar behavior, lends credence to the theory that the CA3 subregion of the hippocampal formation functions as an autoassociative network.

Disclosures: D.J. Hamilton: None. **J.D. Kopsick:** None. **D.W. Wheeler:** None. **G.A. Ascoli:** None.

Poster

P843. Hippocampal Network Properties and Cognition

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P843.08

Topic: H.09. Spatial Navigation

Title: Theory of interaction between networks: Persistent activity and inactivity in vivo

Authors: *K. CHOUDHARY[1], M. R. MEHTA[2], S. BERBERICH[3], T. T. HAHN[4], J. MCFARLAND[5]; [1]Univ. of California Los Angeles (UCLA), Los Angeles, CA; [2]Departments of: Physics & Astronomy, Neurology, Neurobio., Univ. of California at Los Angeles (UCLA), Los Angeles, CA; [3]Central Inst. of Mental Hlth., Mannheim, Germany; [4]Zentralinstitut Fuer Seelische Gesundheit, Mannheim, Germany; [5]Univ. of Maryland, College Park, MD

Abstract: Interactions between large brain networks govern all cognition. A mechanistic understanding of these interactions is a major challenge. Here, we present a simple, analytically tractable, mean field theory of cortico-entorhinal interactions *in vivo* during the 'Up-Down' state oscillation (UDS). The theory predicts new phenomena: spontaneous persistent activity (*SPA*) and inactivity (*SPI*). We confirm these using simultaneously recorded parietal cortical local field potential (LFP) and the membrane potential (V_m) of identified excitatory neurons from several brain areas *in vivo*, especially from layer 3 of the medial (MECIII) and lateral entorhinal cortex (LECIII), which show *SPA* and *SPI*; the latter has never been seen before in experiments or models. Further, the theory reproduces quantitatively, not just qualitatively, several *in vivo* features, on average and on a cell-by-cell basis. The theory predicts, and the

experiments confirm, that *SPA* and *SPI* are quantized by cortical UDS and result from a nonlinear amplification of small fluctuations in afferent cortical gamma power. These convergent, theory-experiment results provide a novel way to generate persistent activity, which has been implicated in a wide range of conditions, and persistent inactivity, and help to understand the rich dynamics of interactions between large networks of neurons *in vivo*.

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Poster

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Title: Theta and gamma band oscillatory decoupling in macaque hippocampus

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Abstract: The rodent hippocampus supports a broad range of spectral frequencies including theta and gamma bands during exploration. The coordination of these rhythms is thought to reflect important canonical mechanisms of temporal coding; however, these rhythms are less apparent in primates, and their coordination during species-relevant exploration in primates is unclear. To investigate the relationship between different frequency bands during primate behavior, we measured local field potentials (LFPs) and single unit activity in the hippocampus of two adult female macaques during visual exploration and in quiescence. In contrast to the nested coupling described in rodents, we found that 3-14 Hz oscillations encompassing the theta band had greater power during quiescence than visual search, whereas 20-50 Hz beta/gamma oscillations had greater relative power during search than quiescence (both results: Wilcoxon rank sum test, $F < 0.05$). To address this more directly, we examined cross-frequency coupling between these oscillations. Consistent with the general behavioral-epoch results, delta/theta band amplitude (2-5 Hz) was negatively correlated with slow gamma band amplitude (25-35 Hz; $p < 0.05$). In contrast, delta/theta band amplitude was positively correlated with higher frequency oscillations (gamma and high-frequency oscillations, 50-150 Hz; $p < 0.05$). Single units were most frequently phase-locked to LFPs in the 3-12 Hz, 25-40 Hz, and >60 Hz bands ($n = 404$ isolated units, Rayleigh test $p < 0.05$). Isolating sharp-wave-ripples (SWRs), however, revealed that the low-frequency (3-12 Hz) and>100 Hz bands were dominated by spikes phase-locking to the slow and fast components of

the SWR. This may account in part for the low-frequency power during quiescent states, when SWRs are most prevalent. Furthermore, spike autocorrelograms (n = 184 cells), yielded no clear examples of intrinsic delta/theta oscillatory modulation resembling those seen in the rodent hippocampus. The present results support a role for ~20-40 Hz slow gamma oscillations during active exploration in the primate that is decoupled from - and therefore not simply a harmonic of - theta oscillations. In contrast, theta oscillations were not prevalent during search in primates, did not modulate single units, and may be susceptible to contamination by other LFP phenomena such as SWRs. These results will be discussed in the broader context of exploratory behaviors, encompassing walking and reaching movements in macaques, as well as active sensing strategies in other species.

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Poster

P843. Hippocampal Network Properties and Cognition

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Program #/Poster #: P843.10

Topic: H.08. Learning and Memory

Support: ERC CoG 647954
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Title: Hippocampal neurons code individual episodic memories in humans

Authors: *L. D. KOLIBIUS[1], F. ROUX[2], G. PARISH[1], M. TER WAL[4], M. VAN DER PLAS[1], R. CHELVARAJAH[5], D. T. ROLLINGS[5], J. LANG[6], S. GOLLWITZER[6], K. WALTHER[6], R. HOPFENGÄRTNER[6], G. KREISELMEYER[6], H. HAMER[6], B. P. STARESINA[3], M. WIMBER[1], H. BOWMAN[7], S. HANSLMAYR[1];
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Abstract: When you remember the last time you had a coffee with a loved one you rely on your hippocampus to reinstate that episode. This episode will contain a multitude of features (weather, smell of the coffee, music playing), but how the hippocampus binds all these elements into one episode remains unsolved. The indexing theory (Teyler and DiScenna, 1986) proposes that neurons in the hippocampus achieve this through a conjunctive code that binds all features within the episode. In contrast, others have suggested that hippocampal neurons code for specific categories (Quiroga, 2012). In search of an answer to this issue, we have recorded the activity of 625 single neurons in the hippocampus of human epileptic patients (N = 16). During a self-paced memory association task patients formed unique episodic memories comprising an animal cue and two associate images (places or faces). Each episode was learned and retrieved only once. We contrasted the empirical firing reinstatement (firing rate at encoding multiplied with retrieval) of every single unit during every episode with a shuffled distribution. Next, we excluded potential concept neurons that showed increased firing to the animal cue at encoding. In a second level

shuffling procedure we show that a significant number (N = 147/625; $p < 0.001$) of single units showed a memory specific reinstatement of neural firing during individual episodes. We termed these single units Episode Specific Neurons (ESNs). We still find a significant number of ESNs when limiting our analysis to single units that reinstate one episode with face associates and one with place associates ($p < 0.01$). Such neurons unlikely code for a specific concept because the stimulus material in these episodes does not overlap. To rule out that single units are firing in response to recurring time points we partitioned all encoding blocks into 40 equally sized bins and used a Kruskal-Wallis test to assess periodic firing. This approach did not reveal a significant number of time cells and there was no significant overlap with ESNs (p values > 0.5). In conclusion, we provide evidence that individual neurons code discrete episodes via an increased firing rate during encoding and retrieval. We demonstrate that these Episode Specific Neurons do not reflect the coding of a particular feature in the episode (i.e., concept or time). Instead, they code for the conjunction of the different elements that make up the episode.

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Quiroga, R. Q. (2012). Concept cells: the building blocks of declarative memory functions. *Nature Reviews Neuroscience, 13*(8), 587-597.

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Poster

P953. Theoretical Network Models III

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Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P953.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIMH Grant RF1MH117155
NINDS Grant R01NS10955

Title: Simulating sleep spindles and slow oscillations EEG and MEG in a multiscale thalamocortical network model with hierarchical connectivity

Authors: *Y. SOKOLOV[1], B. Q. ROSEN[2], E. DELANOIS[2], O. C. GONZALEZ[3], G. P. KRISHNAN[5], E. HALGREN[4], M. V. BAZHENOV[6];
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Abstract: Magneto- and electro-encephalography (M/EEG) are complementary, noninvasive imaging techniques, which are used to investigate macroscopic brain activity. However, how the microscopic activity of ion channels gives rise to these electromagnetic signals is yet to be fully understood. To

address this question, we developed a multi-scale thalamocortical network model that exhibits the essential activity states of NREM sleep: sleep spindles and slow oscillations. Using a recently developed computationally efficient neuronal model, we considered a network of about a hundred thousand of cells, which are embedded on a structural-MRI reconstructed cortex, with realistic laminar organization. The network model incorporates the fundamental principles of cortical connectivity. First, the connection probability between a pair of cortical cells decayed exponentially with respect to the diffusion-MRI derived white matter tract distance between the pair. Second, a hierarchical index was assigned to each functional region that is inversely proportional to region's average myelination. Third, inter-areal hierarchically feed-forward and feed-back connections were pruned into distinct laminarly-separated counter-streams, distinct from local connectivity. The synaptic delays and synaptic strengths of intra-cortical and thalamocortical connections were derived from dMRI distances and laminar patterns. We examined the role of synaptic delays on the propagation of spindles and slow oscillations, and found that a characteristic traveling wave structure is preserved even for relatively high delays consistent with human brain long-range connectivity delays. We analyzed the spatiotemporal patterns of microscopic activity and identified characteristic propagation of activity during the stage 2 and stage 3 of NREM sleep. We compared mesoscale cortical correlativity structure in simulated and empirical data. By embedding the simulated cortical currents in a volume conduction model of the head we produced simulated M/EEG, enabling investigations of how multi-scale dynamics and detailed connectivity give rise to these complex signals.

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Poster

P953. Theoretical Network Models III

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Program #/Poster #: P953.02

Topic: I.06. Computation, Modeling, and Simulation

Title: Optimality of pulsed processing by recurrent neural networks

Authors: *T. MCPHERSON[1], A. KUCZALA[2], T. SHARPEE[2];
[1]UCSD Dept. of Neurosciences, La Jolla, CA; [2]Physics, UCSD, La Jolla, CA

Abstract: Neuronal processing in the brain occurs rhythmically across a set of discrete frequency bands, spanning almost two orders of magnitude. The function of these rhythms remains a matter of debate, as well as why activity seems to be organized in canonical bands. Here we show that the rhythmic structure seen in neuronal activity can be derived from the processing timescales of hierarchically organized recurrent networks operating in an optimal regime. Specifically, we find that to achieve optimal error correction, a recurrent network must receive inputs with noise comparable to what is observed in cortical networks, as well as operate in a pulsed manner where inputs are disconnected for the majority of computation. When input noise is above or below the optimal value, the ability of a network to converge on the correct solution is limited, resulting in reduced error correction. Pulsed inputs need to be brief enough to initially activate the network, but should not exceed the integration time of constituent neurons.

When input duration is too long, continuous drive distorts the endogenous dynamics of the network, disrupting good error correction. In this regime, optimal processing timescale and performance are predominantly independent of network size. The optimal timescale is dictated by the integration time constant of constituent network nodes. At the scale of local neuronal circuits, a typical neuronal time constant of 10 ms yields an optimal timescale of approximately 21 ms (48 Hz), corresponding to gamma oscillations—a fast rhythm observed in cortical networks that is putatively linked to local computation. When circuits exhibiting this timescale are connected to create a higher-order recurrent network, the resulting optimal timescale occurs at 46 ms (22 Hz), representative of canonical beta oscillations**.** In this framework, the timescale for a network at one scale becomes the time constant for a constituent node at a larger scale, affording the theoretical prediction of a hierarchy of discrete timescales. Extending our predictions to larger spatial scales produces a full sequence of frequencies observed in the brain covering gamma (48 Hz), beta (22 Hz), alpha (10 Hz), theta (4.8 Hz), delta (2.2 Hz), and slow wave sleep oscillations (1 Hz). We also find the optimal timescale can be modulated by adjusting the gain of neurons, providing an explanation for why the frequency of rhythmic activity can be variable within bands of finite width. Collectively, our results illustrate the optimality of rhythmic processing observed in the brain and how this property allows for the apparent hierarchical organization of oscillatory activity.

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Poster

P953. Theoretical Network Models III

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Program #/Poster #: P953.03

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH grant NS116589
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Title: Orchestrated Excitatory and Inhibitory Learning Rules that Lead to the Unsupervised Emergence of Self-sustained Inhibition-stabilized Dynamics

Authors: *S. SOLDADO MAGRANER[1], R. LAJE[2], D. BUONOMANO[1];
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Abstract: #2300 characters max (no spaces)
Orchestrated Excitatory and Inhibitory Learning Rules that Lead to the Unsupervised Emergence of Self-sustained Inhibition-stabilized Dynamics.
Self-sustaining dynamics maintained through recurrent connections are of fundamental importance to cortical function. Although a balance between excitatory and inhibitory activity is essential for the generation of self-sustained dynamics, it not known how these two populations coordinate their activity during development to lead to self-sustained inhibition-stabilized regimes. One of the best studied examples of self-sustained network dynamics are Up-states. Using two-photon calcium imaging in cortical organotypic cultures, we first show that Up-states emerge in parallel in excitatory and PV^+ inhibitory neurons across three weeks of *ex vivo* development, establishing the presence of unsupervised

synaptic learning rules that lead to globally stable emergent dynamics. Computational models of excitatory-inhibitory networks have established that four sets of weights (*WE←E, WE←I, WI←E, WI←I*) cooperate to generate stable self-sustained dynamics, but have not addressed how learning rules can operate in parallel at all four weight classes to generate self-sustained inhibition-stabilized regimes. Using a two-population firing rate model and numerical and analytical methods we show that standard homeostatic rules are not robust enough to account for the emergence of self-sustained dynamics due to a characteristic feature of inhibition-stabilized networks: the paradoxical effect. We demonstrate that homeostatic rules are only stable in a narrow parameter regime in which plasticity of synapses onto inhibitory neurons is sufficiently slow. We also show that these results hold for a second family of widely used homeostatic rules, synaptic scaling. We have, however, derived a novel family of rules with cross-homeostatic influences that robustly leads to self-sustained regimes and balanced excitation-inhibition, and additionally, reproduces the experimental developmental emergence of Up-states. Finally, we show that the cross-homeostatic rules are also successful in driving a multi-unit firing rate model to a stable Up regime. We conclude that unless plasticity of inhibitory neurons is negligible, rules other than standard forms of homeostatic plasticity must underlie the emergence of self-sustained inhibition-stabilized regimes.

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Poster

P953. Theoretical Network Models III

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Program #/Poster #: P953.04

Topic: I.06. Computation, Modeling, and Simulation

Title: Optimal degree of recurrent and feedback connections for information storage

Authors: *C.-Y. LIN[1,3], A. KUCZALA[3], T. O. SHARPEE[1,3,2];
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Abstract: As our personal experiences suggest, neural networks have a large capacity for retaining information about input signals. Previous studies have demonstrated that networks need to be primarily feedforward to maximize information recall. However, only small networks were considered. Here we use mean-field methods to characterize information storage in large networks composed of a small number of blocks, with the possibility of recurrent connections within and between blocks. We find that there is an optimal degree of recurrent interactions within each block corresponding to the transition to chaotic behavior within that block. Considering the relative distribution of neurons between blocks, we find that typically networks have larger storage capacity when the first block has fewer neurons than subsequent blocks. Small networks do not benefit from feedback connections between blocks. There is a critical network size beyond which feedback connections increase information storage capacity. These studies highlight previously under-appreciated functions of feedback and recurrent connections in neural circuits. We find the optimal network structures undergo sharp phase transitions as the connection strengths

increase, and these transitions involve redistributing synaptic budgets and reorganizing the population size of different cell types in the network.

Disclosures: C. Lin: None. **A. Kuczala:** None. **T.O. Sharpee:** None.

Poster

P953. Theoretical Network Models III

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Program #/Poster #: P953.05

Topic: I.06. Computation, Modeling, and Simulation

Support: WPI Grant

Title: Circuits for mismatch: Dissecting the structure and dynamics of spiking neural microcircuit models trained to report temporal regularity violations

Authors: *F. B. KERN, Z. C. CHAO;
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Abstract: The predictive coding theory (PC) states that, rather than passively receiving information, the brain actively predicts its future input. According to PC, this is achieved through a cascade of computational modules that receive bottom-up inputs and top-down predictions, which they compare to yield a prediction error that is sent up, and an updated prediction that is sent down along the processing hierarchy. As a domain-general algorithm, PC is believed to be employed widely throughout the brain, supporting its computational goal of Bayesian inference.
PC has been intensely studied in primate and human EEG in auditory sequence learning paradigms, which involve presenting sequences of tones with certain regularities and observing the neural responses to regularity violations, i.e., the prediction error signals. While the dynamics and hierarchical organisation of sequence processing and its concomitant prediction and prediction error signals have been studied in great detail at the mesoscopic scale, there has been comparatively little progress in elucidating the mechanisms underlying these computations.
Since mismatch signals are so readily observed in EEG, we believe that error neurons, that is, neurons that fire specifically in response to unexpected or unpredicted events, must be common in cortex. However, we are not aware of any work identifying such neurons or analysing the circuit mechanisms supporting their function.
To approach this question, we build small, biologically plausible model circuits of leaky integrate-and-fire (LIF) neurons with firing threshold adaptation, a simple short-term plasticity mechanism, and we train these models to generate mismatch signals in response to input regularity violations. We use surrogate gradient backpropagation through time on the machine learning platform PyTorch to adjust the circuit structure, the synaptic weights, as well as the dynamics of threshold adaptation, in order to encourage a subset of neurons to increase their firing probability when a stimulus is turned off (violation of continuity), or when a periodic stimulus is suddenly changed or omitted (violation of regularity).
We analyse the structure of the resulting circuits as well as the activity dynamics leading to the error responses, elucidating in detail the mechanistic underpinnings of mismatch signal generation in the

model. We then draw parallels to known connectivity patterns in mammalian cortex and suggest circuit and activity motifs that may play a key role in signalling prediction errors in sensory processing pathways.

Disclosures: F.B. Kern: None. **Z.C. Chao:** None.

Poster

P953. Theoretical Network Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P953.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH/NINDS RO1 NS109552

Title: Supercomputers, Neural Network Simulations and Reverse Engineering of Neuron Firing Patterns

Authors: *M. CHARDON[1], C. WANG[3], M. GARCIA[4], R. K. POWERS[5], C. HECKMAN[2]; [1]Physiol., [2]Dept. of Physiol., Northwestern Univ., Chicago, IL; [3]Electrical Engin., CalState LA, Los Angeles, CA; [4]Argonne Natl. Lab., Lemont, IL; [5]Dept Physiol & Biophysics, Univ. Washington, Seattle, WA

Abstract: High speed computation via supercomputers offers the possibility of remarkably extensive parameter searches, a capacity well matched to the multitude of possible inputs driving a particular set of neurons. Our recent studies combine 3 advances: 1) novel array electrodes to measure firing patterns of populations of motoneurons in humans, via motoneuron connections to muscle fibers, 2) highly realistic computer simulations of these motoneurons and 3) implementation of these models using the High Performance Computing facility at Argonne National Labs. The huge advantage of the supercomputer approach is that their massive parallelism allows thousands (soon millions) of simulations to be carried out simultaneously. In this particular application, we use this computational power as the basis of a brute force approach to reverse engineer motoneuron firing patterns to identify the organization of their synaptic inputs. More specifically our goal is to identify the patterns of excitatory, inhibitory and neuromodulatory inputs. Our initial simulations show that, although a given motor output pattern could potentially be generated by a huge number of combinations of these three types of input, neuromodulatory input makes motoneuron input-output properties so nonlinear that the effective “solution space” is restricted. These high levels of neuromodulatory inputs are coupled to strong inhibitory inputs, with interaction between these two input types providing the “amplifier” upon which excitation acts to execute the pattern of the movement. This is a novel insight into the synaptic organization of motor commands in humans. Overall our results show that this reverse engineering approach can achieve deep insights about the organization of synaptic inputs that drive a set of neuronal firing patterns. Identifying the separate patterns of excitatory and inhibitory inputs appears to require highly nonlinear processing within the neurons.

Disclosures: M. Chardon: None. **C. Wang:** None. **M. Garcia:** None. **R.K. Powers:** None. **C. Heckman:** None.

Poster

P953. Theoretical Network Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P953.07

Topic: I.06. Computation, Modeling, and Simulation

Support: Swartz Fellowship for Theoretical Neuroscience
NIH Grant DP2NS116768
NSF Center for the Physics of Biological Function PHY-1734030

Title: Nonequilibrium response functions for functional connectivity in the brain

Authors: *F. RANDI[1], A. LEIFER[2];
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Abstract: Despite the power of the *C. elegans* connectome, the community currently lacks systematic direct measures of the strength, sign (excitatory vs. inhibitory), and temporal properties of the connections between neurons. We refer to these properties as functional connectivity, and they are crucial to understand circuit function. Functional connectivity can now be measured on larger scales thanks to the combination of optogenetics and neural activity imaging. These experiments, however, do not directly measure the direct (monosynaptic) connections between neurons, but only the effective connections, which are a combination of the direct and the indirect (polysynaptic) paths connecting neurons in the network. We sought a mathematical framework to describe the results of those experiments and obtain the direct contributions from the effective connections observed in experiments. Conventional models start from a description of the direct connections and then consider network effects through numerical simulations. Response functions, which give the activity of a neuron through convolutions with the inputs to that neuron, allow us instead to obtain explicit relations between the properties of the direct and effective connections between neurons. Traditionally, however, this is possible only for linear networks that do not have synaptic adaptation or neuromodulation. We will present a framework based on nonequilibrium response functions, that extends the application of response functions also to nonlinear and time-dependent networks and allows for the description of time-varying functional connectivity.

Disclosures: F. Randi: None. **A. Leifer:** None.

Poster

P953. Theoretical Network Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P953.08

Topic: I.07. Data Analysis and Statistics

Title: Conserved canonical circuits & computations, continued

Authors: *D. GARDNER[1], E. P. GARDNER[2];
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Abstract: Once you have a good thing, stick with it. Evolution leverages this principle in the design of nervous systems, which are gratifyingly similar across species, even phyla. Nervous systems use evolutionarily-conserved small molecules, neurotransmitters, proteins, synapses, and neurons specialized for excitation or inhibition. At higher levels, vertebrate and mammalian neuroanatomy conserves relative operation and connectivity of nuclei, layers, and regions. At still higher levels, the goals and functions of all nervous systems are similar. But at intermediate levels: are neural circuits and the computations they perform evolutionarily-conserved? At the last SfN, our nanosymposium examined this question, as well as potential candidates for canonical circuits and computations. We now continue the quest by suggesting roles for in-development connectomics and under-scrutiny astrocytology.
Connectomes:
The NINDS and DoE are exploring development of a mouse connectome, but a complete connectome may be less useful than one that confirms multiple canonical microcircuits—and variants—and places their function in context. The distinction between equipment schematic diagrams and wiring paths emphasizes that that the functional ground truth sought may be subtly different from complete images of somas and processes. Also, the behavior of a circuit or device is revealed by viewing it as a set of interconnected modular elements. Physiologically, identification of canonical functional microcircuits would reduce the computational burden of interpreting and analyzing data now routinely obtained from thousands of neurons. Complete connectomes may be less informative than more readily detected repeated, Identifying patterns revealing potentially canonical, functional, microcircuits performing specific computations would be feasible, perhaps in real time, given today's computing power.
Astrocytes:
Artificial neural networks routinely use global error data to adjust specific weights, suggesting that networks of neurons might use a similar mechanism. Recent work on astrocytes emphasizes that their often-multisynaptic spread could be a canonical, conserved way to mediate synapse-specific short- and long-term actions as well as *f-I* nonlinearities under global, modulatory control.
Plans:
Continuing onward, new collaborative approaches are needed to explore this broad question across regions, species and phyla, involving many techniques and analytic tools. Toward this goal, we advance an upcoming Neuromorphic Neural Networks (**N**^{3}, or Encubed) Next Cool Virtual Meeting.

Disclosures: D. Gardner: None. **E.P. Gardner:** None.

Poster

P953. Theoretical Network Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:30 AM - 10:30 AM

Program #/Poster #: P953.09

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF RI:Small 2008741

Title: Plasticity of short-term synaptic dynamics enhances the computational power of neural networks

Authors: *S. ZHOU, D. V. BUONOMANO;
Neurobio., Univ. of California, Los Angeles, Los Angeles, CA

Abstract: The principle that changes in synaptic strength are the primary mechanism underlying learning and memory is among the most influential concepts in neuroscience and has contributed to the revolution in machine learning. Implicit in this principle is that in the absence of learning synapses have a fixed and constant weight. Biologically speaking however, there is no such thing as a fixed synaptic weight in the sense that even in the absence of learning synaptic efficacy is highly dynamic on the time scale of hundreds of milliseconds—i.e., the strength of synapses can facilitate or depress in a use-dependent fashion, a phenomenon referred to as short-term synaptic plasticity (STP). The computational function of STP remains poorly understood, but it has been proposed to contribute to temporal processing (Seay et al, 2018). The vast majority of neurocomputational and machine learning models do not incorporate STP and the few that do assume that STP itself is fixed. Here we propose that STP itself undergoes plasticity, and contributes to learning and memory—i.e., that plasticity of STP (PSTP) enhances the computational power of neural networks. To examine this hypothesis we implemented STP in a *synapse-specific* manner, i.e., each synapse has its own set of STP parameters. In these models the τ_D, τ_F, and U parameters of the Tsodyks STP model were tuned along with the weight through gradient descent. We first demonstrated that PSTP endows simple single-layer feedforward networks with the ability to solve three tasks that would not be solvable by a circuit without STP, or with fixed STP. These tasks included a single-layer feedforward network that can generate a neural sequence. To further test the computational contribution of PSTP in neural networks with more general architecture, we have trained large-scale firing rate recurrent neural networks (RNNs) with synapse-specific PSTP on an interval timing task. To date, we have found that compared to RNNs without STP, that RNNs with fixed STP dramatically faster learning, and more so with PSTP. In ongoing work we contrasting the ability of RNNs without STP, with fixed-STP, and PSTP on a series of standard cognitive tasks. Results to date demonstrate that STP significantly enhances the computational power of neural networks, and that PTSP further enhances performance on some tasks.

Disclosures: S. Zhou: None. **D.V. Buonomano:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.01

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R01 NS093992

Title: Ca2+ activity-mediated gene expression drives aberrant neurogenesis in a mouse model of epilepsy

Authors: *G. CHANGARATHIL[1], P. VARMA[1], Z. LYBRAND[2], M. COPPIN[1], A. ADEYEYE[1], J. HSIEH[1];
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Abstract: Studies show that seizure induced aberrant hippocampal neurogenesis aggravate the development of chronic seizures. We previously identified that 2 week old (2w) adult-born granule cells (abGCs) in mouse dentate gyrus show elevated Ca^{2+} activity after pilocarpine (pilo) induced seizures compared to sham. Moreover, this amplified Ca^{2+} activity is reduced by chemogenetic DREADDs/hM4Di silencing in pilo treated mice. Ca^{2+} transients have been shown to modulate neuronal Ras/Raf/MEK/ERK signalling, as well as govern the migration of mouse cerebellar granule cells – but less is known regarding how Ca^{2+} activity drives aberrant hippocampal neurogenesis and, in turn, epileptogenesis. Based on these studies, we hypothesize that early activity in abGCs alters Ca2+-mediated gene expression programs that promote aberrant maturation, including ectopic migration of abGCs associated with spontaneous recurrent seizures. Therefore, we performed RNA-sequencing analysis from FACS sorted 2w old abGCs after pilo treatment and hM4Di silencing. We identified 387 differentially expressed genes (DEGs) between pilo and sham groups. The gene ontology classification revealed that 149 upregulated genes with pilo treatment belonged to neuron differentiation/development and oxygen carrier activity pathways. However, lipid/small molecule metabolic process, mitochondrial membrane complex, NADH dehydrogenase activity genes were over-represented among 238 genes downregulated with pilo treatment. This could imply that impairments in cellular metabolism of immature neurons might play in role in epileptogenesis. Additionally, we found 33 DEGs between pilo and hM4Di silenced groups. Among these, 25 genes were downregulated and belonged to functional categories such as glutamatergic synapse, while 8 upregulated genes appeared to regulate niche remodeling and cellular migration. Taken together, these results suggest that alterations in Ca^{2+}activity within 2w old abGCs after pilo leads to changes in niche remodeling, migration and metabolism – controlling aberrant neurogenesis. Further experiments with select candidate genes are being performed to address specific pathways that regulate aberrant maturation of abGCs involved in epileptogenesis.

Disclosures: G. Changarathil: None. **P. Varma:** None. **Z. Lybrand:** None. **M. Coppin:** None. **A. Adeyeye:** None. **J. Hsieh:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.02

Topic: A.02. Postnatal Neurogenesis

Support: NIH grant K01 MH125144
NIH R35NS116843
NIH R35NS097370

Title: Single-cell RNA-sequencing reveals discrete steps in the transformation of developmental precursors into adult neural stem cells

Authors: *A. BOND, D. JIMENEZ-CYRUS, G.-L. MING, H. SONG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: The dentate gyrus region of the hippocampus is one of only two regions in the adult mammalian brain where substantial levels of neurogenesis occur throughout adulthood. Quiescent adult neural stem cells in the subgranular zone of the dentate gyrus occasionally become reactivated in adulthood to generate new neurons which integrate into the existing network and contribute an added layer of plasticity to the hippocampus. Previously, our lab showed that $Hopx^+$ embryonic neural stem cells which contribute to developmental cytogenesis in the mouse dentate gyrus transition into quiescent adult neural stem cells, suggesting that a common lineage of neural stem cells contributes to developmental and adult neurogenesis. However, the molecular mechanisms regulating this developmental transition remain completely unknown. Here we used single-cell RNA-sequencing of $Hopx^+$ dentate gyrus progenitors across multiple stages of early postnatal development in mice to identify the molecular cascade associated with the transformation of developmental precursors to quiescent adult neural stem cells. We discover that early postnatal dentate gyrus neural stem cells exist in multiple heterogeneous states, and we identify a trajectory of cycling neural stem cells as they transition into a quiescent state. We also discover that dentate gyrus precursors gradually acquire an adult-like state after they exit cell cycle. This suggests that the developmental transition consists of two sequential steps: first precursors exit cell cycle to enter a quiescent state and then precursors acquire an adult-like state throughout a quiescence maturation period. We further identify transcription factor networks associated with each stage of the transition and biological processes that change over the course of the transition. Collectively, our work identifies molecular and cellular mechanisms associated with the transformation of developmental precursors to quiescent adult neural stem cells, and serves as a foundation for future studies investigating mechanisms that regulate formation of the adult neural stem pool.

Disclosures: A. Bond: None. **D. Jimenez-Cyrus:** None. **G. Ming:** None. **H. Song:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.03

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R01HL139712
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Office of the Assistant Secretary of Defense for Health Affairs Award No. W81XWH2010199
DC-IDDRC Award U54HD090257
Foglia and Hill Families

Title: Characterization of the cellular and molecular diversity in the postnatal piglet subventricular zone following chronic hypoxia

Authors: *C. T. SHEPARD[1], C. LEONETTI[3], Z. LI[1], C. S. FOSTER[1], E. MONAHAN[1], L. BLEICKEN[1], T. F. HAYDAR[2], N. ISHIBASHI[4];
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Abstract: Congenital heart disease (CHD) is among the most common birth defects, affecting nearly 40,000 births each year in the United States. Children with CHD frequently exhibit a wide range of neurological deficits and cognitive impairments that alter brain function later in life. Thus, there is a crucial need to define the mechanisms underlying cortical disturbances to develop therapeutic interventions to lessen the impact of these impairments. Recently, migrating neuroblasts were discovered within the infant subventricular zone (SVZ). These cells migrate tangentially along the lateral ventricles and populate the frontal cortex, a region responsible for higher-order cognitive functions. However, the cellular identity and generation mechanisms of these immature neurons are not yet defined. Our previous work in the piglet has shown that chronic hypoxia induces a significant decrease in SVZ neurogenic activity associated with reduced populations in the frontal lobe. In this project, we first characterized the cellular and molecular heterogeneity of the postnatal normoxic 2-week-old piglet SVZ using single-nuclei RNA sequencing and state-of-of-the-art bioinformatics approaches. This study generated an extensive list of genes that are differentially expressed throughout various stages of neural stem cell differentiation and revealed the complex heterogeneity of neuroblast subpopulations in the postnatal piglet SVZ. From these studies, we identified a unique population of immature excitatory neurons and have verified their existence in normoxic piglet tissue using immunohistochemical quantification and RNAScope. We then sought to determine whether this population of cells was altered as a result of chronic hypoxia by using a piglet CHD model. Overall, our study provides new insights into the underlying molecular mechanisms of cortical dysmaturation and decreased postnatal SVZ neurogenesis after chronic hypoxic insult. Ultimately, these studies will help to identify therapeutic targets in improve long term neurological outcomes in pediatric CHD patients.

Disclosures: C.T. Shepard: None. **C. Leonetti:** None. **Z. Li:** None. **C.S. Foster:** None. **E. Monahan:** None. **L. Bleicken:** None. **T.F. Haydar:** None. **N. Ishibashi:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.04

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant DK124727
NIH Grant GM060507
NIH Grant MD006988

Title: Consumption of high-saturated fat diet during adolescence leads to hippocampal atrophy and impairment of cognitive functions potentially through involvement of TACE/ADAM17.

Authors: *F. SHARAFEDDIN[1], J. D. VEGA-TORRES[1], P. ONTIVEROS-ANGEL[1], E. TERRONES[1], E. STUFFLE[1], S. SOLAK[2], E. TYNER[2], M. OROPEZA[2], I. DELA PENA[2], A. OBENAUS[3], B. D. FORD[4], J. D. FIGUEROA[1];
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Abstract: Background: Adolescent obesity is strongly associated with deviant hippocampal maturation. Molecular mechanisms involved in obesity-induced structural alterations of the hippocampus are yet unknown. Synaptogenesis and synaptic pruning in the hippocampus during brain development depend on balanced signaling between the growth factor neuregulin 1 (NRG1) and its tyrosine kinase receptor ErbB4. NRG1-ErbB4 signaling is tightly regulated by proteolysis, particularly by the metalloprotease TACE/ADAM17. In this study we investigate the potential involvement of TACE/ADAM17-NRG1-ErbB4 pathway in early obesity-induced neuropathological alterations in the adolescent rat hippocampus. **Methods:** Adolescent Lewis rats were fed from PND21 to PND49 with either a Western-like diet, which had a high-saturated fat content (WD, 41% kcal from fat) or an ingredient-matched control diet (CD, 13% kcal from fat). Behavioral assessments were performed between PND43 and PND49. Animals were euthanized at PND49. Ex-vivo magnetic resonance imaging was performed and hippocampal tissue collected to evaluate TACE/ADAM17-NRG1-ErbB4 activities and inflammatory biomarkers using qRT-PCR, Western blot, and flow cytometry. **Results:** We found that consumption of an obesogenic high-saturated fat diet during adolescence leads to anxiety-like behaviors and hippocampal atrophy, specifically in the CA1 region of the hippocampus. Alterations in WD-induced behaviors were concurrent with changes in hippocampal pro-inflammatory cytokine profiles and microglial morphology. WD consumption increased ErbB4 phosphorylation (pErbB4) and TACE/ADAM17 protein levels in the hippocampus.TACE/ADAM17 protein levels were positively associated with pErbB4 and interleukin-6 (IL-6) levels in the hippocampus. Interestingly, TACE/ADAM17 protein levels were associated with reduced ErbB4 and post-synaptic density 95 (PSD95) protein levels in the hippocampus. **Conclusions:** We demonstrate that brief exposure to an obesogenic diet during adolescence is sufficient to induce hippocampal dysfunction and structural impairments in rats. We identify TACE/ADAM17-NRG1-ErbB4 pathway as a potential signaling axis linking adolescent obesity with hippocampal structure abnormalities.

Disclosures: F. Sharafeddin: None. **J.D. Vega-Torres:** None. **P. Ontiveros-Angel:** None. **E. Terrones:** None. **E. Stuffle:** None. **S. Solak:** None. **E. Tyner:** None. **M. Oropeza:** None. **I. dela Pena:** None. **A. Obenaus:** None. **B.D. Ford:** None. **J.D. Figueroa:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

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Program #/Poster #: P009.05

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant MH111773-01
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Title: Neurocircuit-modified hippocampal neurogenesis modulates memory and anxiety

Authors: *Y. LI[1], Y. LUO[1], L. QUINTANILLA[1], Y. CHERASSE[2], M. LAZARUS[2], J. SONG[1];
[1]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]Intl. Inst. for Integrative Sleep Med., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Adult neurogenesis in the dentate gyrus (DG) plays a critical role in regulating memory and emotion, and this process is dynamically regulated by neural circuit activity. It remains unknown whether stimulating neural circuits achieves sufficient long-term neurogenic effects for behavioral modulation. Here we identify a long-range neural circuit projecting from the supramammillary nucleus (SuM) of the hypothalamus to the DG, which co-releases GABA and glutamate to positively regulate hippocampal neurogenesis by acting on multiple developmental stages. By combining circuit manipulation with lineage tracing of adult neural precursors, we demonstrate that chronic stimulation of SuM neurons leads to increased number of behaviorally relevant adult-born neurons with enhanced maturity and improved dendritic and spine features. Functionally, selective manipulation of the activity of these circuit-modified young adult-born neurons further modulates memory performance and anxiety-like behavior. Our study identifies a unique neural circuit that can be manipulated to increase the quantity and improve the quality of adult-born neurons, and importantly, the activity of these neurocircuit-modified young neurons causally modulates hippocampal dependent behavior.

Disclosures: Y. Li: None. **Y. Luo:** None. **L. Quintanilla:** None. **Y. Cherasse:** None. **M. Lazarus:** None. **J. Song:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.06

Topic: A.02. Postnatal Neurogenesis

Support: MH103339
MH106934
MH110926 863
MH109904
MH113257
Fellowship from La Caixa Fundation LCF/BQ/PI19/11690010

Title: Single-cell transcriptomic analysis of neurogenic capacity in the adult human hippocampus

Authors: *J. I. ARELLANO[1], S. MA[1], D. FRANJIC[1], M. SKARICA[1], J. CHOI[1], C. XU[1], C. LI[1], A. T. N. TEBBENKAMP[1], G. SANTPERE[2], I. GUDELJ[1], L. JANKOVIC-RAPAN[1], A. M. M. SOUSA[3], P. RAKIC[1], N. SESTAN[1];
[1]Neurosci., Yale Univ., New Haven, CT; [2]Exptl. and Hlth. Sci., Univ. Pompeu Fabra, Barcelona, Spain; [3]Waisman Ctr. and Dept of Neurosci., Univ. of Wiscosin, Madison, WI

Abstract: The presence of neurogenesis in the adult human dentate gyrus (DG) is a contentious issue. Previous studies based on detection of cell proliferation and doublecortin (DCX) protein expression to identify neuroblasts and immature granule cell neurons have reported controversial results (Eriksson et al., 1998; Spalding et al., 2013; Dennis et al., 2016; Cipriani et al., 2018; Sorrells et al., 2018; Moreno-Jimenez et al., 2019). To add insight to these controversial sets of observations, we performed high-coverage single-nucleus RNA sequencing (snRNA-seq) on the DG and four anatomically defined subregions of the adult human hippocampal-entorhinal system comprising ammonic fields CA4-2, CA1, subiculum and entorhinal cortex. Our results showed widespread expression of DCX in hippocampal cell populations, particularly in inhibitory neurons, but also in some pyramidal and mossy cells, and in glial cells. We did not identify discrete clusters of DCX-expressing cells in the hippocampus,but we found 125 cells within the cluster of 14,703 DG granule cells with at least one DCX mRNA molecule. Although some of these granule cells co-expressed migrating or immature neuron markers including NEUROD2 (61.6%) or FXYD7 (32.8%) (Hochgerner et al., 2018), we found no specific enrichment of these markers compared to DCX non-expressing DG granule cells (nominal p-value > 0.05). Furthermore, we found no evidence of neural stem cells, and for example all nestin-expressing cells in the astrocytic cluster co-expressed AQP4, a marker for cells committed to the astrocytic lineage. Similarly, putative neural progenitor cells expressing MKI67 did not constitute an independent cluster in DG. Additional immunohistochemistry to detect DCX showed numerous cells in the amygdala as previously shown (Sorrells et al., 2019) and occasional cells in the entorhinal cortex, but only rare cells with interneuron morphology in the DG, consistent with our snRNA-seq data. Our results indicate that DCX at the RNA level is not a specific marker of neuroblasts or immature neurons in the adult hippocampus, and overall, show that neurogenesis does not continue, or is extremely rare, in the adult human hippocampus.

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Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

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Program #/Poster #: P009.07

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant T32AG057468
NIH Grant AG060238
NIH Grant AG033570
NIH Grant AG062251

Title: Caveolin-1 cell autonomously regulates neural stem cells in adult hippocampal neurogenesis

Authors: *T. K. L. STEPHEN[1], J. A. BONDS[2], A. SHETTI[1], E. QUIROZ[1], K. OWUSU-ANSAH[1], L. APONTE-COFRESI[1], R. D. MINSHALL[1], O. LAZAROV[1];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Northwestern Univ., Chicago, IL

Abstract: Adult Hippocampal Neurogenesis (AHN) is the generation of new neurons from neural stem and progenitor cells (NSPCs) in the dentate gyrus of the hippocampus. AHN is highly dependent on the cerebrovascular and thought to play a critical role in memory and cognition. Several mouse models of cardiovascular disease risk factors and neurological disease including Type II diabetes (T2DM) and Alzheimer's disease (AD) have impairments in AHN. Caveolin-1 (Cav-1) is a scaffolding protein that is enriched the cerebrovascular. Reduced brain expression of Cav-1 is associated with the cognitive deficits seen in T2DM. We observed that Cav-1 is also expressed in NSPCs. We hypothesize that Cav-1 has a novel cell autonomous role in NSCs and is an endogenous regulator of NSC quiescence. To test this, we have developed a new mouse model harboring conditional deletion of Cav-1 in NSPCs (NestinCreER^{T2};Cav- 1$^{lox/lox}$). Isolation of NSPCs from the hippocampus of these mice at 4-6 weeks of age revealed that deletion of Cav-1 reduces NSPCs proliferation levels. Further, deletion of Cav-1 in NSPCs results in altered expression of key neurogenic pathways regulating quiescence and metabolism of AD link signals such has full length Amyloid Precursor Protein (APP-FL) and β-secretase 1 (BACE-1). These results suggest that Cav-1 regulates neurogenesis via signals implicated in AD, at least in part. Elucidating the role of Cav-1 in neurogenesis may provide novel insight into mechanisms of learning and memory dysfunction in AD.

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Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.08

Topic: A.02. Postnatal Neurogenesis

Support: NS115092

Title: Proteomic analysis of maturing adult-born hippocampal mossy fiber boutons

Authors: *K. MURRAY[1], X.-B. LIU[2], H.-J. CHENG[3];
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Abstract: The birth of new neurons (called neurogenesis) in the adult hippocampus is critical for learning and memory and disruption of this process is associated with human neurological disorders such as Alzheimer's disease. Rates of adult hippocampal neurogenesis (AHN) are tightly linked with changes in physiological activity. Activities such as enhanced exercise or learning as well as pathophysiological changes such as epilepsy, profoundly alter AHN. Knowing how ANH neurogenesis regulates neuronal circuitry is therefore important for understanding its overall impact on brain physiology. Central to this issue is understanding how newborn neurons in adult brain achieve long-term integration. Understand the molecular and cellular mechanisms regulating synaptic integration in AHN could lead to selective pharmacological targets for functional improvement during pathological conditions or in aging where levels of adult neurogenesis are dramatically decreased. Neuronal progenitors in the adult hippocampal

dentate gyrus give rise to newborn granule (GCs) cells that, when fully differentiated, receive synaptic inputs from entorhinal cortex and send axons along the mossy fiber pathway to form synaptic outputs with CA3 pyramidal neurons. We and others have shown that it takes about eight weeks for the newborn GCs to fully differentiate and form mature synaptic inputs and outputs. Here we assessed molecular changes in the synaptic outputs when newborn mossy fiber boutons (MFB) from GC are forming synapses with mature CA3 pyramidal cells in mouse brain. We utilized superresolution immunofluorescent array tomography to profile the proteomic changes of the pre- and post-synaptic elements during the establishment of mature synapses. We present a timeline of proteomic development in the maturing MFB terminals in young adult brain and in aging brain. In addition, we describe a novel heterogeneity in molecular composition of synaptic contacts within single adult-born MFB terminals. These experiments are some of the first to address the intricate proteomic changes essential for establishing new synaptic outputs during adult neurogenesis in young and old mouse brain.

Disclosures: K. Murray: None. **X. Liu:** None. **H. Cheng:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.09

Topic: A.02. Postnatal Neurogenesis

Title: Function of oncogene Mycn in adult neurogenesis and oligodendrogenesis

Authors: J. CHEN, *Z. GUAN;
UCSF, San Francisco, CA

Abstract: Human *MYCN* is an oncogene amplified in neuroblastoma and many other tumors. Both human *MYCN* and mouse *Mycn* genes are important in embryonic brain development, but their function in adult healthy nerve system is completely unknown. Here, with *Mycn*-eGFP mice and quantitative RT-PCR, we found that *Mycn* was expressed in specific brain regions of young adult mice, including subventricular zone (SVZ), subgranular zone (SGZ), olfactory bulb (OB), subcallosal zone (SCZ), and corpus callosum (CC). With immunohistochemistry (IHC) we found that many *Mycn*-expressing cells expressed neuroblast marker doublecortin (DCX) and proliferation marker Ki67. With *Dcx-creER* and *Mki67-creER* mouse lines, we fate mapped *Dcx*-expressing neuroblasts and *Mki67*-expressing proliferation cells, along with deleting *Mycn* from these cells in adult mice. We found that knocking out *Mycn* from adult neuroblasts or proliferating cells significantly reduced cells in proliferation in SVZ, SGZ, OB, SCZ, and CC. We also demonstrated that the *Mycn*-deficient neuroblasts in SGZ matured quicker than wild type neuroblasts, and that *Mycn*-deficient proliferating cells were more likely to survive in SVZ, SGZ, OB, SCZ, and CC compared to wild type. Thus, our results demonstrate that, in addition to causing tumors in nervous system, oncogene *Mycn* has crucial function in neurogenesis and oligodendrogenesis in adult healthy brain.

Disclosures: J. Chen: None. **Z. Guan:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P009.10

Topic: A.02. Postnatal Neurogenesis

Support: R01NS105200
R21NS095632
R01HD064743
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R01AG067025
U01MH116492

Title: Rgs6 mediates effects of voluntary running on adult hippocampal neurogenesis

Authors: Y. GAO[1], M. SHEN[2], J. GONZALEZ[3], Q. DONG[2], S. KANNAN[2], B. EISINGER[1], Q. CHANG[2], D. WANG[2], L. S. OVERSTREET-WADICHE[4], ***X. ZHAO**[2];
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Abstract: Voluntary running enhances adult hippocampal neurogenesis, with consequences for hippocampal dependent learning ability and mood regulation. However, the underlying mechanism remains unclear. Here, we show that voluntary running induces unique and dynamic gene expression changes specifically within the adult-born hippocampal neurons, with significant impact on genes involved in neuronal maturation and human diseases. We identify the regulator of G protein signaling 6 (RGS6) as a key factor that mediates running impact on adult-born neurons. RGS6 overexpression mimics the positive effects of voluntary running on morphological and physiological maturation of adult new neurons and reduced sensitivity of adult-born neurons to inhibitory effect of $GABA_B$ receptor activation. Knocking down RGS6 abolishes running-enhanced neuronal maturation and hippocampal neurogenesis-dependent learning and anxiolytic effect. Our study provides the data resource unveiling the genome-wide intrinsic molecular changes in adult-born hippocampal neurons that contribute to voluntary running-induced neurogenesis.

Disclosures: Y. Gao: None. **M. Shen:** None. **J. Gonzalez:** None. **Q. Dong:** None. **S. Kannan:** None. **B. Eisinger:** None. **Q. Chang:** None. **D. Wang:** None. **L.S. Overstreet-Wadiche:** None. **X. Zhao:** None.

Poster

P009. Postnatal Neurogenesis: Molecular Mechanisms

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Program #/Poster #: P009.11

Topic: A.02. Postnatal Neurogenesis

Support: PRIN 2017AY8BP4
PON ARS01_01226
PhD fellowship from the Excellence Project from the Department of Pharmacological and Bio- molecular Sciences (DiSFeB) - University of Milan

Title: Early postnatal signatures of prenatal stress exposure in rats: corticogenesis and brain activity

Authors: *K. C. CREUTZBERG[1], V. BEGNI[1], F. MARCHISELLA[1], I. PISANO[1], F. DE ROSA[1], N. LOPIZZO[2], M. MAZZELLI[2], V. ZONCA[3], A. CATTANEO[1], M. A. RIVA[1];
[1]Univ. of Milan, Milan, Italy; [2]IRCCS Inst. Ctr. San Giovanni di Dio Fatebenefratelli, Brescia, Italy; [3]King's Col., London, United Kingdom

Abstract: The prenatal period is a sensitive life stage during development since the organism is rapidly evolving and can undergo the influence of positive and negative stimuli from the womb environment. Accordingly, it is known that exposure to prenatal stress (PNS) can lead to long-lasting neurobiological and behavior consequences in the offspring, which may enhance the susceptibility for mental disorders. Indeed, we found that adolescent rats that were exposed to PNS show a range of behavioral changes that may reflect emotional dysregulation. However, it is still unclear if and how such abnormalities may be driven by alterations during early development. On this basis, here we aimed to characterize early postnatal changes in neurogenesis and brain activity following PNS exposure. In this sense, pregnant Sprague Dawley rats were randomly assigned to the control (CT) or PNS group (n = 15, 6 CT and 9 PNS). Briefly, PNS females were restrained in cylinders under bright light for 45 minutes 3 times a day from gestational day 14 to delivery. Two days after birth a maximum of 4 animals per litter was sacrificed, half brain was post fixed for immunofluorescence analysis while the prefrontal cortex (PFC) and hippocampus from the other hemisphere were dissected for transcriptional analysis. Two-way ANOVA was used for all analysis with a sex factor (male x female) and a rearing condition factor (CT x PNS), when an interaction effect was detected Tukey's *post hoc*test was applied. Immunofluorescence analysis of the proliferating marker Ki67 in the PFC showed a PNS effect ($p = 0.0049$), with a significant decrease in the number of Ki67 positive cells in newborn PNS rats. Accordingly, real-time PCR analysis showed that PNS animals have decreased expression levels of *Tbr1* on the PFC, an important transcription factor for the differentiation of glutamatergic neurons ($p = 0.0064$). Next, we analyzed the expression of different activity-regulated genes (*Arc*, *Zif-268* and *Npas4*) and calculated a Z-activation score in order to establish changes in the functional activity of the PFC and hippocampus. PNS animals showed increased Z-activation score in both PFC ($p = 0.0036$) and hippocampus ($p = 0.0148$). The enhanced activity in newborn PNS rats may also lead to an unbalance in redox mechanisms, as measured by a significant decrease of the antioxidant factor *Nrf2*, although such effect was only found in female animals (-22%, $p = 0.0478$ for the PFC; -67%, $p = 0.0198$ for the hippocampus). Our data suggests that exposure to stress in utero produces early changes in the newborn, which may ultimately contribute to functional dysregulation becoming evident later during development.

Disclosures: K.C. Creutzberg: None. **V. Begni:** None. **F. Marchisella:** None. **I. Pisano:** None. **F. De Rosa:** None. **N. Lopizzo:** None. **M. Mazzelli:** None. **V. Zonca:** None. **A. Cattaneo:** None. **M.A. Riva:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Fondazione CARIPLO, MIUR, Angelini, Otzuka, Recordati Pharma, Sumitomo Dainippon Pharma, Sunovion.

Poster

P133. Oscillations and Synchrony: Unit Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P133.01

Topic: B.09. Network interactions

Support: R01EY027402
National Health and Medical Research Council (APP1183280) (Australia)

Title: Cause-effect structures of cortical columnar activity

Authors: *A. MAIER[1], B. M. CARLSON[2], J. A. WESTERBERG[3], N. TSUCHIYA[4];
[2]Psychology, [3]Dept. of Psychology, [1]Vanderbilt Univ., Nashville, TN; [4]Monash Univ., Clayton, Australia

Abstract: Cortical columns have been hypothesized to act as elementary (canonical) units to carry out neuronal computations. However, few columnar computations have been described to date. Thanks to advances in linear microelectrode arrays (LMAs), in vivo measurements of up to several hundreds of neurons within isolated cortical columns are becoming increasingly commonplace. This wellspring of data promises to offer new breakthroughs in understanding the role of cortical columns for neuronal processing. Here we describe a novel technique to derive intra-columnar interactions (cause-effect structures) from LMA data. The specific analytical technique is derived from the mathematically formalized framework of integrated information theory (IIT). A major advance of this approach is that it quantifies neural interactions similar to a cross-correlation at lag+1, but between multiple measurement sites of brain activity rather than just two. Earlier work demonstrated viability of this approach in invertebrates (Leung et al., 2021). Here we extend this approach to sensory responses of primate visual cortex. Cortical responses are non-linear across time, rising steeply at stimulus onset and slowly decaying (adapting) thereafter. We aimed to eliminate these transients by subtracting the average evoked response for each LMA electrode contact (channel) from trial-by-trial individual responses. Next, we binarized the data into periods of activity exceeding or staying below the trial average (UP- vs. DOWN states). Then, we computed the relative frequency with which UP or DOWN states at one columnar location ("causes") preceded UP or DOWN states elsewhere ("effects"). This computation was iterated for sets of channels across the LMA to derive the probabilities with which any possible state at one part of the column transitions to any possible state at other parts of the cortical column (transition probability matrix, TPM). Using IIT, TPM can be further deconstructed into integrated information magnitudes (Phi) as well as information structures for different states or stimuli. Here we show that the onset of a visual stimulus increases both the number and frequency of state transitions of V1 columnar spiking responses. We will discuss these findings in context of other causal and informational structures derived from neural data.

Disclosures: A. Maier: None. **B.M. Carlson:** None. **J.A. Westerberg:** None. **N. Tsuchiya:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P133.02

Topic: B.09. Network interactions

Support: Academy of Medical Sciences and Wellcome Trust (Springboard award SBF002\1045)
BBSRC (grant BB/P020607/1 and PhD studentship 2265967)

Title: Stretching and squeezing of neuronal log firing rate distribution by psychedelic and intrinsic brain state transitions

Authors: *B. DEARNLEY, M. DERVINIS, M. SHAW, M. OKUN;
Neuroscience, Psychology and Behaviour, Univ. of Leicester, Leicester, United Kingdom

Abstract: How psychedelic drugs modulate the activity of cortical neuronal populations and whether transition into a psychedelic brain state has shared features with other brain state transitions is not well understood. Here, we used Neuropixels 1.0 probes to perform acute extracellular recordings from large populations of neurons in medial prefrontal cortex of awake, head-fixed adult mice given the potent synthetic 5-HT2a receptor agonist (4-Bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2). Oral administration of the drug significantly stretched the distribution of log firing rates of the population of recorded neurons, compared to control recordings (N=14 animals, one control and one drug recording were performed in each mouse in a random order). Stretching of the log firing rate distribution was previously observed across transitions between sleep and wakefulness, which suggested that it is a more general phenomenon and prompted us to examine it in more detail. We found that modulation of the width of the distribution of log firing rates of a neuronal population also occurred in different parts of the cortex and the hippocampus during intrinsic increases in the arousal level of awake mice, and thus constitutes a ubiquitous rather than a solely sleep-related phenomenon. Arousal, however, did not explain the stretching of the log-rates by TCB-2. In both psychedelic and naturally occurring brain state transitions, the stretching or squeezing of the log-rate distribution of an entire neuronal population reflected the concomitant changes in the log firing rate distribution of two subpopulations, with one subpopulation undergoing a downregulation and often also stretching of its neurons' log firing rates, while the other subpopulation undergoes upregulation and potentially a squeeze of its log-rates. In both subpopulations, the stretching or squeezing were a signature of a larger relative impact of the brain state change on the rates of the slow-firing neurons. These findings reveal a generic pattern of reorganisation of neuronal firing rates by brain state transitions.

Disclosures: B. Dearnley: None. **M. Dervinis:** None. **M. Shaw:** None. **M. Okun:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P133.03

Topic: B.09. Network interactions

Support: 2R01MH046742-31

Title: Circuits of reciprocally inhibitory neurons with escape and release mechanisms are differentially robust to perturbations and modulation

Authors: *E. O. MOROZOVA, P. NEWSTEIN, E. MARDER;
Volen Ctr. and Biol. Dept., Brandeis Univ., Waltham, MA

Abstract: Identifying key cell-intrinsic and circuit-level properties that influence the output of neural circuits and their resilience to perturbations is key for the brain. Small reciprocally inhibitory circuits provide an excellent platform for studying these questions due to their abundance in the nervous system and well-defined output. We used the dynamic clamp to build reciprocally inhibitory circuits of two gastric mill (GM) neurons of the crab stomatogastric ganglion (STG) by connecting them via artificial inhibitory synapses and adding a hyperpolarization-activated inward (H) current. Depending on the position of the synaptic threshold within the envelope of membrane potential oscillations, the circuit operates in either an “escape”, “release” or “mixed” mode. The release mechanism is characterized by the presynaptic cell falling below its synaptic threshold, releasing the suppressed cell from inhibition. The escape mechanism is characterized by the inhibited cell depolarizing above its synaptic threshold, terminating the firing of the active cell. We characterized the behavior of the circuits with different mechanisms of oscillation to alterations in circuit parameters, such as synaptic threshold, conductances and activation rates of synaptic and H currents. We further explored how circuits with escape and release mechanisms respond to temperature perturbations and neuromodulation. We showed that reciprocally inhibitory circuits with different underlying mechanisms of oscillation are not equally robust to perturbations. Particularly, circuits with a release mechanism are robust to variations in synaptic and H conductances but are fragile in response to an increase in temperature, while circuits with an escape mechanism rely on the tight correlation between synaptic and H conductances to generate robust bursting but are resilient to an increase in temperature. Further, the circuits with a release mechanism are significantly more sensitive to neuromodulators, such as serotonin, proctolin, oxotremorine and artificially generated modulatory current (I_{MI}), than the circuits with an escape mechanism. The differences in the dynamical mechanisms of oscillation can potentially explain a significant variability in individual responses of reciprocally inhibitory circuits to neuromodulation. These data indicate that the same perturbation can have dramatically different effects depending on the circuit mechanisms that may not be observable from baseline circuit output. Thus, knowing the dynamical mechanisms underlying the generation of antiphase oscillations is crucial for predicting the effects of perturbations.

Disclosures: E.O. Morozova: None. **P. Newstein:** None. **E. Marder:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

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Program #/Poster #: P133.04

Topic: B.09. Network interactions

Support: European Research Council - FRONTHAL - 742595

Title: A novel frontal cortical input to the thalamic reticular nucleus (TRN) mediates instantaneous correlation between cortical and TRN activity

Authors: *N. HADINGER, L. ACSADY;
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Abstract: Neocortex is known to be organized into areas with different cognitive functions. However, we are only beginning to understand how cortico-thalamic interactions are regionally specialized. Emerging data shows that thalamus is involved in basically all cortical functions, including higher order cognitive processes. Thus, understanding regions specific cortico-thalamic communication is necessary to disentangle the rules of these long range interactions. In the present study we revealed an instantaneous and graded correlation between the frontal cortical LFP activity and the spiking of the anterior TRN cells. This correlation was mediated by a newly described pathway, specific for the frontal cortex. Until know, layer 5 (L5) cortical output, which otherwise exerts profound control over thalamic activity, was thought to reach thalamus without innervating its GABAergic nucleus, the TRN. Conditional viral tracing from the frontal (but not from other) cortical areas in the L5-specific Rbp4-Cre mouse however revealed dense, topographically-organized L5 projection in the anterior TRN. Optogenetic activation of L5 cells in anesthetized mice elicited bursts in anterior TRN cells with short latency and high fidelity. Gradually increasing the number of optogenetically actived L5 cells converging on the TRN neurons resulted in gradual change of the TRN burst properties. It increased both the intraburst frequencies and the number of spikes per bursts. Spontaneous firing actvity of L5-recipient TRN neurons showed tight and graded correlation with the ongoing frontal cortical oscillations. While single spike events showed low correlation with the cortical LFP, burst firing was tightly coupled to the LFP activity. Higher frequency burst with more spikes were correlated with faster, high amplitude cortical events. This correlation disappeared upon optogenetic perturbation of L5 to TRN input via ArchT. The data suggests powerful and temporally precise cortical control in frontal cortico-thalamic circuits by the strong coupling of anterior TRN cells to the ongoing cortical oscillations. Since the L5-TRN connection is region specific and is restricted to frontal cortex and anterior TRN our data demonstrate a qualitative regional difference in the organization of thalamocortical circuits.

Disclosures: N. Hadinger: None. **L. Acsady:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

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Program #/Poster #: P133.05

Topic: B.09. Network interactions

Support: NIH Grant R01 MH119102
Drexel University College of Medicine
NIDA-IRP

Title: Median raphe heterogeneous neuronal populations differentially regulate hippocampal theta oscillations

Authors: *W. HUANG[1], S. IKEMOTO[2], D. V. WANG[1];
[1]Drexel Univ. Col. of Med., Philadelphia, PA; [2]Behav Neurosci Br, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Theta oscillation during rapid eye movement (REM) sleep plays an important role in mnemonic processes by coordinating hippocampal and cortical activities. However, how the theta activity is regulated by subcortical regions including the median raphe nucleus (MnR) is not fully understood. It is thought that the MnR mainly suppresses hippocampal theta activity through its serotonergic outputs. Complementally, our study revealed a more complex framework indicating a role of non-serotonergic MnR outputs in regulating hippocampal theta oscillation. By using Optogenetics and dual-site electrophysiological recordings on wild-type and transgenic mice, we found that most Vglut3+, but not serotonergic or GABAergic MnR neurons exhibited decreased or silent activity during hippocampal theta activity. Additionally, most GABAergic and a small subset of Vglut3+, but not serotonergic MnR neurons exhibited hippocampal theta phase-locked activity, and that the GABAergic MnR neurons innervated nearby Vglut3+ and serotonergic MnR neurons. Lastly, optogenetic activation of the MnR induced robust hippocampal theta activity, and that Granger causality analysis confirmed a causal effect from MnR theta to hippocampal theta. These results suggest that MnR non-serotonergic neurons have a causal role in driving hippocampal theta activity during REM sleep associated memory processes.

Disclosures: W. Huang: None. **S. Ikemoto:** None. **D.V. Wang:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

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Program #/Poster #: P133.06

Topic: B.09. Network interactions

Support: NIH Grant U01NS117839
German Academy of Sciences Leopoldina

Title: A single cell correlate of theta-gamma phase amplitude coupling during working memory in the human hippocampus

Authors: *J. DAUME[1], A. G. P. SCHJETNAN[3], T. A. VALIANTE[3], A. MAMELAK[1], U. RUTISHAUSER[1,2,4];
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Abstract: Theta-gamma phase amplitude coupling (PAC) reflects the coordination of neural activity across different frequency bands. Especially in working memory, where prolonged interactions between cognitive control and stimulus processing take place, theta-gamma PAC has been observed in various brain regions of the animal and the human brain. To date, however, there is no established single-cell correlate demonstrating the effect of local field potential (LFP)-level PAC on the activity of single cells. Here, we recorded single cell activity and population level LFPs from the human medial temporal lobe

and medial frontal cortex while patients performed a Sternberg working memory task with pictures (36 sessions in 29 patients, 1444 neurons). We observed local theta-gamma PAC in the amygdala and hippocampus during the working memory delay period. Only in the hippocampus, however, PAC differed as a function of working memory load with stronger PAC observed in load 1 as compared to load 3, reflected by longer bouts of gamma activity coupled to the underlying theta rhythm with higher memory load. Weak to no PAC coupling was observed in the frontal lobe. We identified neurons in the hippocampus that followed the phase of theta oscillations and the power of gamma oscillations. These "PAC cells" showed stronger phase coupling to local high gamma oscillations in load 3 then in load 1. At the same time, they were more closely coupled to the phase of remote theta oscillations recorded in ventromedial prefrontal cortex in load 3 as compared to load 1. Thus, more information maintained in working memory led to stronger coupling to fast local oscillations in the hippocampus as well as to slow remote oscillations in the frontal lobe. Moreover, spiking-timing of PAC cells differed as a function of memory load with spikes being more tightly coupled to the theta phase corresponding to the gamma power peak in load 3 then in load 1, as well as a function of picture category during memory encoding. While firing rates did not differ between experimental conditions, such theta phase shifts speak to the fact that PAC cells encode memory content using a phase rather than a firing rate code. Taken together, we identified neurons that relate their activity to ongoing interactions of theta and high gamma oscillations in the human hippocampus and frontal lobe. These interactions might be the neural marker of the ongoing coordination between frontal cognitive control and posterior stimulus processing that are necessary to hold information in mind for a brief period of time.

Disclosures: J. Daume: None. **A.G.P. Schjetnan:** None. **T.A. Valiante:** None. **A. Mamelak:** None. **U. Rutishauser:** None.

Poster

P133. Oscillations and Synchrony: Unit Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P133.07

Topic: B.09. Network interactions

Support: NIH-MH122023 (SSN)

Title: Effects of variations in network features on characteristics of gamma bursts

Authors: *D. DOPP[1], M. STROUD[1], F. FENG[2], S. S. NAIR[3], Z. CHEN[4];
[1]Univ. of Missouri, Columbia, MO; [2]Electrical and Computer Engin., Univ. of Missouri-Columbia, Columbia, MO; [3]Electrical & Computer Engin., [4]Electrical Engin. and Computer Sci., Univ. of Missouri Columbia, Columbia, MO

Abstract: Effects of variations in network features on characteristics of gamma bursts
Daniel Dopp, Matthew Stroud, Feng Feng, Ziao Chen, Satish S. NairElectrical Engineering & Computer Science Dept., University of Missouri, Columbia, MO
Abstract Computational models to explore rhythmic activity in neuronal networks have used single cells that range in complexity from the integrate-and-fire and Izhikevich formulations defined by one or two

parameters to detailed biophysical models with over tens of parameters. Connectivity configurations have, similarly, varied from homogeneous to different heterogeneous types. Gamma oscillations (30-80 Hz) are expressed in many brain regions, where they are reflected in electroencephalogram (EEG) and local field potential (LFP) signals. In a recent study, we reported a large scale biophysical computational model of the basal amygdala (BL) that replicated several features of transient gamma oscillations seen in *in vivo* local field potentialLFP recordings from BL, via PING interactions involving principal cells (PNs) and fast-spiking interneurons (ITNs) (Feng et al., 2019).
The present modeling study uses the 1000-cell version of the amygdala model to explore the effects of variations in 'network features' including single cell model dynamics, heterogeneity in connectivity, and synaptic short-term plasticity, and neuromodulatory effects, on the genesis and characteristics of gamma. These characteristics include frequency of occurrence of bursts in the filtered LFP as well as frequency within a burst and burst duration. The genesis of burst will be explored via a temporal averaging approach that was recently found to reveal interesting insights. Preliminary results using the approach showed that average firing rates across the entire network model for afferents, PNs and FSIs were temporally correlated with the LFP. The time lags between the bursts revealed the causal connection between afferents, PNs and ITNs in this PING-type burst generation. Aligning the average firing rates using phase of significant cycles within bursts of the LFP revealed distinct phases of population activity for afferents, PNs and ITNs. How network features impact these and other characteristics of the genesis mechanism are being studied presently.

Disclosures: D. Dopp: None. **M. Stroud:** None. **F. Feng:** None. **S.S. Nair:** None. **Z. Chen:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.01

Topic: B.10. Epilepsy

Support: Ministry of Science and Technology grant, Mongolia

Title: The study of SLC6A1 and SCN1A gene hot spot mutation in families with idiopathic epilepsy

Authors: S. DUU[1], T. SURJAVKHLAN[2], T. AVIRMED[3], P. ICHINKHORLOO[2], ***J. JAMIYANSUREN**[2,4];
[1]Sch. of Med., Mongolian Natl. Univ. of Med. Sci., Dornogovi, Mongolia; [2]Dept. of Mol. biology and Genet., [3]Dept. of Neurol., Mongolian Natl. Univ. of Med. Sci., Ulaanbaatar, Mongolia; [4]Dept. of Biochem., Intl. Univ. of Hlth. and Welfare, Narita, Chiba, Japan

Abstract: Introduction. Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked spontaneous seizures, and is one of the most common neurological condition regardless of age group and gender. According to the WHO statistics, there are 50 million patients with epilepsy worldwide, with 5 million newly diagnosed cases each year. In addition, 50 percent of the diagnosed epilepsy is idiopathic and the role of the hereditary factors are essential. More than 500 genes related to epilepsy seizures have identified and they divided into ion channels and other types of genes. As for ion

channel genes, *SLC6A1* (Solute Carrier Family 6 Member 1) gene is located in the 3p25.3 locus, and encodes the voltage-dependent gamma-aminobutyric acid (GABA) transporter (GAT1). GAT1 is responsible for re-uptake GABA from the synaptic cleft. Therefore, one of major ion channel gene is *SCN1A*, located on 2q24.3 and encodes the voltage-gated sodium channel alpha 1 subunit (Nav1.1, alpha 1). Mutations in this gene lead to channel dysfunction and results epileptic seizures in patients. **Objective.** To determine hot spot mutations of *SLC6A1* and *SCN1A* mutations in families with idiopathic epilepsy. **Material and methods.** The study included six patients and their healthy four relatives, total 10 persons on voluntary basis to comply with ILAE criteria. Peripheral blood samples collected from each participants and DNA extracted using DNA extraction kit. DNA purity and concentration were measured using spectrophotometer. *SLC6A1* (c.889G>A and c.1369_1370 delGG) gene mutations detected by using allele specific PCR and confirmed by gel electrophoresis. *SCN1A* (530G>A and 1264A>G) mutations were detected by Sanger sequencing. **Results.** According to genealogical studies, except for the cases of children from the same mother, the disease inherited in every generation regardless of gender without regular pattern. In the DNA sequencing test, the c.889G> A mutation contained exactly the same G allele in 3 healthy and 5 cases with epilepsy. c.1369_1370 del GG mutation was identified in only one patient and did not contain deletion. The mean age of the participants was 23.5 for controls and 12.7 for patients. Pedigree analysis shows that epilepsy inherited by autosomal dominant type in this family. When, the *SCN1A* mutations were determined in these participants, the minor risk allele of 530G>A 1264A>G mutations were not identified. *SCN1A* 311T>C mutation was unable to analyze. **Summary.** In clinical genealogy, epilepsy inherited by autosomal dominant in the family. Hot spot mutations of *SLC6A1* and *SCN1A* are maybe not the cause of contributing factor of epileptic status for this family.

Disclosures: S. Duu: None. **T. Surjavkhlan:** None. **T. Avirmed:** None. **P. Ichinkhorloo:** None. **J. Jamiyansuren:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.02

Topic: B.10. Epilepsy

Title: Cytochrome polymorphisms in the therapeutic response of cannabidiol in patients with drug-resistant epilepsy

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Abstract: Abstract: Problem statement: In Mexico, 30% of epileptic patients are resistant to drug treatment. (Perez Almengor., et; al, 2015). Given the low response to current anti-epileptic drugs (AEDs) for the control of drug-resistant epileptic seizures, the use of cannabidiol (CBD) is a current alternative already used in patients who are resistant to conventional treatment, although CBD it is not part of the basic treatment. This molecule is metabolized mainly by the cytochrome family (CYP), due to this it is important to determine the type of polymorphisms that would better respond to CBD (Lakhan, R., et; al, 2011, Makowska, M., et; al, 2020). Knowledge about those CYP genetic variants that affect CBD metabolism can provide relevant information to the physician. (Consroe P., et; al, 1982, Jones NA., et; al, 2010) Aim: To analyze the association between CYP polymorphisms and the therapeutic response of CBD in Mexican patients with drug-resistant epilepsy. Results: We demonstrate a low-risk association in epilepsy drug-resistant patients with unknown etiology in rs17879239 variant of *CYP2C19* gene [OR= 1.30 (1.005 - 1.702); p=0.04]; however, although SNP rs16947 of *CYP2D6* gene associated with greater toxicity by AEDs administration, it was not a significant relevance. Conclusion: Risk association in variant rs17879239 of *CYP2C19* was demonstrated in our population with unknown etiology.

Disclosures: A.V. Montes: None. **I.A. Feria:** None. **A. Reyes:** None. **V. Ramírez:** None. **D. Rayo:** None. **L. Rocha:** None. **S.A. Orozco:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.03

Topic: B.10. Epilepsy

Support: NIH Training grant T32MH020065
NIH Training grant T32DA434693
NIH Grant R01NS111122
Donald F. Steiner Scholarship Fund
Iowa Neuroscience Institute Fellowship

Title: Diet modifies allele-specific phenotypes in Drosophila carrying epilepsy-associated PNPO variants

Authors: *W. CHI[1], A. IYENGAR[2], W. FU[1], W. LIU[3], A. E. BERG[2], C.-F. WU[2], X. ZHUANG[1]; [1]Neurobio., Univ. of Chicago, Chicago, IL; [2]Univ. of Iowa, Iowa City, IA; [3]China Med. Univ., Shenyang, China

Abstract: Pyridox(am)ine 5'-phosphate oxidase (PNPO) catalyzes the rate-limiting step in the synthesis of pyridoxal 5'-phosphate (PLP), the active form of vitamin B6 required in the synthesis of neurotransmitters GABA and the monoamines. Pathogenic variants in *PNPO* have been repeatedly identified in patients with neonatal epileptic encephalopathy and early-onset epilepsy. These patients often exhibit different types of seizures and variable comorbidities, including developmental impairment and intellectual disability. It is unclear how seizure types and associated comorbidities are linked to specific *PNPO* alleles and to what degree diet can modify their expression. Furthermore, the molecular characteristics of *PNPO* variants have not been examined in model systems. Using CRISPR/Cas9, we

generated four knock-in *Drosophila* alleles, h^{WT}, h^{R116Q}, h^{D33V}, and h^{R95H}, in which the endogenous *Drosophila PNPO* (*sugarlethal*) was replaced by wild-type human *PNPO* cDNA and epilepsy-associated variants corresponding to R116Q, D33V, and R95H, respectively. We examined these knock-in flies at different levels. Collectively, we found a wide range of phenotypic variation in an allele- and diet-dependent manner. Specifically, the D33V mutation reduces the mRNA level, R95H reduces the protein stability, and R116Q alters the protein localization of *PNPO* in the brain. D33V and R95H mutations lead to partial and complete lethality during development, respectively and R116Q and D33V mutations shorten lifespan. At the behavioral level, h^{D33V}/h^{R95H} flies are hypoactive on all tested diets whereas h^{R116Q} homozygotes show diet-dependent behavioral outcomes. At the circuitry level, h^{D33V} homozygotes show rhythmic burst firing and h^{D33V}/h^{R95H} flies exhibit spontaneous seizure discharges. In h^{R95H} homozygotes rescued with PLP supplementation, we further uncovered that PLP deficiency abolishes development and causes extreme seizures in adults. Lastly, genetic and electrophysiological analyses demonstrate that h^{WT}/h^{R95H} flies are prone to seizures due to a dominant-negative effect of h^{R95H}. Together, this study demonstrates that human *PNPO* variants interact with diet to contribute the phenotypic variations; and that knock-in *Drosophila* model offers a powerful approach to systematically examine clinical manifestations and the underlying mechanisms of human PNPO deficiency.

Disclosures: W. Chi: None. **A. Iyengar:** None. **W. Fu:** None. **W. Liu:** None. **A.E. Berg:** None. **C. Wu:** None. **X. Zhuang:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.04

Topic: B.10. Epilepsy

Support: R01NS104428

Title: A Circadian Mechanism of Epilepsy Observed in PAR bZip Triple-Knockout Mice

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Abstract: D site-binding protein (DBP), hepatic leukemia factor (HLF) and thyrotroph embryonic factor (TEF) are the 3 members of the PAR (proline and acidic amino acid-rich) subfamily of bZIP (basic region/leucine zipper) transcription factors. Epileptic tissue resected from pediatric patients with focal cortical dysplasia exhibits decreased expression of DBP, among other circadian rhythm proteins. Furthermore, in a genetic model of epilepsy in mice—in which the *Clock* gene is excised in excitatory neurons—there are decreased levels of DBP and HLF. Most importantly, excision of all 3 PAR bZip proteins in mice causes them lethal intractable seizures. The mechanistic cause of the seizures exhibited in the PAR bZip triple-knockout mouse is unknown. Immunohistological findings here represented and a unique circadian-based pattern observed in seizure frequency provide valuable insights into the possible mechanism of epileptogenesis in the PAR bZip triple-knockout mouse.

Disclosures: L. Goicouria: None. **S. Feeney:** None. **H. Higashimori:** None. **J.S. Liu:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.05

Topic: B.10. Epilepsy

Support: R44MH119621

Title: Neuronal models to test compounds for beneficial or toxic effects relevant to pediatric epilepsy: quantification of synchronized activity via kinetic image cytometry

Authors: *P. MCDONOUGH[1], K. L. GORDON[2], C. G. RINES[1], R. C. B. BASA[1], C. HADLEY[1], D. RAKIC[1], J. H. PRICE[1,3];
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Abstract: Epilepsy, a common brain-disorder, affects ~3.5 million people in the US, including ~460,000 children. Epileptic seizures are episodes of abnormally increased and synchronized neuronal activity in the brain cortex which cause convulsions, repetitive movements/behaviors, and loss of consciousness. Seizures can result from metabolic imbalance, brain injury, drug toxicity, fever, and inherited mutations (primarily in genes encoding ion channels). Epilepsy in neonates and children (pediatric epilepsy) may lead to abnormal development, brain damage, and cognitive impairment (epileptic encephalopathy). Our goal is to develop high throughput screening assays, based upon hiPSC-neurons and glial cells, to test agents for beneficial effects relevant to pediatric seizures, as hiPSC-derived neurons may be relevant to fetal and neonatal CNS. We have utilized fluorescent indicators of intracellular calcium (Fluo-4) or voltage (FluoVolt), hiPSC-neurons plated in 384-well dishes, and Kinetic Image Cytometry (automated digital microscopy and cell-image analysis software) to quantify effects of 4-aminopyridine (4-AP) to elicit synchronized activity of the neurons. Coculture with astrocytes facilitates synchronized activity in response to 4-AP and we can quantify changes in the degree of synchronization and recruitment of neurons into active circuits via analysis of the kinetic signatures, on a cell-by-cell basis. Our assay system will enable testing of hiPSCs representing different genotypes and inclusion of additional cell types (e.g., hiPSC-microglial cells) to facilitate drug-discovery towards a pediatric epilepsies (e.g., Dravet Syndrome, Childhood Absence Epilepsy, Lennox-Gastaut Syndrome). The assay system will also enable elucidation of mechanisms relevant to adult forms of epilepsy and testing of candidate therapeutics for epileptogenic side effects (neurotoxicity).

Disclosures: P. McDonough: A. Employment/Salary (full or part-time):; Vala Sciences Inc. **K.L. Gordon:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **C.G. Rines:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **R.C.B. Basa:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **C. Hadley:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **D. Rakic:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **J.H. Price:** A. Employment/Salary (full or part-time):; Vala Sciences Inc..

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.06

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: DOD-TSCRP W81XWH-17-1-0151

Title: Dissecting the role of genetic modifiers on mTOR pathway activity in Tuberous Sclerosis Complex (TSC)

Authors: *P. SWAMINATHAN[1], H. FRY[1], S. KANESHAMOORTHY[1], V. NARAYANAN[2], S. RANGASAMY[1];
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Abstract: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by heterozygous mutations in the TSC1 or TSC2 gene, resulting in dysregulation of the intracellular mammalian target of rapamycin (mTOR) signaling pathway. Neurocognitive phenotypes associated with TSC range in severity from seizures, cognitive impairment, developmental delay, and autism, to a milder phenotype. Phenotypic variability has been observed within single families where all affected members have the same TSC1 or TSC2 mutation. To investigate the molecular basis of phenotypic variability, we established primary dermal fibroblast cell lines from a severely affected child and their mildly affected parent, both of which carry a heterozygous germline TSC2 mutation [c.2621dupC (p. Tyr875fs)]. We evaluated the expression levels of different key players involved in the mTOR network via western blot analysis of fibroblasts from the parent-child pair and an unrelated control. Experimental observations indicated decreased phospho-Akt (Thr308) and augmented p70S6K1 levels in the child with severe phenotype compared to the mildly affected parent and control cells. Our biochemical results suggest impaired Akt phosphorylation to be a potential biomarker of mTOR signaling in cells from severely affected patients. Further genetic analysis between the parent-child pair exhibited heterozygous germline variants in other mTOR pathway genes such as EIF4G1, PIK3R3, and TNFRSF19 in the child. Our studies revealed differential mTOR activity in cells from patients with phenotypic variability in familial TSC, which could be influenced by genetic modifiers in the mTOR network.

Disclosures: P. Swaminathan: None. **H. Fry:** None. **S. Kaneshamoorthy:** None. **V. Narayanan:** None. **S. Rangasamy:** None.

Poster

P142. Human and Animal Genetics: Epilepsy

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P142.07

Topic: B.10. Epilepsy

Support: NIH NS111122

NIH AG051513
Iowa Neuroscience Institute Fellowship

Title: Fly seizure EEG: field potential activity in the Drosophila brain

Authors: *A. IYENGAR, C.-F. WU;
Univ. of Iowa, Iowa City, IA

Abstract: Hypersynchronous neural activity is a characteristic feature of seizures. Although many *Drosophila* mutants of epilepsy-related genes display clear behavioral spasms and motor unit hyperexcitability, field potential measurements of aberrant hypersynchronous activity across brain regions during seizures have yet to be described. Here, we report a straightforward method to observe local field potentials (LFPs) from the *Drosophila* brain to monitor ensemble neural activity during seizures in behaving tethered flies. High frequency stimulation across the brain reliably triggers a stereotypic sequence of electroconvulsive seizure (ECS) spike discharges readily detectable in the dorsal longitudinal muscle (DLM) and coupled with behavioral spasms. During seizure episodes, the LFP signal displayed characteristic large-amplitude oscillations with a stereotypic temporal correlation to DLM flight muscle spiking. ECS-related LFP events were clearly distinct from rest- and flight-associated LFP patterns. We further characterized the LFP activity during different types of seizures originating from genetic and pharmacological manipulations. In the 'bang-sensitive' sodium channel mutant *bangsenseless* (*bss*), the LFP pattern was prolonged, and the temporal correlation between LFP oscillations and DLM discharges was altered. Following administration of the pro-convulsant $GABA_A$ blocker picrotoxin, we uncovered a qualitatively different LFP activity pattern, which consisted of a slow (1-Hz), repetitive, waveform, closely coupled with DLM bursting and behavioral spasms. Our approach to record brain LFPs presents an initial framework for electrophysiological analysis of the complex brain-wide activity patterns in the large collection of *Drosophila* excitability mutants.

Disclosures: A. Iyengar: None. **C. Wu:** None.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.01

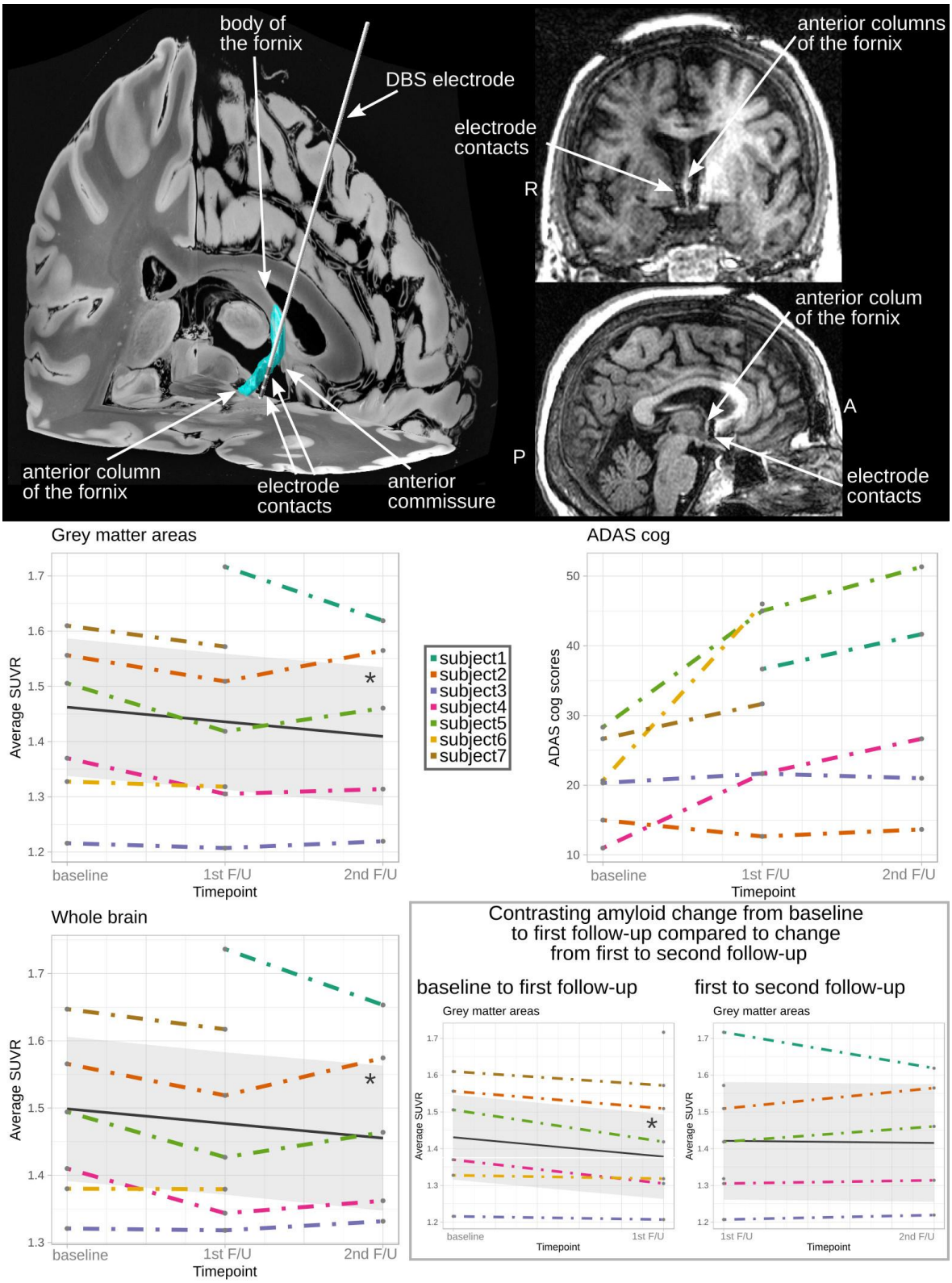
Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Fornix deep brain stimulation lowers beta-amyloid levels in Alzheimer's disease patients.

Authors: *J. GERMANN[1], J. TOMASZCZYK[1], G. S. SMITH[2], K. YAMAMOTO[1], F. V. GOUVEIA[3], A. BOUTET[1], G. J. B. ELIAS[1], A. LOH[1], M. P. MCANDREWS[1], D. F. TANG-WAI[1], A. M. LOZANO[1];
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Abstract: Alzheimer's disease (AD) is a highly prevalent neurodegenerative disease of aging. The pathological hallmarks of AD at autopsy are the accumulation of aggregated proteins and formation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary hyperphosphorylated tau tangles.

Amyloid and tau deposition can be quantified in vivo using positron emission tomography (PET). Clinically, AD is characterized by progressive memory impairment, and other cognitive deficits known to be caused by disturbances in widespread brain networks. Deep brain stimulation (DBS) is a neurosurgical therapy in which intracranial electrodes are employed to deliver current to specific brain structures modulating dysfunctional neural circuits. DBS targeting the fornix (fx-DBS) is being investigated for the treatment of AD. Active fx-DBS has been shown to alter neuronal activity, increase glucose metabolism, slow cognitive decline, and attenuate disease-related hippocampal atrophy in certain patients. Preclinical studies have demonstrated that stimulation of the fornix improves cognitive performance and reduces Aβ plaques in rodent models of AD. This open-label trial (ClinicalTrials.gov, NCT04856072) aimed to investigate if the disease-modifying effects of DBS can be observed in human fx-DBS patients. Cognitive performance (ADAS-cog) and imaging biomarkers (T1w MRI and Flutemetamol PET) were assessed in seven AD patients treated with fx-DBS at baseline (post implantation), at ~ 6months (1st follow-up (F/U)) and ~12 months (2nd F/U). The results show that fx-DBS significantly reduces PET-indexed brain-wide amyloid deposition. We observed an average decrease of 3% in patients undergoing active fx-DBS. Further analysis suggests this reduction is particularly pronounced in the first few months and subsequently drops off. This work suggests that fx-DBS has disease-modifying potential for the treatment of AD.



Disclosures: J. Germann: None. **J. Tomaszczyk:** None. **G.S. Smith:** None. **K. Yamamoto:** None. **F.V. Gouveia:** None. **A. Boutet:** None. **G.J.B. Elias:** None. **A. Loh:** None. **M.P. McAndrews:** None. **D.F.**

Tang-Wai: None. **A.M. Lozano:** F. Consulting Fees (e.g., advisory boards); Medtronic, Abbott, Boston Scientific.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Masupirdine (SUVN-502): A promising clinical candidate for the management of agitation in patients with dementia of Alzheimer's type

Authors: *R. NIROGI, P. JAYARAJAN, J. TADIPARTHI, A. SHINDE, R. BADANGE, A. MOHAMMED, V. GOYAL, V. BENADE, R. PALACHARLA, R. SUBRAMANIAN, J. RAVULA, S. JETTA;
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Abstract: 5-HT_6 receptors are G-protein coupled receptor mainly localized in the brain regions primarily involved in cognition and behavior i.e., cortex, dorsal hippocampus and striatum. Evidence from the studies in animal models suggests that 5-HT_6 receptor antagonists may have a potential role in controlling neuropsychiatric behavior such as agitation. Masupirdine is a potent and selective 5-HT_6 receptor antagonist. Masupirdine was evaluated in a phase-2a proof-of-concept, 26-week, randomized, double-blind, placebo-controlled, multicenter, parallel groups study in moderate Alzheimer's disease (AD) patients in United States under active US IND. Subgroup analyses of phase-2a results were carried out to evaluate the effects of masupirdine on domains related to agitation/aggression on the Neuropsychiatric Inventory (NPI-12) scale. Masupirdine was also evaluated in resident-intruder task, an animal model for aggressive behaviors. Additionally, masupirdine was evaluated using brain microdialysis to assess its effects on the modulation of monoaminergic neurotransmitters in rats. In phase-2a clinical study subgroup analyses, masupirdine showed robust efficacy in agitation/aggression scores in subjects who had baseline symptoms of agitation/aggression. The effect sustained till end of 26 week treatment. Masupirdine was generally found to be safe and well tolerated. In preclinical animal models, masupirdine reduced the aggressive behaviour in resident intruder task and increased neurotransmitters with role in attenuating symptoms of agitation and aggression. Masupirdine showed clinically meaningful improvement in the neuropsychiatric symptoms associated with agitation/aggression in patients with AD, and reduced aggression in animal models. Masupirdine could be a differentiated therapeutic option for the management of agitation/aggression in Alzheimer's patients. Masupirdine is currently being studied for the management of agitation in patients with dementia of Alzheimer's type.

Disclosures: R. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Tadiparthi:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Benade:** A. Employment/Salary (full or

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Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Clinical development of SEMA4D blocking antibody, pepinemab, a novel potential treatment for neurodegenerative disease

Authors: *E. EVANS[1], T. FISHER[1], V. MISHRA[2], A. READER[1], E. SMITH[1], J. LEONARD[1], A. FEIGIN[3], E. SIEMERS[4], J. WITTES[5], M. ZAUDERER[1];
[1]Vaccinex, Rochester, NY; [2]Vaccinex Inc., Rochester, NY; [3]The Marlene and Paolo Fresco Inst. for Parkinson's and Movement Disorders, NYU Langone Hlth., New York, NY; [4]Siemers Integration LLC, Zionsville, IN; [5]Statistics Collaborative, Washington DC, DC

Abstract: Pepinemab (VX15/2503), a humanized IgG4 monoclonal antibody, blocks the binding of semaphorin 4D (SEMA4D) to its plexin receptors. SEMA4D is upregulated in diseased neurons and triggers glial activation. Downstream effects of chronic activation can aggravate neurodegeneration. Blocking antibody to SEMA4D has been shown to ameliorate pathology and symptoms of disease in preclinical models of Huntington's disease (HD), Alzheimer's disease (AD), multiple sclerosis, and Rett Syndrome. SIGNAL-HD (NCT02481674) is a completed Phase 2 placebo-controlled study of pepinemab in HD. SIGNAL-AD (NCT04381468) is an ongoing Phase 1b/2a placebo-controlled trial in AD that opened for enrollment in June 2021. Enrollment updates for SIGNAL-AD, as well as proof of concept safety, clinical, and biomarker data from the SIGNAL-HD trial will be presented. The SIGNAL-HD study included 301 subjects with late prodromal and early manifest (EM) HD, treated monthly by intravenous infusion for at least 18 months. Pepinemab was well-tolerated and detected in cerebrospinal fluid at the dose level targeted for biological efficacy. Co-primary efficacy measures consisted of a two-item HD cognitive assessment family including One Touch Stockings of Cambridge and Paced Tapping components of the HD-Cognitive Assessment Battery (HD-CAB), and clinical global impression of change (CGIC), a global measure of clinical meaningfulness. The primary endpoints did not achieve statistical significance in this study, however, positive trends in the direction of pepinemab benefit were observed and were supported by additional analysis of secondary and exploratory endpoints. Treatment benefits in clinical and imaging endpoints appeared to be restricted to the EM subjects. A treatment benefit was observed in 6/6 components of the HD-CAB cognitive assessment battery, with a significant HD-CAB composite score (p=0.007). In a posthoc subgroup analysis of EM subjects with somewhat more advanced disease (baseline TFC 11 vs TFC 12 and 13), treatment appeared to improve CGIC status (p=0.04). Effects on cognition were further supported by prespecified exploratory imaging endpoints, demonstrating that pepinemab treatment reduced brain atrophy (volumetric MRI; caudate p=0.017) and inflammation (TSPO-PET), and slowed or reversed decline in metabolic activity in 26/26 brain regions,

with 15/26 regions showing a significant positive treatment effect ($p \leq 0.05$) in FDG-PET imaging. Pepinemab did not achieve primary efficacy outcome measures in the SIGNAL study, but favorable safety profile and positive trends in cognition and imaging endpoints encourage continued development in HD and AD.

Disclosures: E. Evans: A. Employment/Salary (full or part-time):; Vaccinex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vaccinex. **T. Fisher:** A. Employment/Salary (full or part-time):; Vaccinex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vaccinex. **V. Mishra:** A. Employment/Salary (full or part-time):; Vaccinex. **A. Reader:** F. Consulting Fees (e.g., advisory boards); Vaccinex. **E. Smith:** A. Employment/Salary (full or part-time):; Vaccinex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vaccinex. **J. Leonard:** A. Employment/Salary (full or part-time):; Vaccinex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vaccinex. **A. Feigin:** F. Consulting Fees (e.g., advisory boards); Vaccinex, Oxford BioMedica, Teva, Voyager. **E. Siemers:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly and Company, Acumen Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Vaccinex, Acumen Pharmaceuticals Inc, Biogen Inc., Cogstate Ltd., Prothena Inc., Sangamo Therapeutics Inc., Takeda Development Center Americas, Inc. **J. Wittes:** F. Consulting Fees (e.g., advisory boards); Vaccinex. **M. Zauderer:** A. Employment/Salary (full or part-time):; Vaccinex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vaccinex.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Annovis Bio

Title: Positive Clinical Outcomes of Posiphen in Two Phase 2a Studies—Alzheimer’s Disease and Parkinson’s disease

Authors: *C. FANG[1], M. MACCECCHINI[1], H. ZETTERBERG[2], M. CHEN[3], P. HERNANDEZ[4]; [1]Annovis Bio, Berwyn, PA; [2]Univ. of Goteborg, Goteborg, Sweden; [3]TCM group, Berkeley heights, NJ; [4]Ezy Med. Res., miami, FL

Abstract: Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function. By inhibiting the translation of amyloid precursor protein, tau and alpha-synuclein, our drug Posiphen has been shown in animal models to restore axonal transport, lower inflammation and protect nerve cells from dying. Posiphen preserved and restored full function in 7 animal models including Down Syndrome, Alzheimer’s disease (AD)

,stroke, traumatic brain injury, Parkinson's disease (PD), frontotemporal dementia, and blindness in acute glaucoma. Posiphen was proven safe in over 130 healthy and sick people [Maccecchini et al 2012]. To show that Posiphen reverses the toxic cascade and potentially shows efficacy in humans, we started two double-blind, placebo- controlled clinical phase 2a studies in AD and PD patients. In the first part of the study, we enrolled 14 AD and 14 PD patients (4 placebo and 10 treated with 80 mg posiphen QD). We took their blood, CSF and conducted safety evaluation and psychometric tests appropriate to the respective disease. The patients were treated for 25 +/- 2 days and had a second round of safety and psychometric tests. The plasma and CSF samples are being analyzed for markers of the toxic cascade leading to nerve cell death: AD and PD specific biomarkers, markers of axonal transport, inflammation, neurodegeneration and synapse health. The second part of the study is enrolling an additional 40 PD patients with the same study design to test the result on markers as well as on efficacy of different concentrations of posiphen. This second part will be completed and analyzed shortly. From the first part of the study, we are reporting statistically significant improvements in ADAS-Cog 11 in treated AD patients. In treated PD patients, we also see a strong trend in function improvements in the MDS-UPDRS. In both patient populations our drug statistically significantly improves speed, coordination, accuracy and attention in the WAIS coding test. We measured biomarkers and saw that inflammation was statistically reduced in AD and PD patients. The statistical significance holds whether the levels are compared within the same patients at 0 and at 25 days or between placebo treated and Posiphen treated at 25 days. Posiphen also reduced sAPPalpha, and beta, Tau, p-Tau and improved the Ab42/40 ratio. The other markers, such as aSYN oligomers, transport and synaptic markers are still being analyzed. In conclusion, we showed that Posiphen improves cognition in AD and motor function in PD patients and reverses the toxic cascade leading to nerve cell death.

Disclosures: C. Fang: A. Employment/Salary (full or part-time):; Annovis Bio. **M. Maccecchini:** A. Employment/Salary (full or part-time):; Annovis Bio. **H. Zetterberg:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Annovis Bio. **M. chen:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Annovis Bio. **P. Hernandez:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Annovis Bio.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Longterm results of Alzheimer's disease treatment with TPS (Transcranial Pulse Stimulation)

Authors: *P. NOVAK[1], H. LOHSE-BUSCH[2];
[1]Storz Med. AG, Taegerwilen, Switzerland; [2]Rheintalklinik, Bad Krozingen, Germany

Abstract: Low intensity shockwaves proved to be efficient for the treatment of non-unions, tendon and muscular pain, wound healing, heart insufficiency, erectile dysfunction, aesthetic disorders and since 1990 also neurological indications. The working principle is the mechanical stimulation of biological processes called mechanotransduction resulting in increased cell metabolism, release of nitric oxide (eNO) and of numerous growth factors. There is also an anti-inflammatory effect, stimulation of stem cells and of the innate immune system.Transcranial Pulse Stimulation TPS) uses shockwave pulses for mechanical stimulation of the brain tissue. Detailed animal evaluation conformed the experience from years of shockwave applications in other medical disciplines that the treatment is safe. There have been no negative side effects observed.Six Alzheimer's disease patients have been treated with TPS since 2010. The treatment consists of a booster block of 6 treatment sessions within 2 weeks and one re-treatment session per month after 3 months follow-up. 6000 shockwave pulses with energy flux density of 0.2mJ/mm^2 are applied in one session. The CERAD score is typically improved by 10-17% within the first 3 months. The long-term data exists for more than 3 years. The results to date show that the monthly re-treatment is sufficient for maintaining the improvement for at least one year. Thereafter a further improved treatment protocol has to be developed. As can be derived on behalf of the available data, the booster block will have to be repeated approximately every 18 months.The current experience proves that the treatment is safe and effective. A two-center trial with Neurolith (Storz Medical) has been successfully completed with 35 patients and resulted in regulatory clearance in Europe. Still, further trials with larger number of patients are necessary. A placebo controlled, randomized trial is ongoing.

Disclosures: P. Novak: A. Employment/Salary (full or part-time):; Storz Medical AG. **H. Lohse-Busch:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Storz Medical AG.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Social Media Narratives around Genetic Testing for Alzheimer's Disease

Authors: A. TAHAMI[1], S. DOOGAN[2], ***N. FARID**[2], M. BRAY[1], E. KARAHAN[1], Q. ZHANG[1]; [1]Eisai, Woodcliff Lake, NJ; [2]Real Life Sci., Wayne, PA

Abstract: Background: Apolipoprotein E- ε4 (APOE-4) is a gene variation known to increase the risk for Alzheimer's disease (AD). Increasingly, people are discussing APOE-4 genotyping in AD on social media. The goal of this study was to compare barriers, planning, and rationale of decisions for genetic testing among the AD population and the general public.
Objective: To investigate the differences between conversations around genetic testing within the AD population compared to the general population.
Methods: We used the RLytics Natural Language Processing (NLP) platform to aggregate and analyze narratives from over 100 social media portals. The posts were extracted from AD-specific social media using the search terms "APOE" or "Genetic Testing" and included in the AD group.

Additionally, we extracted posts from non-AD-specific social media sites using only the “APOE” as a search term to exclude posts referring to non-AD-specific genetic tests. This group of narratives was included in the general population group.
RLytics used relational concept models to classify the ways in which medical conditions and functions were reported in raw text.
Results: A total of 3729 narratives were included in the study. The AD population had 2106 narratives from 169 users. Of which, 70 were caregivers, 54 were patients, and 92 were unclassified. 1623 narratives were posted by 673 users in the general public. Next, these narratives were categorized into low level categories and then eight high-level categories: 1. Unmet Needs, Education and Support 2. Financial Concerns 3. Logistics Challenges 4. Emotional Reactions 5. Genetic Counseling 6. Personal/Family Planning 7. Data privacy, Security, and Protection 8. Concerns or skepticism about the accuracy of test/test results. Analysis revealed that persons in the AD population showed similar trends to the general population in terms of education and costs. But they were more concerned about the eligibility for testing and privacy of results.
Conclusion: Social media narratives provide us meaningful insights about genetic testing in AD and associated patient journeys. The AD population showed a need for resources that provide more information around where they can get tested and the privacy implications that come with genetic testing. Whilst the general population sought general educational resources for genetic testing.

Disclosures: A. Tahami: A. Employment/Salary (full or part-time):; Eisai. **S. Doogan:** A. Employment/Salary (full or part-time):; Real Life Sciences. **N. Farid:** A. Employment/Salary (full or part-time):; Real Life Sciences. **M. Bray:** A. Employment/Salary (full or part-time):; Eisai. **E. Karahan:** A. Employment/Salary (full or part-time):; Eisai. **Q. Zhang:** A. Employment/Salary (full or part-time):; Eisai.

Poster

P239. Therapeutic Strategies: Clinical Trials

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P239.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Osher Lifelong Institute
American Goldstar Manor

Title: Dual-task Intervention on Strength, Balance, and Executive Function Among Older Adults with Various Cognitive Levels

Authors: *N. VISNJEVIC[1], J. LEE[1], C. `. DAVIS[2], K. IP[2], J. IGNACIO[2], K. FAILDO[2], Y.-H. CHO[3], V. KRISHNAN[4];
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Abstract: Falls continue to be a leading cause of fatal and nonfatal injuries among older adults. Although dual-task (DT) interventions have shown to improve gait functionality in older adults (Agmon et al.,

2014), only limited studies have investigated the effects of dual-task intervention on muscle strength and clinical balance as a function of cognitive health in older adults (Elnaz et al., 2020). This study sought to investigate the effects of a DT training on strength, balance, and executive function in older adults with different levels of cognitive health. We hypothesized that both the mild, and cognitively impaired older adults will show larger improvement on strength, clinical balance, and executive function than would the older adults with no cognitive impairment from a DT intervention. Forty-one community-dwelling older adults (M_{age} = 76.46 ±7.88) participated in this study. Cognitive impairment was measured using the Montreal Cognitive Assessment (MoCA). Participants were classified as having no cognitive impairment (n = 17, MoCA ≥ 26), mild impairment (n = 13, 22 ≤ MoCA ≤ 25), and impairment (n = 11, MoCA < 22). Muscle strength was assessed using the Senior Fitness Test (SFT) with Arm curl, 30-second Chair Stand and 2-minute Step tests. Clinical balance was assessed with Fullerton Advanced Balance (FAB) Scale. Executive functioning was measured using the Trail Making Test (TMT). The intervention consisted of two sessions per-week (75 minutes per session) for eight weeks. Participants started with strength and balance exercises and then performed the same exercise while performing a cognitive task (e.g., word association, verbal fluency). Results of a two-way MANOVA indicated a marginally significant interaction of Time X Group on FAB only, Wilks λ=.863, $F(2, 38) = 3.016$, p =.061. Also, both FAB (Wilks λ =.227, $F[1, 38] = 129.235$, $p < .001$) and SFT (Wilks λ =.533, $F[3, 36] = 9.692$, $p < .001$), but not TMT, scores improved after the intervention for all groups. The level of cognitive impairment played a role such that the cognitively healthy group had higher FAB score ($p = .017$) and arm-curl score of SFT ($p = .055$) than the cognitively impaired group, and the cognitively healthy group had higher TMT score than each of the other two groups ($p < .0001$ for both).The DT intervention improved both balance and strength for all groups, providing evidence for the effectiveness of the DT intervention in reducing fall risks regardless levels of cognitive health. This result is particularly important for cognitively impaired older adults who have poorer balance and muscle strength than those who have no or mild impairment and thus are more prone to falls.

Disclosures: N. Visnjevic: None. **J. Lee:** None. **C.`. Davis:** None. **K. Ip:** None. **J. Ignacio:** None. **K. Faildo:** None. **Y. Cho:** None. **V. Krishnan:** None.

Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.01

Topic: C.10. Brain Injury and Trauma

Support: NIH/NINDS-UG3/UH3 Cooperative Agreement 5UG3/UH3NS106945-02
State of California Brain Injury Research Center

Title: Astrocyte injury subpopulations and fluid biomarkers validate acute neurotrauma MRI phenotypes in mild to moderate rat controlled cortical impact

Authors: *I. WANNER[1], A. TOBAR[1], S. ARREDONDO[1], J. LOPEZ[1], T. E. VAN METER[3], G. SHAW, Dr[4], N. VANDERVEER-HARRIS[2], A. PAYDAR[2], N. G. HARRIS[2];

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Abstract: This is a TOP-NT consortium project. Successful translation of preclinical research needs noninvasive classification tools to assess TBI in rat and human. To inform on context of use, biomarkers and neuroimaging need to reflect underlying injury phenotypes. Our objective was to achieve unbiased association of astrocyte injury-defined biomarkers (Halford et al., 2017) and volumetric MRI with quantitative histopathology. We used mild to moderate controlled cortical impact at 0.5-35 hours postinjury with sex, time, and region as covariates and randomly assigned sham (anesthesia, scalp incision; 8-24/group). We developed new rat and human compatible serum biomarker ELISAs for GFAP and aldolase C (ALDOC). Pan-astrocyte marker ALDOC stained gray matter astrocytes that were assessed for microstructural changes validated by morphometry. Immunofluorescence of ALDOC and immunoglobulins, for interstitial bleeding, were measured using standardized densitometry in juxtaposed areas of peak injury indicated by MRI. Unbiased MRI maps of individual injury burden, deviation (z=3.1) from the mean sham template, included deformation, T2*, diffusivity, kurtosis, modeled intra- and extracellular spaces. Undirected, multiple comparison-corrected (FDR $p<0.05$) bivariate regressions (R^2: 0.2-0.87) were done on outlier-removed datasets, a priori using marginal means (>3xSD) and posthoc by Mahalonobis distance (>3) and Cook's D (>1). Hyperacute serum ALDOC (0.5-4 hours) and serum GFAP associated with astrocyte decline. CSF GFAP correlated with pericontusional structurally compromised and ALDOC-depleted astrocytes. Astrocyte demise was associated with cortical gray matter volumes of T2* hypointensity (hemorrhage), mean kurtosis and decreased radial diffusivity. Astrocyte demise and blood extravasation covaried with increased acellular ALDOC proteinopathy. This novel astrocyte pathology was predicted by hyperacute rise in serum ALDOC and was proportional to gray matter increased FA and decreased radial kurtosis. White matter edema, volumes of elevated MD, covaried with CSF GFAP levels while gray matter brain swelling was linked to serum ALDOC elevation, matching predominant expression in fibrous (GFAP) and protoplasmic (ALDOC) astrocytes. Serum ALDOC elevation correlated with reduced gray matter microscopic diffusivities. These noninvasive measures of acute cytotoxic edema concur with compromised astrocyte subpopulations and blood-brain barrier breach, collectively reflecting damage to the neurovascular unit. This unique TBI endophenotype may support diagnostic monitoring of TBI and bidirectional experimental-clinical translation.

Disclosures: I. Wanner: None. **A. Tobar:** None. **S. Arredondo:** None. **J. Lopez:** None. **T.E. Van Meter:** None. **G. Shaw:** None. **N. Vanderveer-Harris:** None. **A. Paydar:** None. **N.G. Harris:** None.

Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.02

Topic: C.10. Brain Injury and Trauma

Title: Stochastic resonance elicited in the mice injured brain

Authors: *P. E. TRUJILLO GARIBAY[1], J. A. MARTINEZ CABRAL[1], L. P. OSUNA CARRASCO[1], C. TORO-CASTILLO[1], M. TREVINO-VILLEGAS[2], B. *DE LA TORRE-VALDOVINOS[1];

[1]Electrónica, Univ. de Guadalajara - CUCEI, Guadalajara, Mexico; [2]Neurociencias, Univ. de Guadalajara - Inst. de neurociencias, Guadalajara, Mexico

Abstract: Rodents interact with the environment mostly through their vibrissae, making them capable to recognizing objects and textures; afterwards, the sensory information is collected and processed when crossing ventral posterior medial nucleus and posteromedial nucleus of the thalamus and get to the barrel cortex (primary somatosensory cortex known as well as S1). A lesion in the cortex S1 in rodents produces a decrease in the amplitude of the record of Local Evoked Field Potentials (LEFP), as well to disturb the rodent's proprioception. In the present work we used male C57BL Black (24±4 grams) mice and we performed a radially symmetrical (0.5mm diameter) Penetrating Brain Injury (PBI) to track S1 LEFP amplitude during 30 days in mice treated with Tamoxifen and without treatment. Additionally, we added white gaussian noise to evaluate the stochastic resonance effect in both treated and not treated injured mice. We design a protocol which consist in two experimental groups: 1) mice lesioned with treatment (MWT n=10) and 2) mice lesioned without treatment (MWOT n=10). Tamoxifen was applied 3 continues days after injury (1mg/kg). The response of the LEFP was recorded to assess functional recovery before and after injury. Two electrodes were implanted on the surface of the cortex S1 for the recording of LEFP 3, 7, 14 and 30 days after the injury of both groups. In addition, the LEFP with white noise added to the record were also analyzed, which generates the effect of stochastic resonance (SR). The amplitude and the Signal to Noise Ratio (SNR) from LEFP´s recordings were analyzed with a signal analyzer self-designed script in MATLAB. After 30 days, the amplitudes of the LEFP´s were favored in both groups, the treated and no treated groups had a recovery. Animals treated with tamoxifen showed a statistically significant recovery ($p < 0.05$) in the amplitude and the SNR. Furthermore, the latency in the treated group was reduced 20%. We examine the statistical significance of the amplitude between the three conditions: Optimal Noise (ON), Zero Noise (ZN), and High Noise (HN) in both groups. An analysis uncovered significant differences between ZN and ON ($p<0.05$) and between ON and HN ($p<0.05$). Additionally, in the condition ON the latency was reduced 20%. In conclusion, Tamoxifen could help the functional recovery of the brain. These results are the first where is experimenting in a PBI protocol with SR.

Disclosures: P.E. Trujillo Garibay: None. **J.A. Martinez Cabral:** None. **L.P. Osuna Carrasco:** None. **C. Toro-Castillo:** None. **M. Trevino-Villegas:** None. **B. *de la Torre-Valdovinos:** None.

Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.03

Topic: C.10. Brain Injury and Trauma

Support: NIA AG053524

Title: Mild Traumatic Brain Injury Impairs Episodic Memory in Rats

Authors: *G. D. NAH, M. ANTONOPOULOS, N. L. PORT, J. D. CRYSTAL;
Indiana Univ., Bloomington, IN

Abstract: Mild traumatic brain injury (mTBI) is the most common type of traumatic brain injury, and it leads to temporary memory impairment as well as a probable excitotoxic response in the brain, including the hippocampus. While many animal models of mTBI exist, it is difficult to fully replicate the injury seen in humans, and the effects of mTBI on the microenvironments of the brain are unclear. Additionally, few treatments specifically for mTBI currently exist. Notably, the Wayne State modified weight drop rat model of mTBI simulates many accurate elements of sport-related injuries, as well as the excitotoxic response in the hippocampus. Yet, this model has not previously been evaluated using a complex memory task. In this study, rats were trained in an odor-based item-in-context task which dissociates episodic and non-episodic memory. The animals then underwent either a weight drop or sham treatment using the Wayne State model. After the manipulation, animals continued in the item-in-context task. Episodic memory was moderately impaired in the injured rats, but not in the sham rats. Non-episodic memory was not impaired in either group. These findings are the first to document episodic memory impairment in an animal model of mTBI.

Disclosures: G.D. Nah: None. **M. Antonopoulos:** None. **N.L. Port:** None. **J.D. Crystal:** None.

Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.04

Topic: C.10. Brain Injury and Trauma

Support: VA ORD, Career Development Award
Buroughs Wellcome Fund, Career Award for Medical Scientists

Title: Large-scale mapping of local field potentials associated with deficits in probabilistic reversal learning task in rats after traumatic brain injury

Authors: S. HULYALKAR[1], J. CRAMER[1], M. FRANCOEUR[1], *D. RAMANATHAN[1,2];
[1]UC San Diego, La Jolla, CA; [2]Mental Hlth., VA San Diego Healthcare Syst., San Diego, CA

Abstract: Behavioral flexibility describes the ability to respond flexibly to a changing environment. It is a key aspect of executive control, and is impaired after traumatic brain injuries. A probabilistic reversal learning (PRL) task is often used in both humans and animals to measure aspects of behavioral flexibility. In this task, responses are rewarded probabalistically (one response will be rewarded with an 80% probability and the other with a 20% probability). When subjects need to learn the reward contingencies and respond accordingly, reward contingencies are switched and subjects need to re-learn the new reward contingencies.
A bilateral frontal injury model in rats has been shown to recapitulate many executive function deficits, including this deficit in reversal learning. In this study, using distributed recordings of field potentials across brain targets, we have begun to characterize electrophysiological deficits associated with these impairments in behavioral flexibility after injury. Rats were given either a bilateral frontal traumatic brain injury or a sham-injury, followed by implantation of a neural probe that measures local field potentials across up to 32 brain sites. Our approach allows for an unbiased sampling of brain activity across visual,

limbic, motor, cognitive and reward related brain networks.
Following injury/implantation, animals were then trained on the PRL task for up to 3 months. We observed significant differences in performance on the task after the TBI injury, including differences in the number of reversals animals perform, and their tendency to repeat a rewarded trial (a key aspect of reinforcement learning). In association with these behavioral deficits, we observed clear differences in both reward processing within prefrontal and ventral striatal brain regions after the injury. Some of these changes normalized, but many remained. These electrophysiological deficits occurred in brain regions both adjacent and distal to the site of the injury.

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Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.05

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R21NS108223

Title: Use MRI to assess changes in dopaminergic function in adolescent mice acutely after mild traumatic brain injury

Authors: *Y. I. CHEN[1], S. CHAN[1], S. GENET[1], L. WU[2], K. K. KWONG[1], M. WHALEN[2];
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Abstract: Major sequelae of mild traumatic brain injury (mTBI) in adolescence include attention deficit hyperactivity disorder (ADHD) symptoms and cognitive deficits. As cognitive deficits are linked to abnormal dopamine (DA) function in the brain, we aimed to examine DA function after repetitive closed head injury (rCHI) in mice. Here we showed the result in the acute phase after rCHI. We used BOLD fMRI and cerebral blood flow (CBF) to assess neuronal DA reactivity in responding to D-amphetamine (AMPH) to examine the DA transmission, to dihydrexidine (DHDD) and quinpirole (QUIN) to examine the D1- and D2-like receptor reactivity.
Method
rCHI model: Male C57Bl/6 mice (DOL 38) were subjected to weight drop (53 g, 46 in) daily for 3 days which produces deficits in Morris water maze and rotarod tests but no structure damages. Around 9 months, rCHI mice show hyperactivity phenotype.
MRI: Mice were imaged at a 9.4T Bruker MRI scanner. BOLD responses to ip challenge of AMPH 1mg/kg, DHDD 3mg/kg, or QUIN 2mg/kg were acquired via repetitive FLASH images (30 sec/time point for total of 65 min, DA ligand was injected at t = 15 min). pCASL was used to measure CBF at baseline and at 1 hour after drug challenge.
Results
BOLD results (Figure 1) AMPH led to significant BOLD increases ($p<0.05$) in nucleus accumbens (NAc) in rCHI (n=9) but significant decreases in sham mice (n=7). In thalamus, only rCHI mice showed

significant increase. QUIN led to significantly greater BOLD decreases in NAc in sham (n=6) than in rCHI (n=6) mice. DHDD led to bigger BOLD activated area in cortex in rCHI (n=7) than in sham mice (n=9).
CBF results (Figure 2) Both AMPH and DHDD led to significantly greater CBF decreases in rCHI (n=4) than in sham (n=5) mice ($p<0.01$) in the insular cortex, thalamus, and hypothalamus. DHDD led to significantly greater CBF decreases in Caudate/putamen in rCHI mice. QUIN had greater CBF decreases in cortex in rCHI mice (n = 5 / group).
Conclusion Although we anticipated DA function to deteriorate progressively and slowly after rCHI, we started to observe functional differences in key DA areas such as NAc and thalamus acutely after rCHI.

Figure 1. BOLD responses to DA ligands

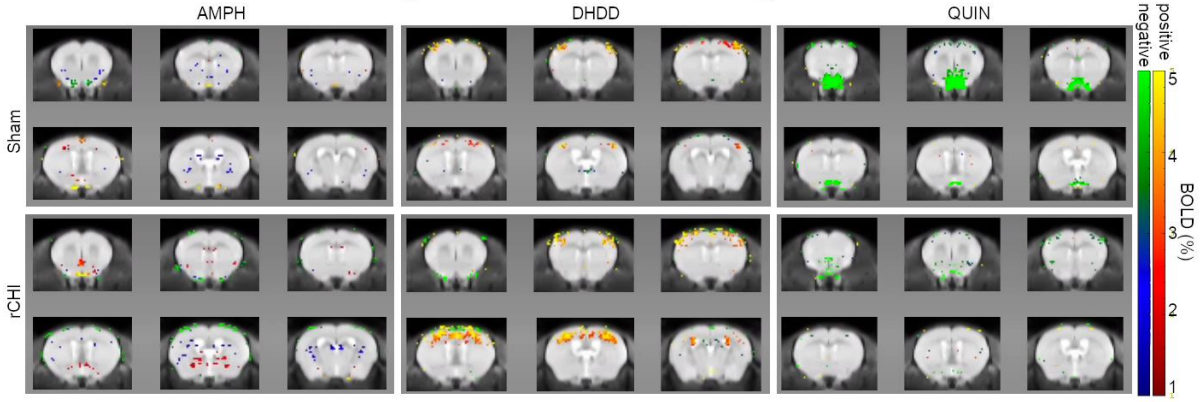
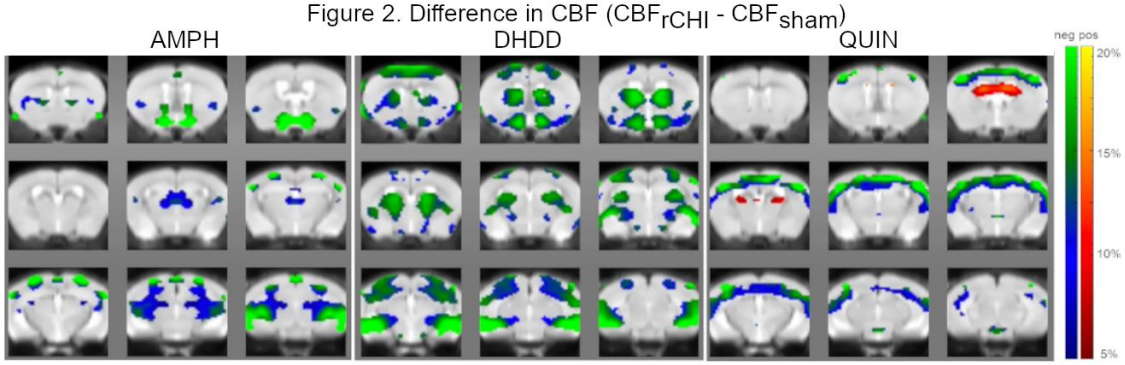


Figure 2. Difference in CBF (CBF_{rCHI} - CBF_{sham})



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Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.06

Topic: C.10. Brain Injury and Trauma

Support: NIH-NINDS R21NS102991

NIH-NINDS R21NS111174
NIH-NIA R21AG028680

Title: Sex differences in recovery of fine motor function in a rhesus monkey model of cortical injury

Authors: *K. R. BOTTENFIELD[1], B. G. E. BOWLEY[1], M. A. PESSINA[1], M. MEDALLA[1,2], D. L. ROSENE[1,2], T. L. MOORE[1,2];
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Abstract: Stroke disproportionately affects women over 65 who evidence increased severity of impairment and higher mortality rates than men. Human studies have explored risk factors that contribute to these differences in impairment and mortality, but additional research is needed to investigate sex differences in the rate and extent of functional recovery. In the present study, we used our rhesus monkey model of cortical injury and fine motor impairment to investigate sex differences in the rate and degree of motor recovery following injury. Aged male (n=4) and female (n=5) rhesus monkeys were trained on a task of fine motor function of the hand before undergoing surgery to produce a cortical lesion limited to the hand representation in the primary motor cortex. Post-operative testing began two weeks after the damage and continued for 12 weeks. All trials were video recorded and latency to retrieve a reward was quantitatively measured to assess the trajectory of post-operative response latency and grasp pattern compared to pre-operative levels. Results showed that in terms of recovery of fine motor performance, during the first five days of post-operative testing females returned to their pre-operative latency significantly faster than males ($p = 0.04$). In addition, females returned to their pre-operative finger-thumb grasp pattern significantly faster ($p = 0.04$) and more completely ($p = 0.004$) than males. Postmortem analysis showed no differences in lesion volume between males and females. To evaluate the possible role of estrogen, we compared pre-operative estrogen levels to all measures of recovery of function but found no significant relationship of estrogen levels to any recovery measures. To evaluate brain markers of recovery, immunohistochemistry experiments are underway to determine if there are sex differences in microglial mediated inflammation in the brain tissue. The findings of this study demonstrate the importance of including sex as a variable and the need to further explore the role of sex hormones that may differentially affect recovery outcomes in the primate brain.

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Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

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Program #/Poster #: P350.07

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R61/R33 NS115089
NIH Grant P30 DA048742
Minnesota Spinal Cord Injury and Traumatic Brain Injury Research Grant

Title: Widespread changes in cerebral cortical functional connectivity following mild, repetitive traumatic brain injury in the mouse

Authors: S. W. CRAMER[1], *L. S. POPA[2], S. HALEY[1], E. P. SCOTT[2], R. E. CARTER[2], J. DOMINGUEZ[3], J. D. ARONSON[2], L. SABAL[2], E. FLAHERTY[2], C. C. CHEN[1], S. B. KODANDARAMAIAH[3], T. J. EBNER[2];
[1]Neurosurg., [2]Neurosci., [3]Mechanical Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Mild traumatic brain injury (mTBI) often results in brief loss of consciousness, impaired attention and concentration, memory problems, impulsivity, and headache without associated hemorrhage or structural pathology on CT imaging. Effects of repeated mTBI are cumulative and can lead to chronic traumatic encephalopathy, suggestive of global alterations in cortical networks. Using a transparent, morphological conformant polymer skull, we performed mesoscopic Ca^{2+} imaging to evaluate how mTBI alters patterns of interactions across the dorsal cerebral cortex. Transgenic mice (Thy1-GCaMP6f) were subjected to single injury directly to the motor cortex, for 3 consecutive days. Sham mice underwent the same injury protocol without cortical impacts. Histopathological examination of the brain following mTBI demonstrated ipsilateral elevation of GFAP (marker for reactive astrocytosis) and Iba1 (marker for microglial activation) signal at 24 hours post-injury with recovery after 48 hours post-injury. There was a transient microglial activation to mTBI, with reduced ramification ipsilateral to injury at 24 hours with recovery at 48 hours and beyond. Motor and cognitive effects performed using rotarod and Barnes maze, respectively, did not demonstrate deficits following TBI. On mice head-fixed to a freely moving disk we performed dual-wavelength mesoscopic Ca^{2+} imaging (7 mm x 7 mm field of view, 20 Hz) of the dorsal cerebral cortex during spontaneous behaviors. To assess for changes in cortical function, we used spatial independent component analysis to segment the hemodynamics-corrected mesoscopic Ca^{2+} imaging data into functional independent components (ICs) in sham and mTBI mice starting 2 weeks prior and up to 7 weeks post-injury. Correlations between IC time courses determined cerebral functional connectivity. We observed significant widespread, bilateral changes in functional connectivity between ICs immediately following impact that persisted for up to 7 weeks, far exceeding the changes observed in sham controls. Further analyses showed that the mTBI effects are driven by correlation decreases between specific nodes. We also observed an increase in the clustering of reduced correlations during the first three weeks post injury. These results suggest our repetitive mTBI mouse model produces a transient neuroinflammatory response, no identifiable alterations in cognitive or motor behavior but widespread, chronic alterations in cortical connectivity. The findings recapitulate salient features of human mTBI thus providing a means to study disease mechanisms and possible therapeutic interventions for traumatic brain injury.

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Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.08

Topic: C.10. Brain Injury and Trauma

Support: TriService Nursing Research Program
USU Center for the Study of Traumatic Stress

Title: Inflammation and post-traumatic headache after Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) injury in rats

Authors: *H. SPENCER[1,2], K. RADFORD[3,2], M. BOESE[3,2], R. BERMAN[4,2], S. KIM[5,2], Y. KIM[6,2], A. FU[6,2], J. MCCABE[7,2], K. CHOI[8,2];
[1]Program in Neurosci., [3]Daniel K. Inouye Grad. Sch. of Nursing, [4]Ctr. for the Study of Traumatic Stress, [5]Sch. of Med., [6]Preclinical Behavior and Models Core, [7]Anatomy, Physiology, and Genet., [8]Psychiatry, [2]Uniformed Services Univ., Bethesda, MD

Abstract: Traumatic brain injury (TBI) affects millions of people each year and constitutes a critical public health problem, yet has no standard approved therapeutics. In addition to increased inflammation following TBI, post-traumatic headache (PTH) is one of the most frequent adverse outcomes of TBI and may have detrimental effects on the quality of life for TBI patients. For this study we used the Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA), a recently developed technique that replicates the biomechanical mechanism of how humans sustain an impact TBI. To our knowledge, no CHIMERA studies have investigated the relationship between inflammation and PTH outcomes. Male Sprague-Dawley rats with an indwelling jugular vein catheter were exposed to 1x, 2x, or 3x repetitive CHIMERA impacts (~5-15 seconds between impacts). Catheter blood was collected 2, 4, and 6 hours after injury and 1, 2, 3, and 7 days after injury to determine the levels of plasma inflammatory cytokines. Brain tissue was collected at 7 or 14 days post-CHIMERA to determine effects on microglial and astrocyte activation. To determine the presence of PTH after CHIMERA, animals also underwent behavioral testing: (1) periorbital and hindpaw allodynia assessment by von Frey filament stimulation, and (2) photosensitivity by the light/dark box test. Animal weight and locomotor activity after injury were also monitored. Preliminary results indicate that repeated CHIMERA produced minimal allodynia, and short-term effects on weight loss and locomotor activity. Further analysis is in progress to determine CHIMERA effects on neuroinflammation and plasma cytokine levels in the same animals. Thorough characterization of clinically relevant rodent TBI models will enhance our understanding of the mechanisms of TBI that drive frequently experienced adverse symptoms and ultimately aid in the development of potential therapeutics.

Disclosures: H. Spencer: None. **K. Radford:** None. **M. Boese:** None. **R. Berman:** None. **S. Kim:** None. **Y. Kim:** None. **A. Fu:** None. **J. McCabe:** None. **K. Choi:** None.

Poster

P350. Brain Injury: New Animal Models and Systems Level Biomarkers

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P350.09

Topic: C.10. Brain Injury and Trauma

Support: NRF MSIT 2020M3E5D9080660

Title: Quinpirole-mediated regulation via dopamine D2 receptors/Akt/GSK3-β signaling inhibits neurodegeneration in traumatic brain injury

Authors: M.-G. JO, S. ALAM, J.-S. PARK, M. IKRAM, H.-J. LEE, M.-W. KIM, M.-H. JO, *M.-O. KIM;
Div. of Applied Life Sci. (BK21 FOUR), Col. of Natural Sci., Gyeongsang Natl. Univ., Jinju, 52828, Korea, Republic of

Abstract: Brain injury is a significant risk factor for chronic gliosis and neurodegenerative diseases. Currently, no treatment is available for neuroinflammation caused by the action of glial cells following brain injury. In this study, we investigated the quinpirole-mediated activation of dopamine D2 receptors (D2R) in a mouse model of traumatic brain injury (TBI). We also investigated the neuroprotective effects of quinpirole (a D2R agonist) against glial cell-induced neuroinflammation secondary to TBI in adult mice. Our results showed suppression of D2R expression and deregulation of downstream signaling molecules in ipsilateral cortex and striatum after TBI. Quinpirole administration regulated D2R expression and significantly reduced glial cell-induced neuroinflammation via the D2R/Akt/glycogen synthase kinase 3 beta (GSK3-β) signaling pathway after TBI. Quinpirole treatment concomitantly attenuated increase in glial cells, neuronal apoptosis, synaptic dysfunction, and regulated proteins associated with the blood-brain-barrier, together with the recovery of lesion volume in the TBI mouse model. This study showed that quinpirole administration after TBI reduced secondary brain injury-induced glial cell activation and neuroinflammation via regulation of the D2R/Akt/GSK3-β signaling pathways. Our study suggests that quinpirole may be a safe therapeutic agent against TBI-induced Alzheimer's disease and Parkinson's disease.

Disclosures: M. Jo: None. **S. Alam:** None. **J. Park:** None. **M. Ikram:** None. **H. Lee:** None. **M. Kim:** None. **M. Jo:** None. **M. Kim:** None.

Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P370.01

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Closed loop electrical neuroprosthesis to restore urodynamic function after spinal cord injury

Authors: *L. MAHE[1], R. HUDELLE[2], S. AMIR[3], E. LAVEIX[4], S. KOMI[5], M. GAUTIER[5], G. ROBAIN[6], F. FALLENGER[5], S. P. LACOUR[7], J. SQUAIR[7], J. BLOCH[9], A. PHILLIPS[10], G. COURTINE[8];
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Abstract: A spinal cord injury (SCI) scatters the communication between supraspinal centers and the spinal cord circuitry responsible for maintaining urodynamic functions. This loss of communication disrupts the coordination of detrusor muscle contractions and the necessary relaxation of the external urethral sphincter. Consequently, people with SCI experience constant incontinence, chronic urine retention, recurrent urinary tract infections, and other uro-renal complications. Here, we developed a conceptual and engineering framework to design an electrical spinal cord neuroprosthesis that targets circuitry in the spinal cord responsible for modulating the detrusor muscle and the external urethral sphincter. We first established a rodent model of chronic urodynamic dysfunction after SCI. Clinically-inspired assessments of urodynamic functions revealed a complete impairment of normal micturition and significant bladder overactivity that developed over time after injury. To identify the spinal segments most capable of modulating detrusor and external urethral sphincter contractions, we applied epidural electrical stimulation (EES) to each spinal segment, while measuring the activity of both muscles. We identified highly-specific hotspots over the lumbosacral spinal cord that, when stimulated with EES, enable contraction or relaxation of the detrusor and external urethral sphincter. Chemogenetic experiments revealed that EES induces detrusor contractions through a circuitry involving large-diameter parvalbumin neurons located in the dorsal root ganglia and excitatory interneurons within the urodynamic hotspots. We then combined CT scans, MRI sequences, and computational modelling to design a neuroprosthesis that targets urodynamic hotspots in the spinal cord. This neuroprosthesis was fabricated using e-dura technology. Closed-loop algorithms adapted the onset and amplitude of EES bursts to restore the coordination between bladder contraction and sphincter relaxation. The restoration of this coordination reduced bladder hyperreflexia and triggered micturition. These experiments provide a foundation to develop a neuroprosthesis to manage bladder dysfunction in people with SCI.

Disclosures: L. Mahe: None. **R. Hudelle:** None. **S. Amir:** None. **E. Laveix:** None. **S. Komi:** None. **M. Gautier:** None. **G. Robain:** None. **F. Fallenger:** None. **S.P. Lacour:** None. **J. Squair:** None. **J. Bloch:** None. **A. Phillips:** None. **G. Courtine:** None.

Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P370.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Defitech foundation
Onward medical
RESTORE.network
Wings for Life Foundation
Compute Canada
Natural Sciences and Engineering Research Council
Canadian Institutes of Health Research

Title: Targeted neurotechnologies reverse autonomic dysreflexia after spinal cord injury

Authors: *J. E. SORIANO[1], R. HUDELLE[2], J. W. SQUAIR[1,2], S. AMIR[2], L. MAHE[2], M. GAUTIER[2], M. TSO[1], A. BICHAT[2], O. RIZZO[2], K. GALAN[2], Q. BARRAUD[2], S. P. LACOUR[2], J. BLOCH[3], A. A. PHILLIPS[1], G. COURTINE[2];
[1]Univ. of Calgary, Calgary, AB, Canada; [2]Swiss Federal Inst. of Technol. (EPFL), Lausanne, Switzerland; [3]CHUV, Paudex, Switzerland

Abstract: Spinal cord injury (SCI) induces a syndrome called autonomic dysreflexia (AD), in which there is a dangerous onset of excessively high blood pressure. AD induces debilitating headaches and contributes to increased risks of stroke and heart disease. Recently, we developed a *neuroprosthetic baroreflex* based on epidural electrical stimulation (EES) of the thoracic spinal cord that controls blood pressure in closed-loop. We reasoned that the *neuroprosthetic baroreflex* may also have the capacity to treat AD. To study this possibility, we conducted a series of experiments to understand the circuitry underlying AD, and to determine whether this circuitry is compatible with the hypothesis that EES could prevent the development of AD. To enable these experiments, we established mouse and rat models of upper-thoracic SCI that lead to the development of AD over the course of four weeks. First, we asked whether the induction of AD triggers transcriptional activation of neurons in the lower thoracic spinal cord segments, since we previously identified these segments as the key hemodynamic hotspots required to restore hemodynamic stability. We found that AD elicited neuronal activity primarily in two regions: the hemodynamic hotspots in the lower thoracic spinal cord, and lower lumbar segments, where colorectal afferents are located. This activity coincided with an increased density of synaptic projections from lower lumbar segments to the hemodynamic hotspots in mice with SCI. Subsequent chemogenetic experiments revealed that AD is dependent on the activation of specific interneurons embedded within the hemodynamic hotspots. Likewise, chemogenetic inactivation of these interneurons in the hemodynamic hotspots blunted pressor responses induced by EES. We therefore surmised that chronic application of the *neuroprosthetic baroreflex*, called autonomic neurorehabilitation, could enable a circuitry remodelling that would prevent the development of AD. After two weeks of daily autonomic neurorehabilitation, AD decreased in intensity and eventually completely reversed. Future work will thus aim to establish a framework to develop a mechanistically-informed neuroprosthetic therapy for AD.

Disclosures: J.E. Soriano: None. **R. Hudelle:** None. **J.W. Squair:** None. **S. Amir:** None. **L. Mahe:** None. **M. Gautier:** None. **M. Tso:** None. **A. Bichat:** None. **O. Rizzo:** None. **K. Galan:** None. **Q. Barraud:** None. **S.P. Lacour:** None. **J. Bloch:** None. **A.A. Phillips:** None. **G. Courtine:** None.

Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P370.03

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Defitech foundation

Title: Neuroprosthetic management of orthostatic hypotension in multiple system atrophy restores walking

Authors: *J. SQUAIR[1], M. BERNEY[2], M. CASTRO JIMENEZ[2], N. HANKOV[1], R. DEMESMAEKER[1], S. AMIR[1], A. PALEY[2], G. DUMONT[1], L. ASBOTH[2], F. BECCE[2], P. SCHOETTKER[2], G. WUERZNER[2], J. F. BALLY[2], G. COURTINE[1], J. BLOCH[2];
[1]EPFL, Geneva, Switzerland; [2]CHUV, Lausanne, Switzerland

Abstract: Multiple system atrophy is an adult-onset, sporadic, rapidly evolving neurodegenerative disorder characterized by parkinsonian features (MSA-P), cerebellar features (MSA-C), or a combination of both. Central to the definition of MSA is the presence of autonomic failure, which manifests as orthostatic hypotension and/or urodynamic dysregulation. This hemodynamic instability is due to the degeneration of catecholaminergic neurons located in the rostral ventrolateral medulla and of sympathetic preganglionic neurons embedded in the thoracic spinal cord, among other relevant areas. We recently developed a *neuroprosthetic baroreflex* that leverages the ability of epidural electrical stimulation (EES) applied over the thoracic spinal cord to modulate the activity of sympathetic preganglionic neurons. We showed that EES activates sympathetic preganglionic neurons through the recruitment of large-diameter afferent fibers where they enter into the spinal cord. This *neuroprosthetic baroreflex* stabilized hemodynamics in humans with severe orthostatic hypotension due to cervical spinal cord injury. Although the etiology of orthostatic hypotension observed in individuals with MSA differs from those with spinal cord injury, both conditions disrupt the communication between brainstem vasomotor regulatory centres and sympathetic preganglionic neurons embedded in the thoracic spinal cord. Therefore, we reasoned that the neuroprosthetic baroreflex could manage orthostatic hypotension in patients with MSA, thereby enabling prolonged verticalization and walking. Here, we implanted this neuroprosthesis in a patient with MSA who presented with critical hemodynamic instability. The *neuroprosthetic baroreflex* restored sufficient hemodynamic regulation to enable the patient to stand and walk despite more than a year of immobility. While the therapeutic efficacy of the neuroprosthetic baroreflex in patients with MSA must be confirmed in a large-scale clinical trial, these results open the possibility that hemodynamic instability of patients with MSA may be managed effectively using bioelectronic medicine.

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Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

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Program #/Poster #: P370.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation
Wyss Centre for Bio and neuroengineering

Title: Cellular and molecular choreography of spinal cord injury

Authors: *M. GAUTIER, J. W. SQUAIR, M. A. SKINNIDER, C. KATHE, T. H. HUTSON, N. REGAZZI, Q. BARRAUD, M. A. ANDERSON, G. COURTINE;
EPFL, Genève, Switzerland

Abstract: A spinal cord injury (SCI) triggers a complex and progressive cascade of secondary injuries involving inflammatory cell infiltration and cytokine release, apoptosis, demyelination, excitotoxicity, ischemia and the formation of fibrotic scar and surrounding astrocyte scar border. How the individual types and subtypes of cells of the central nervous system coordinate to mediate this response remains incompletely understood. This lack of understanding hinders both our basic understanding of SCI biology as well as the development of new therapeutics. Here, we present a multi-omic atlas of spinal cord injury in mice at single-cell resolution. We applied single-nucleus transcriptomics, spatial transcriptomics, and single-nucleus ATAC-seq to profile 18 experimental conditions spanning the natural history of SCI. In total, we collected single-cell profiles from >600,000 nuclei from the lesion site. Cell type prioritization of the resulting dataset revealed distinct perturbation-responsive cell types and subpopulations across experimental conditions, allowing us to unravel variations in cellular phenotype associated with injury severity, sex, age, and pharmacotherapy. Spatial transcriptomics resolves the locations of SCI-associated cellular phenotypes on a spatiotemporal atlas of the lesion site as it evolves over the first months post-injury. This comprehensive single-cell atlas of SCI will open new avenues to understand and redirect disease pathobiology.

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Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: SNF grant PZ00P3_185728
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Dr. Miriam and Sheldon G. Adelson Medical Foundation

Title: Guiding and maintaining regenerating propriospinal axons after complete spinal cord injury

Authors: *M. MILANO[1], J. W. SQUAIR[1], N. D. JAMES[1], N. CHO[1], S. L. CETO[1], T. H. HUTSON[1], C. KATHE[1], A. DE COUCY[1], T. J. DEMING[2], Z. HE[3], M. V. SOFRONIEW[4], G. COURTINE[1], M. A. ANDERSON[1];
[1]EPFL, Genève, Switzerland; [2]Univ. of California Los Angeles, Los Angeles, CA; [3]Children's Hosp Boston, Boston, MA; [4]UCLA Schl Med., Los Angeles, CA

Abstract: Propriospinal neurons spontaneously form relay circuits which mediate function following incomplete spinal cord injury (SCI) and are therefore desirable to target for regenerative intervention following complete SCI. Propriospinal axons can be induced to regrow past anatomically complete SCI by following a developmentally inspired biological repair strategy which (i) upregulates neuron intrinsic

growth capacity, (ii) provides permissive substrate, and (iii) chemoattracts axons into and past injury sites. Yet, despite impressive growth, functional recovery remains elusive. Potential reasons for this include improper targeting of regenerating axons to their appropriate targets in the lumbar spinal cord, and a lack of persistence of regenerating axons at chronic timepoints post injury. In this study, we are examining methods to overcome these challenges by using additional spatially and temporally spaced hydrogel depots of glial derived neurotrophic factor (GDNF) to chemoattract axons to relevant targets in the lumbar spinal cord, and by using a lentivirus expressing GDNF to maintain these connections over time. Supported by SNF grant PZ00P3_185728, Wings for Life, and the Dr. Miriam and Sheldon G. Adelson Medical Foundation.

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Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Defitech Foundation
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ONWARD medical
Swiss National Science Foundation (NCCR Robotics)
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Title: Identification of a specific spinal neuron subpopulation that is both necessary and sufficient to regain walking after spinal injury

Authors: *T. H. HUTSON[1], C. KATHE[2], J. SQUAIR[3], M. A. SKINNIDER[4], N. REGAZZI[5], M. GAUTIER[5], S. L. CETO[5], N. D. JAMES[6], N. CHO[7], S. A. KOMI[9], R. DEMESMAEKER[7], K. MATSON[10], L. ASBOTH[11], Q. BARRAUD[12], A. LEVINE[13], S. P. LACOUR[8], J. BLOCH[14], G. COURTINE[7];
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Abstract: Epidural electrical stimulation of the lumbar spinal cord combined with neurorehabilitation (EES^{REHAB}) restored walking in nine people with chronic spinal cord injury (SCI). This recovery was associated with an unexpected reduction in the metabolic activity in the lumbar spinal cord, which might reflect an activity-dependent selection of specific neuronal subpopulations that become essential to walk after SCI. To identify these putative neurons, we modelled the technological and therapeutic features underlying EES^{REHAB} in mice. We applied single-nucleus RNA sequencing and spatial transcriptomics to elaborate a spatially-resolved molecular atlas of recovery in the spinal cord. A single population of excitatory interneurons located in intermediate laminae emerged as essential for recovery of walking. While these neurons were not necessary to walk before SCI, chemogenetic or optogenetic inactivation or targeted ablation demonstrated that they are essential to regain walking after SCI. In turn, chemogentically augmenting their activity instantly phenocopied the recovery of walking enabled by EES^{REHAB}. Together, these results identify a specific spinal neuron subpopulation that is necessary and sufficient to regain walking after SCI, and establish a molecular cartography framework that allows the identification of neurons underlying complex behaviours.

Disclosures: T.H. Hutson: None. **C. Kathe:** None. **J. Squair:** None. **M.A. Skinnider:** None. **N. Regazzi:** None. **M. Gautier:** None. **S.L. Ceto:** None. **N.D. James:** None. **N. Cho:** None. **S.A. Komi:** None. **R. Demesmaeker:** None. **K. Matson:** None. **L. Asboth:** None. **Q. Barraud:** None. **A. Levine:** None. **S.P. Lacour:** None. **J. Bloch:** None. **G. Courtine:** None.

Poster

P370. Spinal Cord Injury: Training, Rehabilitation, and Repair II

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Program #/Poster #: P370.07

Topic: C.11. Spinal Cord Injury and Plasticity

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Swiss National Science Foundation (subside 310030_192558)
Rolex for Enterprise
Carigest Promex
Defitech Foundation

Title: Modelling EES^{Rehab} in mice to identify neurons necessary for functional recovery after paralysis

Authors: *C. KATHE[1], T. H. HUTSON[2], J. SQUAIR[3], M. SKINNIDER[7], N. REGAZZI[4], M. GAUTIER[4], S. L. CETO[8], N. D. JAMES[5], N. CHO[6], S. A. KOMI[9], R. DEMESMAEKER[6], K. MATSON[10], A. LEVINE[11], L. ASBOTH[12], Q. BARRAUD[13], J. BLOCH[14], G. COURTINE[6];
[1]Swiss Federal Inst. of Technol. Lausanne, Geneve, Switzerland; [2]Dept. of Med., Imperial Col. London, London, United Kingdom; [3]EPFL, Lausanne, Switzerland; [4]EPFL, Geneva, Switzerland; [5]SV BMI UPCOURTINE, [6]EPFL, Geneve, Switzerland; [7]Univ. of British Columbia, Vancouver, BC, Canada; [8]UCSD, La Jolla, CA; [9]Ecole Polytechnique Fédérale De Lausanne, Lausanne, Switzerland; [10]NINDS, NIH, Bethesda, MD; [11]Natl. Inst. of Neurolog. Disorders and S, Bethesda, MD; [12]Swiss Federal Inst. of

Technol., Lausanne, Switzerland; [13]EPFL - Ctr. For Neuroprosthetics, Geneve, Switzerland; [14]CHUV, Paudex, Switzerland

Abstract: Rehabilitation enabled by epidural electrical stimulation after spinal cord injury (EES^{REHAB}) leads to robust functional improvement. Here, we show that epidural electrical stimulation of the lumbar spinal cord combined with neurorehabilitation (EES^{REHAB}) restored walking in nine people with chronic spinal cord injury (SCI). This recovery was associated with a reduction of abnormal late muscle reflexes and of the metabolic activity in the lumbar spinal cord during walking. We hypothesized that this unexpected reduction reflects activity-dependent selection of specific neuronal subpopulations that become essential to walk after SCI. To identify these putative neurons, we modelled all the technological and therapeutic features underlying EES^{REHAB} in mice. We applied single-nucleus RNA sequencing and spatial transcriptomics to the spinal cord of these mice and then employed cell type and spatial prioritization to uncover the neurons involved in the recovery of walking. A single population of excitatory interneurons located in intermediate laminae emerged. These results identify a specific neuron subpopulation that is necessary and sufficient to regain walking after SCI, and establish a framework to identify the neurons producing complex behaviour using molecular cartography.

Disclosures: C. Kathe: None. **T.H. Hutson:** None. **J. Squair:** None. **M. Skinnider:** None. **N. Regazzi:** None. **M. Gautier:** None. **S.L. Ceto:** None. **N.D. James:** None. **N. Cho:** None. **S.A. Komi:** None. **R. Demesmaeker:** None. **K. Matson:** None. **A. Levine:** None. **L. Asboth:** None. **Q. Barraud:** None. **J. Bloch:** None. **G. Courtine:** None.

Poster

P425. Olfactory Circuits and Network Dynamics

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P425.01

Topic: D.05. Olfaction and Taste

Support: CRCNS: NSF 1724221

Title: Serotonergic input to the olfactory bulb modulates odor detection in rats

Authors: *O. ESCANILLA, A. AGGARWAL, B. COSTA, I. LEE, D. SCOTT, C. LINSTER; Neurobio. and Behavior, Cornell Univ., Ithaca, NY

Abstract: We examine the behavioral function of serotonin (5-HT) inputs for processing olfactory information in the first olfactory network, the olfactory bulb (OB). Previous data have suggested that 5-HT modulation in the OB acts both presynaptically on sensory input and enhances principal cell activation and dynamics. We use a simple non-associative behavioral paradigm, paired with local bulbar infusions of 1 µM 5-HT HCl, 5 µM 5-HT HCl and 200 µM of the 5-HT antagonist cinanserin HCl to probe the role of 5-HT in odor detection and discrimination. Rats are tested using an odor recognition paradigm similar to the one used in Hackett et al. (2015). During encoding, rats are presented with odor vials containing the carrier only (mineral oil). After a short delay, during the recall or recognition trials rats are presented with odor vials containing the carrier or an odor at one of 5 concentrations. Significant investigation of an odor signals that rats can detect this odor and differentiate from the carrier. We find

that manipulations of 5-HT signaling in the OB modulated the rats' odor detection performance in this task. These findings will be followed up with a reward motivated task, previously shown to enhance detection of low odor concentrations. We then show in a computational model of OB in which known cellular effects of 5-HT have been integrated that our observed behavioral results could be mediated by changes in overall dynamics and signal to noise ratio mediated by 5-HT receptor activation. We first reproduce cellular effects reported from brain slice experiments and then test how these would affect odor responses in vivo. We observe stronger and more synchronous activity in response to odor stimulation leading to changes in odor detection thresholds in the network. We have yet to implement the reported presynaptic effects on sensory inputs in addition to the cellular effects we added here.

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Poster

P425. Olfactory Circuits and Network Dynamics

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Program #/Poster #: P425.02

Topic: D.05. Olfaction and Taste

Support: NIDCD F32DC018232
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NIDCD R01DC016519

Title: Selective attention to odors engages an olfactory-prefrontal network.

Authors: *H. L. CANSLER[1], E. E. IN 'T ZANDT[1], W. KHAN[1], M. MA[2], D. W. WESSON[1]; [1]Pharmacol. and Therapeutics, Ctr. for Smell and Taste, Univ. of Florida, Gainesville, FL; [2]Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Sensory perception is influenced by a variety of factors aside from the stimuli themselves, including cognitive states like attention. In olfaction, secondary olfactory structures, especially the tubular striatum (also known as the olfactory tubercle), display sharpening of odor-evoked activity during selective attention in both humans and rodents. Here, we used rats to identify interregional networks underlying the effects of attention on olfaction. First, we used multiple cell-type specific tracing approaches to establish that the TuS is a privileged recipient of dense input from the medial prefrontal cortex (mPFC). Retrograde tracing revealed a strong population of TuS-projecting glutamatergic neurons in the prelimbic and infralimbic regions of the mPFC. Through anterograde tracing with AAVs encoding synaptophysin-GFP or -mRuby into the prelimbic and infralimbic cortex, respectively, we found that these projections most densely target the TuS, yet only weakly target other olfactory regions. Next, we used multisite local field potential recordings in combination with an olfactory selective attention task developed by our lab to investigate the functional role of this pathway. We found that odor-directed attention drove elevated gamma band power in the olfactory bulb (OB) and mPFC. We also found that spectral coherence in the beta range between the OB-mPFC and the mPFC-TuS was higher when rats attempted an intermodal attentional switch, indicating a role for these pathways in flexible attention.

Coherence in the respiratory theta range between the OB-mPFC was also greatly upregulated during the intermodal attentional switch. Finally, we recorded sniffing to determine whether active sampling dynamics could explain these changes in respiratory theta coherence. We found that while rats precisely structure their sniffing to the task, their sampling strategies were inflexible, despite agile behavioral shifts in olfactory attention. This indicates that top-down (e.g., from mPFC) versus bottom up (from sniffing) mechanisms are likely responsible for the effects of selective attention on olfactory cortex activity. Overall, these results begin to reveal an olfactory attention network and bring us closer to understanding the circuits that underlie odor-directed attention.

Disclosures: H.L. Cansler: None. **E.E. in 't Zandt:** None. **W. Khan:** None. **M. Ma:** None. **D.W. Wesson:** None.

Poster

P425. Olfactory Circuits and Network Dynamics

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P425.03

Topic: D.05. Olfaction and Taste

Support: NIDCD R01-DC014367

Title: Neural dynamics underlying retronasal olfaction and the consolidation of olfactory memory

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Abstract: Retronasal olfaction refers to the process by which odorants enter the nasal cavity through the mouth, particularly during eating, and produce olfactory percepts. To understand the neura ldynamics underlying retronasal olfactory processing as it relates to reward, gustatory, and learning circuits, we implanted bipolar electrodes and recorded local field potential in the ipsilateral olfactory bulb, olfactory tubercle, piriform cortex, gustatory cortex and hippocampus. In addition to neural signals, we monitored nasal respiration and jaw muscle movement to track sensorimotor inputs during breathing and licking of reward stimuli. Fast neural oscillations in the olfactory system denote different stages of a retronasal odor discrimination Go/No-Go task, with gamma (40-110Hz) present in the pre-sampling period in the OB local network and beta (15-35Hz) later after odor sampling in a more global network. These are somewhat different from the patterns seen during orthonasal olfaction (odors which come into the nose through sniffing). The dynamical patterns measured with coherence depend on the presence of retronasal odorant, reinforcement type, and interaction with breathing and licking. We also report the behavior of these same circuits during pre- and post-training sleep to track consolidation at the systems level and better characterize sleep states using neural signals in the olfactory system.

Disclosures: R. He: None. **L.M. Kay:** None. **A.E. Stuart:** None. **J. Zeng:** None. **M. Xu:** None.

Poster

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Program #/Poster #: P425.04

Topic: D.05. Olfaction and Taste

Support: NIGMS R25 GM069234 (KBA)
NINDS T32NS043124-15 (EH)

Title: Basal forebrain GABAergic neurons are important for behavioral-state dependent sensory processing.

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Abstract: Behavioral states including attention and arousal influence neuronal activity, affecting the processing of external stimuli and subsequent behavioral responses. This allows adaptation towards constantly changing contexts. In particular, top-down modulation of sensory regions from the basal forebrain (BF) allows flexibility in sensory processing. The BF contains various cell types including a heterogeneous population of GABAergic and cholinergic neurons projecting to the olfactory bulb. However, the role of GABAergic neurons in behavioral-state dependent sensory processing remains unclear. Here, we used fiber photometry and a genetically encoded calcium indicator to visualize GABAergic neuronal activity in the BF during an olfactory-cued discrimination task. We also chemogenetically manipulated BF GABAergic neuronal subtypes to observe how sensitivity and response bias are impacted by BF GABAergic signaling. We observe bidirectional response patterns in GABAergic neuronal activity which are time-locked to specific epochs of the behavioral task. Additionally, chemogenetically inhibiting BF GABAergic neurons significantly impacts task engagement and performance. Overall, we demonstrate a role for BF GABAergic neurons in modulating olfactory-guided behavioral responses.

Disclosures: K. Brandel-Ankrapp: None. **E. Hanson:** None. **B.R. Arenkiel:** None.

Poster

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Program #/Poster #: P425.05

Topic: D.05. Olfaction and Taste

Support: R01DC016063

Title: Neural Circuit Basis for Generating Spindle Oscillations in the Developing Olfactory System

Authors: *Z. ZHANG, D. C. COLINS, J. X. MAIER;
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Abstract: The brain changes throughout the life of an animal. Especially in early life, brains are structurally very different from adult brains and often considered "immature." However, animals must interact with their surroundings—process sensory input and transforming it into an appropriate behavioral output—as soon as they are born. We recently demonstrated that the neonatal olfactory system processes information in a stable manner: odor stimuli evoke spindle oscillations that are modulated by respiration and coherent between the olfactory bulb (OB) and piriform cortex (PC). The frequency of spindle oscillation remains stable between 10 and 20 Hz during the first two weeks of life, followed by a rapid increase of 20-30 Hz around postnatal day 15 (P15).
In work presented here, we investigated the circuit-level mechanisms underlying the generation of olfactory spindle oscillations. We recorded local field potential (LFP) activity simultaneously from OB and PC in awake rats ranging in age between P4 to P9 (n=27). Discrete Fourier transform (DFT) revealed that there was a significant information flow from bulb to cortex and cortex to the bulb in the spindle frequency range, suggesting that the generation of spindle oscillations relies on the feedback projections from the PC to OB. To investigate the causal effect of feedback projections on oscillatory activity, we recorded odor-evoked activity from the OB before and after pharmacological inactivation of the lateral olfactory tract through lidocaine injection (P5-P8, n=5). Inactivation caused a significant increase in oscillation frequency and shifted the temporal profile of oscillatory power relative to respiration. Thus, feedback projections modulate temporal and spectral characteristics of oscillations generated in the OB and may control different functional states of the neonatal olfactory system. Together, our results suggest that the neonatal olfactory system already exhibits adult-like circuit motifs, including net inhibitory feedback projections, capable of generating various complex activity patterns. Ongoing work is testing the relevance of these modes for neonatal odor perception behavior.

Disclosures: Z. Zhang: None. **D.C. Colins:** None. **J.X. Maier:** None.

Poster

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Topic: D.05. Olfaction and Taste

Support: T32 HL 007909 to LKS
Stanley Manne Children's Research Institute Visionary Award to LM
K23 AI 139337 to LM
R01 DC 015426 to TK

Title: Investigating the physiological and neural correlates of olfaction in infants

Authors: *L. K. SHANAHAN, L. B. MITHAL, S. OTERO, L. WAKSCHLAG, P. C. SEED, T. B. PARRISH, T. KAHNT;
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Abstract: The olfactory system serves critical functions in the earliest stages of human development. For instance, newborn infants show preference for maternal odors and are comforted by the scent of maternal breast milk. However, infant olfaction research is limited. Behavioral studies often rely on measures that are difficult to quantify (e.g., facial expression), and there are very few functional magnetic resonance imaging (fMRI) studies in this area. To address this gap, we exposed one-month-old infants to olfactory stimuli during fMRI. Infants were fed and swaddled prior to the scan to facilitate sleep, and they were fitted with (1) a custom nasal mask for odor delivery, and (2) a spirometer to measure breathing. Once asleep, infants were exposed to odors in blocks (5-seconds on/5-10-seconds off). Olfactory stimuli included two pleasant scents (ethyl hexanoate and isoamyl acetate) and two unpleasant scents (isovaleric acid and cyclopentanethiol). Preliminary breathing analysis suggests that odor valence may modulate respiration in infants, such that pleasant odors evoke a larger inhalation than unpleasant odors. fMRI data analysis is ongoing, and will shed light on the neural basis of olfaction in infants. Our work will promote a better understanding of the physiological and neural mechanisms underlying human olfaction at an early developmental stage.

Disclosures: L.K. Shanahan: None. **L.B. Mithal:** None. **S. Otero:** None. **L. Wakschlag:** None. **P.C. Seed:** None. **T.B. Parrish:** None. **T. Kahnt:** None.

Poster

P425. Olfactory Circuits and Network Dynamics

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Program #/Poster #: P425.07

Topic: D.05. Olfaction and Taste

Support: Lawnboy

Title: Mapping the human brain network for chemosensory perception

Authors: *A. BUSH[1], Z. A. KONS[1], A. HADANNY[1], T. PARKER[1], V. SARAVANAN[1], E. HOLBROOK[2], D. COELHO[3], R. CONSTANZO[3], M. RICHARDSON[1];
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Abstract: Background: Olfaction and gustation are chemosensory perceptions with a strong impact on quality of life and safety. However, the neurophysiological response to chemosensation has received less attention than other sensory modalities in humans. Here, we map the functional neuroanatomy and electrophysiology of olfactory and gustatory processing in the human brain. **Methods:** 13 epilepsy patients implanted by clinical indication with stereo EEG electrodes in areas with putative involvement in chemosensory responses performed an olfactory task. Participants were presented with 3 different smells and a blank using smell wands in block-randomized sequence and instructed to indicate detection of a smell (or certainty that none was present) with a keypress. After each trial, participants identified the stimulus with a multiple-choice question. 11 of these patients subsequently performed a similar gustation task using waterless taste strips. Timing of stimulus onset was recorded from video EEG review. **Results:** No olfactory or gustatory stimulus was identified more reliably than the others as assessed by a mixed-

effects model. However, olfactory stimuli reported as pleasant by each participant were identified more reliably than those reported as neutral. Response times and the fraction of correctly identified stimuli were variable across participants, but reproducible patterns were observed between individual stimuli. Cortical electrode coverage included the piriform cortex (7 [37]; # patients [# electrodes]), entorhinal cortex (7 [42]), middle insular area (7 [23]), posterior insular area (7 [20]), frontal opercular area (6 [17]), posterior orbitofrontal cortex (5 [18]) and perirhinal ectorhinal cortex (5 [14]). Time-frequency analysis of Local Field Potentials from these regions revealed stimulus-specific increases in low-gamma and broad-band gamma power following olfactory and gustatory stimulus presentation. Different cortical regions showed preferential activation in response to specific chemosensory modalities, including a stronger olfactory gamma response in the piriform cortex, entorhinal cortex, orbitofrontal cortex, and stronger gustatory gamma response in the insula, though significant overlap was observed. **Conclusions:** This study shows evidence of increases in gamma-band activity during olfactory and gustatory processing in humans, consistent with other sensory modalities and previous reports in animal models. Mapping the cortical chemosensory network in humans is an important step to explore the feasibility of neuroprosthetic devices for olfaction and gustation.

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Poster

P425. Olfactory Circuits and Network Dynamics

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Program #/Poster #: P425.08

Topic: D.05. Olfaction and Taste

Support: OIST corporation

Title: State-dependent linearisation of mixture responses in the olfactory bulb

Authors: A. M. ADEFUIN, J. REINERT, S. LINDEMAN, ***I. FUKUNAGA**;
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Abstract: One of the common challenges for sensory systems is to analyse complex signals from the environment and to segregate them into relevant and irrelevant parts. For the olfactory system, there is a unique difficulty associated with this task, due to a widespread nonlinear summation of component signals. Nonlinear summation is present at various stages of processing, including in the olfactory nerve input, and persists to the olfactory cortex, making it unclear whether the olfactory system can accurately analyse mixture responses. Here, we investigate how mice represent and utilise binary mixtures of odours, using a combination of behavioural and imaging experiments.
To probe how well mice are able to analyse binary mixtures, we trained head-fixed mice to perform Go/No-Go task, where water reward was associated with ethyl butyrate presentations (target odour), either as a single odour or in binary mixtures. The other odours in the panel comprised simple esters and other, structurally unrelated compounds. Odours were presented at relatively high concentrations, namely 1-5% of the saturated vapour, to increase the overlap in activity patterns. A two-photon imaging of

GCaMP6f from the apical dendrites of Tbet-expressing neurons showed the masking indices to range from 0.5 to 0.9, with methyl butyrate having the largest overlap with ethyl butyrate. An analysis of the behavioural data confirmed previous findings, where mice tend to make more mistakes when the stimulus contained odours with high masking indices. However, short training, the behavioural accuracy improved significantly, demonstrating the ability of the system to improve on the binary mixture analysis, even when the components evoke highly overlapping activity patterns.
To investigate possible mechanisms, we observed the activity of olfactory bulb output neurons in Tbet-Cre::Ai95D mice with a two-photon microscope. Contrary to previous reports from anaesthesised preparations, in mice performing the odour detection task, we found the overall summation to be relatively linear, with just 16.3% of ROIs (33/202 ROIs, 5 mice) showing significant deviation from linear summation. When the same mice were later anaesthetised with ketamine/xylazine, this proportion increased to 41.8% (43/103 ROIs). Investigating the mixtures in untrained but awake and engaged mice revealed that the majority of the above, state-dependent difference is explained by wakefulness, even though a small difference remained, accompanied by a residual difference in sniff patterns.
Altogether, our results demonstrate that the property of mixture representations in the olfactory system is highly state-dependent.

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Poster

P425. Olfactory Circuits and Network Dynamics

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Topic: D.05. Olfaction and Taste

Support: NIDCD DC014253
NIDCD DC000566

Title: The olfactory epithelium response to Herpes Simplex Virus 1 infection

Authors: *L. MERLE, C. S. NIEMEYER, B. D. BAXTER BOLT, A. GENTILE POLESE, J. HASSELL JR, A. N. BUBAK, M. A. NAGEL, D. RESTREPO;
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Abstract: Olfactory deficits related to viral infection have been highlighted during the COVID-19 pandemic. The sense of smell relies on the detection of odorant molecules by olfactory sensory neurons (OSNs) in the olfactory epithelium (OE). The OE lies within the nasal cavity and is constantly exposed to airborne pathogens. In addition, the OE constitutes a direct route of entry to the brain since OSNs axons project to the olfactory bulb (OB). However, viral infections of the OE do not necessarily result in encephalitis. This implies that the OE likely mounts robust inflammatory / immune responses that enable clearance of viruses and prevent direct spread to the brain. The OE includes different cell types that could contribute to fight against viruses. Microvillous cells (MVCs) are part of a family of TRPM5-expressing cells found in the airways and the intestine that respond to virus and bacteria, and we recently published a transcriptional analysis that revealed that MVCs express high levels of transcripts involved in immunity,

inflammation, and viral response. Here we investigated the OE response to infection with Herpes Simplex Virus 1 (HSV-1), a virus shown to promote Alzheimer's disease (AD). Mice were intranasally inoculated with HSV-1 strain McKrae (10^6 PFU, 15 µL in each nostril) and sacrificed 5 days later for tissue collection. At this timepoint, RT-qPCR revealed the presence of HSV-1 DNA in the OE and OB. Immunostainings showed sparse HSV-1 antigen presence in the OE and no HSV-1 antigen was detected in the OB. Iba1 staining suggested increased monocytes/microglia recruitment in the OE and OB. HSV-1 infection of 5xFAD mice (a mouse model of AD) appeared to increase amyloid-beta presence in the OE. We also used mice expressing channelrhodopsin under the ChAT promoter to investigate whether MVCs could play a role in triggering an antiviral response in the OE. Repeated optogenetic activation of MVCs induced an increase in the number of Ki67-positive cells in the basal side of the OE, suggesting increased proliferation of horizontal basal cells. We hypothesize that the OE response to HSV-1 prevents its spread through OSNs axons to the OB, and MVCs could play an antiviral role by interacting with olfactory stem cells.

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Poster

P441. Auditory Processing: Information Coding and Hearing Loss

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P441.01

Topic: D.06. Auditory & Vestibular Systems

Support: DNRF 117

Title: Sensory versus cultural expectations in the neural processing of music

Authors: *D. QUIROGA-MARTINEZ[1,4], M. KLIUCHKO[5], L. BONETTI[1], N. C. HANSEN[2,1], A. HØJLUND[3], M. PEARCE[6], E. BRATTICO[1,7], P. VUUST[1];
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Abstract: When listening to music, our brain constantly attempts to predict the sounds that will follow. Consequently, we often end up humming, singing along or tapping our foot to the beat, and find pleasure in listening to pieces we know very well. However, the nature and brain basis of musical predictions or expectations remain poorly understood. Concretely, we do not know the extent to which these expectations arise from a representation of the sensory properties of sounds or from a more cognitive and culturally shaped learning of the statistics of musical pieces and styles. Here, we employed computational modelling and MEG data to investigate the neural correlates of melodic expectations. We compared the performance of a cognitive model of music statistical learning (IDyOM) and a sensory model based on pitch distance, in predicting neural responses to sounds in listeners with different cultural backgrounds

and levels of musical expertise (N = 150). For this, an encoding model based on regularized linear regression was used. Our results show that, across listening conditions, datasets and types of listeners, the pitch distance model outperforms statistical learning models. Furthermore, in exploratory analysis, a Gaussian predictive coding model reproduced the relationship between pitch distance and neural activity, thereby pointing to a potential neurophysiological mechanism based on prediction errors. Our work suggests that sensory expectations play a prominent role in shaping neural responses to musical sounds.

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Poster

P441. Auditory Processing: Information Coding and Hearing Loss

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Program #/Poster #: P441.02

Topic: D.06. Auditory & Vestibular Systems

Title: Measuring fatigue in children with hearing loss

Authors: *B. ADAMS, S. THORNTON, I. WIGGINS, G. NAYLOR, P. KITTERICK;
NIHR Nottingham Biomed. Res. Ctr., Nottingham, United Kingdom

Abstract: Children with hearing loss appear to experience a greater level of fatigue than children with normal hearing (NH). This effect has been observed using self-report questionnaires in children with bilateral hearing loss (BHL) and more recently, in children with unilateral hearing loss (UHL). These questionnaires have often been designed for use in children with other chronic health conditions and only the Vanderbilt Fatigue Scale (VFS) measures listening-related fatigue. Little is known about the validity of any of these measures for use in children with hearing loss. The current objectives were to: (1) examine the sensitivity of these measures to distinguish fatigue levels in children with and without hearing loss; and (2) determine the extent to which each questionnaire measure unique aspects of fatigue. The study is still open to recruitment; to date 75 children aged 6-16 (31 NH; 18 UHL; 26 BHL) have completed the PedsQL™ Multidimensional Fatigue Scale (MFS), the VFS and the PROMIS Pediatric Fatigue Scale. They also completed the PedsQL™ Core and the HearQL questionnaires, which measure general and hearing-related quality of life respectively. Physical Activity Energy Expenditure (PAEE) was also measured using the Children's and Young Person's Physical Activity Questionnaire. Analyses of mean scores identified greater fatigue in children with hearing loss, and qualitatively similar levels of fatigue in children with UHL and BHL, regardless of which measure of fatigue was used. The Kaiser-Meyer-Olkin measure indicated that the strength of the relationships among variables was high, and a preliminary principal component factor analysis was performed. Of the two factors with eigenvalues >1, the first accounted for 86% of the variance and correlated with all fatigue and quality of life measures, and the second primarily accounted for variance in the physical activity measure explaining a further 14% of the variance. These results suggest that both generic and hearing-related measures of fatigue may be assessing similar constructs. The strong correlations between fatigue measures and both generic and hearing-related quality of life questionnaires may also indicate that these constructs may not be specific to fatigue. Alternatively, it is possible that fatigue impacts children with hearing loss in a similar way to

children with other physical chronic diseases, and that impact has a strong association with poorer quality of life. The disassociation between fatigue and PAEE suggests that current measures are assessing forms of fatigue that are distinct from physical tiredness.

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Poster

P441. Auditory Processing: Information Coding and Hearing Loss

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Topic: D.06. Auditory & Vestibular Systems

Support: CIHR Grant

Title: Grey matter thickness covariance in hearing and deaf cats using ultra-high field MRI

Authors: *S. G. GORDON[1], S. G. LOMBER[2];
[2]Physiol., [1]McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada

Abstract: Grey matter thickness derived from high-resolution magnetic resonance images is a useful non-invasive method of characterizing a macroscopic property of the cerebral cortex. When combined with an atlas of the species in question, these measurements can be used to distinguish anatomically relevant regions of thinning or thickening in an experimental or disease group from healthy controls. In this investigation we sought to examine if high-resolution MRI could be used to assess differences in cortical thickness covariance across regions between the brains of deaf cats and those of hearing controls. In this study we scanned 29 normal hearing and 26 deaf cats at 0.5mm isotropic resolution to look for areas of differing thickness using regions of interest (ROIs) from a digital cat brain atlas. All animals were examined in adulthood and deafness was induced during the first postnatal month by systemic administration of ototoxic drugs). Thickness maps were obtained using the Advanced Normalization Tools (ANTs) software package and this data was then processed in MATLAB. Age and gender were regressed out of the raw thickness values independently for each group, and all subjects' values were normalized to the mean of that group. These corrected regional thickness values were then correlated against each other for each pair of ROIs across all subjects within each group. After correcting for False Discovery Rate (FDR) using the Benjamini-Hochberg method, significant covariances were compared within and across the two groups. Plots of covariance vs. Euclidean distance between the ROI pairs were similar across hearing and deaf subjects, with each group showing increased significant covariances at very short distances (&gt5mm apart) and a more consistent distribution out to the extremes (~35mm). The mean covariance for bilaterally homologous ROIs were found to be significantly higher than for non-homologous ROI pairs in both groups. Numbers of significant covariances within and across sensory modalities differed between groups, with a notable result being an increase within the auditory modality in the deaf group as compared to the hearing group. Results from this work point to a change in the structural covariance across the cat brain following deafness, supporting the plasticity of the brain seen in past tracer and behavioral studies. While overall the covariance of ROIs in the hearing and deaf brain

remain similar, there are marked differences when looking at the regional and modal levels that require further analysis. Funding was provided by CIHR.

Disclosures: S.G. Gordon: None. **S.G. Lomber:** None.

Poster

P441. Auditory Processing: Information Coding and Hearing Loss

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Program #/Poster #: P441.04

Topic: D.06. Auditory & Vestibular Systems

Support: CIHR

Title: Diffusivity differences in the feline cerebral cortex following early-onset deafness

Authors: *A. SACCO, S. GORDON, S. LOMBER;
McGill Univ., Montreal, QC, Canada

Abstract: Following sensory deprivation, such as deafness, sensory-specific brain areas will reorganize to optimize processing, relying more heavily on remaining modalities - a phenomenon known as compensatory plasticity. For instance, following visual deprivation, higher-order visual areas adapt to process tactile stimuli, providing somatosensory enhancement to visually-deprived individuals. Considering the consequences of plasticity following visual deprivation, what changes occur throughout the brain following the loss of auditory input? Previous studies have examined microstructural alterations due to deafness using various techniques including behavioral paradigms, electrophysiology or imaging protocols. However, a more recent method is diffusion tensor imaging (DTI), which reveals differences in cerebral water diffusion, but nearly all prior investigations have studied these microscopic changes in humans rather than animals. The purpose of the present study was to extend microstructural investigations to cats - an animal model which is well studied for both auditory processing and hearing loss. Using DTI, diffusivity scalars including fractional anisotropy (FA) and mean (MD), axial (AD) and radial diffusivity (RD) were derived for 27 adult hearing control and 19 adult deaf cats (deafness onset in the first postnatal month), and compared across 155 grey and 21 white matter regions. All processing was accomplished using FSL and ANTs, followed by Wilcoxin rank sum and Benjamini-Hochberg statistical tests in MATLAB. Results indicate structural plasticity in various regions throughout the deaf brain in both tissue types, noted by a significant change in scalar value. As a general pattern, regions with significant scalar differences demonstrated an increased AD, RD and/or MD value in deaf felines compared to hearing, with substantially more white matter tracts affected than grey matter regions. Grey matter regions affected in the cat were the perirhinal cortex and frontalis agranularis, and white matter tracts affected include the corpus callosum, superior longitudinal fasciculus, and more. Overall, this is the first study to examine DTI alterations following auditory deprivation in cats, and it demonstrates that early-deafness incites plasticity throughout the brain well beyond auditory cortex.Funding was provided by CIHR.

Disclosures: A. Sacco: None. **S. Gordon:** None. **S. Lomber:** None.

Poster

P441. Auditory Processing: Information Coding and Hearing Loss

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Program #/Poster #: P441.05

Topic: D.06. Auditory & Vestibular Systems

Support: Human Frontier Science Program Long-Term Fellowship

Title: Neural mechanisms underlying reduced discriminability of speech in noise at high sound intensities

Authors: *C. G. HUANG, N. A. LESICA;
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Abstract: Hearing loss is a widespread global problem with an economic impact as well as individual detriments to those affected, decreasing overall quality of life. It is known that hearing loss causes distortions in the neural code, which subsequently leads to misinterpreted neural representations of complex sounds as information ascends the auditory pathway. As a result, perception of complex sounds such as speech is compromised. This problem is further complicated by the fact that sound intensity level varies in natural settings, both in quiet and in noisy backgrounds, and plays a critical role in speech perception. Therefore, we aimed to investigate how speech sounds heard at various intensity levels are represented and processed in the inferior colliculus (IC), using an established noise-induced hearing loss model in the Mongolian Gerbil, *Meriones Unguiculatus*. We hypothesized that the neural representation of speech at different sound intensity levels will vary and that this representation will change in noise-induced hearing loss. Specifically, we predicted that there will be strong effects of temporal masking in the boundaries between consonant and vowels in syllables, and that these effects will be most pronounced at higher intensity levels and in hearing loss conditions. To test this prediction, we recorded the responses of neurons in the central nucleus of the IC and assessed responses using a variety of information quantification techniques. We found that the neural discrimination between consonant classes at high intensity levels became worse in normal hearing animals in noisy conditions. In animals with hearing loss, however, consonant discrimination plateaued at high intensity levels in noisy listening conditions. Furthermore, when we introduced gaps between syllable elements, we observed an improvement in discriminability in both control and hearing loss conditions at high intensity levels, showing a mitigation of the masking effect between elements. Through improved understanding of the neural mechanisms that contribute to impaired perception with noise-induced hearing loss, we may be able to identify new directions for improved hearing aids and potential therapeutic treatments in the future.

Disclosures: C.G. Huang: None. **N.A. Lesica:** None.

Poster

P441. Auditory Processing: Information Coding and Hearing Loss

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Program #/Poster #: P441.06

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant 1T32DC016853

Title: The Role of Envelope and Temporal Fine Structure in Auditory Neural Coding of Timbre in Normal and Impaired Hearing

Authors: *A. SIVAPRAKASAM[1], H. BHARADWAJ[1,2], M. HEINZ[1,2];
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Abstract: A common psychoacoustic feature of both speech and music is *timbre*: defined as the "character or quality" of sound that allows it to be distinguished from others with the same pitch and intensity. Because of our inherent ability to perceive timbre we can distinguish between different instruments or voices, even when they play or sing the same note. However, the neurophysiological basis for our perception of timbre is enigmatic. It is not well-understood how biological and neurological deficits in the auditory periphery impact our coding and perception of timbre-related cues. To provide insight on this question, we developed a framework to investigate how auditory nerve (AN) coding of envelope (ENV) and temporal fine structure (TFS) features of stimuli with distinct timbre is affected by a flat 40 dB hearing loss. The first stimulus group consisted of recorded bassoon, flute, violin, and banjo sounds with the same pitch (A4). The second group consisted of *spiccato* and *martele* articulations recorded on the violin. A third group consisted of 4 synthetic instrument sounds with harmonic magnitudes estimated from the first group, and temporal envelopes modeled using sinusoidal amplitude modulation or (in the banjo) a decaying exponential. The AN response to each stimulus was simulated using a previously described 2018 AN-fiber model by Bruce, Erfani, and Zilany. ENV and TFS spectra were computed for auditory neurons with characteristic frequencies (CFs) at the first 7 harmonics of A4 using alternating-polarity peristimulus time histograms (apPSTHs). The original stimuli were processesed through a gammatone filterbank and the Hilbert analytical signal was used to extract ENV and TFS of the filtered stimuli. As CF increased, TFS magnitude-squared coherence between the AN model and filterbank was increasingly reduced in the hearing impaired simulations, despite a compensatory 40 dB volume increase. Mean ENV coherence within a low-frequency band (0-440 Hz) was enhanced in impaired vs non-impaired responses at low CFs, but diminished at CF>1320 Hz. Despite these general trends, the magnitude of these effects greatly varies depending on instrument and articulation. This implies that with hearing loss, one's ability to rely on timbre to differentiate instrumental sounds may not be consistent for every sound source. This framework can be further applied to study more sound sources, including speech, and may be paired with behavioral and neurophysiological experiments to explore individual differences in perception that arise from peripheral differences in etiology. All relevant code and figures may be found at: https://github.com/sivaprakasaman/Timbre_SfN_2021.

Disclosures: A. Sivaprakasam: None. **H. Bharadwaj:** None. **M. Heinz:** None.

Poster

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Title: Probing hierarchical prediction errors under different prediction precisions in auditory sequences: an ERP study

Authors: *Y.-Y. HUANG[1], F. B. KERN[1], C.-T. WU[1,2], Z. C. CHAO[1];
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Abstract: Perceiving sensory inputs from our external world highly depends on our internal model of prior experience. According to the predictive-coding theory, such perception is achieved by two bidirectional and interdependent processes operating across multiple hierarchies: top-down predictions which are generated through learning the probabilistic structure of sensory inputs, and bottom-up prediction errors which are the residuals between the predicted and actual inputs and which are sent back to update the predictions. However, it remains unclear how prediction errors are modulated by different prediction precisions established in a hierarchical structure of auditory sequences. In this study, we recorded 64-channel EEG in 30 subjects during an auditory local-global oddball paradigm, where auditory sequences with local regularity (tone-transition probability, TP) and global regularity (sequence probability, SP) were manipulated. We used 8 different auditory blocks, each consisting of 3 different sequences delivered with controlled probabilities, and established predictions with 8 different precisions. Prediction-error signals were quantified as the differences between event-related potential (ERP) responses to oddball stimuli and those to standard stimuli. Two ERP components were evaluated: mismatch negativity (MMN) and P300 which are thought to reflect lower-level and higher-level prediction-error processes, respectively. By using regression analysis, we found that the peak amplitude of MMN negatively correlated with TP, while the peak amplitude of P300 positively correlated with both TP and SP. Furthermore, regressing prediction-error signals at each time point against TP and SP showed that the signals in the early stage (128 to 190 ms) were correlated with TP, and the signals in the late stage (222 to 242 ms) were correlated with both TP and SP. These key findings support a hierarchical interpretation of the predictive-coding theory where prediction errors propagate across hierarchies modulated by that level's prediction precision. Our study also opens the door to potential future research examining atypical prediction precisions in individuals with mental illness.

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Poster

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Title: Vowel Encoding In The Human Superior Temporal Gyrus

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Abstract: Understanding natural speech requires listeners to map the continuous acoustics of vowel sounds onto discrete categories, compensating for variability in vowel production within and across speakers. Vowel identity is mainly determined by the central frequencies of the first two spectral peaks in the sound signal, the first (F1) and second (F2) formants. Behavioral experiments have shown that the auditory perception of vowels is non-linearly warped in continuous F1-F2 space towards the prototypes of each vowel category. Neuroscience research has suggested that cortical areas on the superior temporal gyrus (STG) responsive to speech encode the relative spectral location of F1 and F2. It remains unclear, however, how such a representation supports the warped perception of vowel categories. We exploited the spatial and temporal resolution of high-density intracranial recordings using natural speech and artificial vowel sound stimuli to study how neural representations at the local and population level encode the identity of vowel sounds. In Experiment 1, native speakers of Spanish (n = 7) listened to naturally produced Spanish sentences, while we recorded neural activity from the STG. Local neural populations in the STG were sensitive to either one or both formants, with a majority encoding both F1 and F2. Formant tuning resembled a nonlinear sigmoidal function, with heightened sensitivity to a narrow section of the full formant range. Formant tuning also shifted to adjust for speakers with different formant ranges. Decoding analyses showed that while neural responses recorded from a single electrode contact did not reliably discriminate between vowel categories, category representations did emerge at the population level when the range of F1 F2 encodings spanned the entire vowel formant space. Population level responses to vowel instances from the same category clustered together, as predicted by behavioral perceptual warping. The formants produced in natural speech are limited and as a result, Experiment 1 did not let us test whether neural activity in the STG is speech specific. To address this, in Experiment 2, native speakers of English (n = 8) listened to artificial vowel sounds with formant combinations extending beyond those encountered in natural speech. We found that the neural representation of formants did extend beyond the natural vowel formant space. Our results reveal that vowel-discriminating neural populations on STG are best characterized by complex, nonlinear two-dimensional formant receptive fields. When presented with human speech, these neural populations work in concert to encode vowel category and category boundary information.

Disclosures: I. Bhaya-Grossman: None. **Y. Oganian:** None. **E.F. Chang:** None.

Poster

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Title: State-dependent contributions of inhibitory transcriptomic subtypes to the activity of mouse visual cortex

Authors: S. BUGEON, T. HAULING, M. DIPOPPA, J. DUFFIELD, D. NICOLOUTSOPOULOS, I. PRANKERD, D. ORME, A. RITOUX, H. PENG, Y. ISOGAI, M. CARANDINI, K. D. HARRIS; Univ. Col. London, London, United Kingdom

Abstract: [Introduction] Cortical computations rely on microcircuits that involve multiple neuronal subtypes. While cortical neurons have been classically subdivided into broad subtypes (i.e. Vip, Sst and Pvalb positive interneurons), transcriptomic analysis has revealed more subpopulations of finely distinguished cortical neurons (Tasic et al., *Nature* 2018). [Methods] To decipher the functional properties and network activity of these fine cell types in primary visual cortex (V1), we applied post-hoc in situ transcriptomic analysis to cortical neurons after imaging their activity in vivo. We first recorded the activity of V1 neurons using two-photon calcium imaging in head-fixed, freely running mice, during visual stimulation. The visual stimuli comprised drifting gratings, sparse noise, and natural scenes. After these recordings, we collected consecutive brain slices and used landmarks to register them to a reference z-stack obtained in vivo. We then matched individual cells between the in vivo recordings and the brain sections. These brain sections were then processed for post-hoc transcriptomic analysis using in situ sequencing (Qian et al., *Nature Methods* 2020), a multiplexed single-RNA detection procedure that characterizes the expression of 73 genes at the single cell level. Based on this gene expression, we assigned a transcriptomic cell type to the recorded cells. [Results] To confirm that this procedure can reveal the functional properties of transcriptomic cell types, we first reproduced findings on the size tuning of the main V1 cell types, and their modulation by running (Dipoppa et al., *Neuron* 2018). We then explored finer distinctions among inhibitory transcriptomic subtypes. These could be arranged in a genetic continuum based on the first principal component of gene expression, and the position of a cell type in this continuum predicted how its spontaneous activity correlated with running. Transcriptomic subtypes also responded differently to other behavioral variables (eye saccades, running onset etc.) and to network events associated with bursts of activity in Sst cells. Finally, the visual response of given excitatory cell subpopulations could be predicted solely based on which interneuron subtypes they correlate with during spontaneous activity. [Conclusions] This method provides a high-throughput approach to characterize the in vivo activity of fine transcriptomic cortical cell types, revealing a striking role for the great diversity of interneurons subtypes in following the animal state gradient and shaping visual response according to it.

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Poster

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Title: Ndnf interneurons in layer 1 gain-modulate whole cortical columns according to an animal's behavioral state

Authors: *K. COHEN-KASHI[1], E. TSIVOURAKIS[1], D. KUSHINSKY[1], D. APELBLAT[1], S. SHTIGLITZ[1], E. ZOHAR[1], M. SOKOLETSKY[1], G. TASAKA[2], A. MIZRAHI[2], I. LAMPL[1], I. SPIEGEL[1];
[1]Neurobio., Weizmann Inst. of Sci., Rehovot, Israel; [2]Edmond & Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Processing of sensory information in neural circuits is modulated by an animal’s behavioral state, but the underlying cellular mechanisms are not well understood. Focusing on the mouse visual cortex, here we analyze the role of GABAergic interneurons that are located in layer 1 and express Ndnf (L1 NDNF INs) in the statedependent control over sensory processing. We find that the ongoing and sensory-evoked activity of L1 NDNF INs is strongly enhanced when an animal is aroused and that L1 NDNF INs gain-modulate local excitatory neurons selectively during high-arousal states by inhibiting their apical dendrites while disinhibiting their somata via Parvalbumin-expressing interneurons. Because active NDNF INs are evenly spread in L1 and can affect excitatory neurons across all cortical layers, this indicates that the state-dependent activation of L1 NDNF INs and the subsequent shift of inhibition in excitatory neurons toward their apical dendrites gainmodulate sensory processing in whole cortical columns.

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Poster

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Topic: D.07. Vision

Support: European Union's Horizon 2020 and FP7 Research and Innovation Program (grant agreement 945539) "Human Brain Project SGA3"

Title: Connectivity and function of chandelier cells in mouse primary visual cortex

Authors: *K. SEIGNETTE, N. JAMANN, R. PORNESO, L. DE KRAKER, C. VAN DER TOGT, E. RUIMSCHOTEL, P. NEERING, M. W. SELF, M. H. P. KOLE, C. N. LEVELT;
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Abstract: The mammalian cortex contains a large variety of inhibitory interneurons. The functions of many of these interneuron subsets are slowly becoming clear. However, one particular subtype of interneuron remains elusive: the chandelier cell. Chandelier cells are a unique GABAergic cell type that exclusively targets the axon initial segment of pyramidal neurons. Although chandelier cells were first identified decades ago, their exact function in the cortical network remains a mystery. Here, we studied connectivity, plasticity and function of chandelier cells in mouse primary visual cortex (V1). We made use of a novel genetic approach to label V1 chandelier cells for chronic two-photon calcium imaging and optogenetics in mice performing a behavioral task in a virtual tunnel. We further employed viral tracing and electrophysiology to study their connectivity with pyramidal cells. Our findings suggest that chandelier cells predominantly encode feedback information and that they target a subpopulation of pyramidal cells to modulate feedforward and feedback information streams in the cortical network.

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Poster

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Title: Excitatory cortical inputs produce distributed suppression via recurrent mechanisms described by a balanced network model

Authors: *J. F. O'RAWE, Z. ZHOU, P. K. LAFOSSE, A. LI, H. C. GOLDBACH, M. H. HISTED;
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Abstract: Local recurrent connections in the cortex are numerous and strong, yet their role in computation is not well-understood. Here we study the influence of recurrent connections in awake mouse V1 by probing network response to strong excitatory drive.
We first observed with two-photon cellular imaging that intense visual inputs created a salt-and-pepper pattern of suppressed and excited neurons. We then stimulated excitatory neurons optogenetically and

measured responses using both electrophysiology and calcium imaging at the 2-photon cellular level and widefield population level. When cortical excitatory cells are excited directly, we found suppressed cells in a similar salt-and-pepper pattern as with strong visual input. Though excitatory neurons were recruited a few milliseconds before inhibitory neurons, as expected (Excitatory latency: median 5.4 ms, inhibitory 7.9 ms, U = 1256, $p < 0.01$), excitatory and inhibitory cell populations relaxed to similar steady-state firing rates (mean difference t (134) = -0.21, $p = 0.83$), with some cells elevated and some suppressed. Further, the elevated and suppressed cells relaxed to their steady states with similar dynamics (Elevated steady state median latency: 39.9 ms, suppressed: 40.5 ms, U = 801, $p = 0.32$), suggesting a network mechanism where strong excitatory input drives the network to a new fixed point. Suppressed cells were highly intermixed even at the center of stimulation, though widefield imaging revealed a surround that is on average suppressed at ~500 microns away from the center of stimulation. A moderate- or strongly-coupled balanced-state cortical model with heterogeneous local connectivity can account for the results. Cortical inhibition-stabilized networks produce paradoxical suppression when inhibitory cells are stimulated. Here, we also found paradoxical suppression of excitatory cells, but via a different mechanism. The widespread yet distributed pattern of single-cell suppression arises from individual cells receiving different amounts of recurrent input from the excitatory and inhibitory network, not population-level changes in the mean excitatory and inhibitory rates. Together, these results show recurrent connectivity in mouse visual cortex can have dramatic effects on responses to input.

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Poster

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Title: Spatially specialized dendrites support orientation tuning in mouse visual cortex

Authors: *L. F. ROSSI[1], N. GHANI[2], C. REDDY[1], K. D. HARRIS[3], M. CARANDINI[1];
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Abstract: [Introduction] A longstanding hypothesis holds that the orientation selectivity of a neuron in primary visual cortex (V1) is related to the spatial pattern of the neuron's dendrites (Colonnier, J Anat, 1964). This hypothesis has eluded confirmation (Anderson et al, Nat Neurosci, 1999), but seems consistent with recent evidence that presynaptic inputs to a V1 neuron favor an elongated region of cortex coaxial with the neuron’s preferred orientation (Niel & Scanziani, Annu Rev Neurosci, 2021). We thus asked whether we could causally relate the shape of a neuron’s dendritic tree to the neuron’s orientation

selectivity and to the retinotopy of the surrounding cortex. [Methods] We applied 2-photon calcium imaging to record the orientation tuning and retinotopy of V1 populations using GCaMP, with sparse L2/3 pyramidal neurons labelled with a red fluorescent protein. We reconstructed the dendritic arbors of the red cells from structural z-stacks. We estimated the visual position of each dendritic segment from their path through the retinotopic map of V1. We then recorded longitudinally from the same neurons after pruning up to half of their total length of basal dendrites using laser dendrotomy (Park, Nat Commun, 2019). In one group of neurons we pruned 'parallel' dendrites which extended co-axially with the neuron's preferred orientation, and in a second group of neighbouring neurons, we pruned instead dendrites that extended orthogonally to the preferred orientation. [Results] Parallel dendrotomies significantly reduced responses to both the preferred ($p < 0.001$) and the orthogonal orientations ($p < 0.05$). On average, these effects were captured by a strong divisive scaling and a mild subtractive shift of the tuning curve. By contrast, orthogonal dendrotomies did not significantly change responses to either orientation. Changes in preferred orientation were not significantly different between the two groups (16 ± 4 deg, $p = 0.6$). Pruning larger portions of the parallel dendrites, but not of orthogonal dendrites, further reduced the responses ($R = 0.73$, $p<0.001$). [Conclusions] These results suggest a causal link between the dendritic architecture and the function of V1 neurons: by extending towards, and receiving more of, the appropriate co-tuned inputs, spatially specialised dendrites may provide a morphological substrate to establish orientation selectivity.

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Poster

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Title: Binocular receptive field match in primary visual cortex

Authors: *F. OLIANEZHAD, J. JIN, J.-M. ALONSO;
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Abstract: The primary visual cortex integrates convergent thalamic inputs from both eyes to generate binocular receptive fields. The receptive fields from the two eyes have to be precisely matched to process stimuli at the focus plane but also mismatched to extract information about visual depth. To quantify the precision of the binocular receptive-field match, we performed multielectrode recordings in cat visual cortex and measured visual responses to static stimuli and moving bars separately through each eye. The orientation selectivity (OS) and direction selectivity (DS) of each cortical site were calculated as (P-NP)/P, where P and NP are maximum responses to preferred and non-preferred stimuli. The ocular dominance (OD) and light-dark polarity dominance (PD) were calculated as (X-Y)/(X+Y), where X/Y are

maximum responses driven by contralateral/ipsilateral eyes (OD) or light/dark stimuli (PD). The binocular match in orientation preference was very accurate across cortical sites with diverse orientation selectivity and ocular dominance (OS ≥ 0.1, OD = -1 to 1, r = 0.96, mean orientation difference = 2.82 ± 17.87 degrees, n = 541 cortical sites). The binocular match in direction preference was also very accurate in cortical regions with high direction selectivity (DS ≥ 0.4, OD = -1 to 1, opposite/same direction preferences: 0/148 cortical sites). However, cortical regions with less direction selectivity included a small subset (7%) that had opposite direction preferences for contralateral and ipsilateral eyes (DS ≥ 0.2, OD = -1 to 1, opposite/same: 21/292 cortical sites). The orientation and direction selectivity were also binocularly matched but the correlations across eyes were weaker than for orientation preference (OS: r = 0.52, C/I means = 0.72/0.70; DS: r = 0.51, C/I means = 0.45 /0.44; OD = -1 to 1 and n = 541 for both). The response latency to static stimuli was binocularly matched but the average was ~2 msec faster for the contralateral than ipsilateral eyes (OD = -1 to 1, r = 0.44, n = 495, C/I means = 32.1/34.3 msec, p = 0.0003, Wilcoxon test). Finally, light-dark polarity dominance was also correlated across eyes. However, the correlation was strongest at cortical regions with high binocularity (OD = -0.1 to 0.1, r = 0.50, n = 92, C/I means = -0.16/-0.10) and became weaker in regions dominated by one eye (OD = -1 to 1, r = 0.19, n = 495, C/I means = -0.10/-0.10). We conclude that binocular receptive fields in primary visual cortex are precisely matched in orientation preference, direction preference, orientation/direction selectivity, response latency, light-dark polarity, and the match is most accurate at cortical regions with high stimulus selectivity and binocularity.

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Poster

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Support: NIH Grant EY014924

Title: Border ownership selectivity in neurons across layers of macaque V1 measured with high-density Neuropixels recordings

Authors: *S. ZHU[1,2], X. CHEN[2], T. MOORE[1,2];
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Abstract: It is known that neurons in visual cortex integrate visual information from far beyond their classical receptive fields (RFs). One example is the encoding of border-ownership in early macaque visual cortex, particularly in area V2, where the responses of almost half of the orientation-selective neurons signal the side to which an object's edge belongs. At present, it remains unclear to what extent neurons at earlier processing stages, particularly those across different layers in V1, signal border ownership. To address this question, we examined the responses of large populations of macaque V1 neurons to standard border ownership test stimuli. Neuronal activity was recorded using high-density, linear array Neuropixels probes (384 channels). In each session (N = 8), Neuropixels recordings were

largely confined to single cortical columns with RF eccentricities spanning between 4º and 8º, and in each session the neuronal RFs of recorded neurons were highly overlapping. Border ownership test stimuli consisted of solid white or black objects (4º or 8º squares) on a black or white background, respectively. The orientation of the object varied in 45º steps, and in each trial, one of the object's edges fell within the RFs of the neuronal population. As in previous studies, border ownership was quantified as the difference in neuronal responses to edges with identical orientation and local contrast but belonging to opposite sides of the object. Across recording sessions, we found that ~10% of V1 neurons responded differently to objects appearing on different sides even though orientation and local contrast remained constant within the RF. Neurons exhibiting border ownership selectivity were found within all cortical layers, including input layer 4C. We further measured the degree to which local populations of V1 neurons (n = 10) across layers could signal border ownership by testing the performance of a binary decoder in identifying the side to which the object's edge belonged. We found that the performance of the decoder exceeded chance level for populations of neurons across all cortical layers and occurred within ~70 ms in layer 4C. These results suggest that border ownership signals are present at the earliest stages of visual cortical processing.

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Poster

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Title: Mapping visual experience-dependent functional connectivity of feedback projections in the visual cortex of Fmr1 KO mice using channelrhodopsin-2-assisted circuit mapping

Authors: *X. CHENG, S. NAREDDULA, Y. TANG, A. A. CHUBYKIN;
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Abstract: Fragile X syndrome (FXS) is the most common form of inheritable autism spectrum disorders (ASD), which is often characterized by intellectual disability and visual learning deficits. Previous studies have described disrupted excitatory to inhibitory (E/I) balance, impaired short-term plasticity (STP), and altered functional connectivity in Fmr1 KO mice, the model of FXS. The feedback projections from higher visual areas to the primary visual cortex (V1) have been implicated in the regulation of cognitive processes such as prediction, attention, and visual learning. However, the mechanism of this regulation and how it is changed in FXS is poorly understood. To gain more insight into this process, we developed a new perceptual experience paradigm leading to the emergence of familiarity-specific theta oscillations. We measured the strength and properties of the long-range synaptic connections between the mouse higher visual area, lateromedial area (LM), and V1 in wildtype (WT) and Fmr1 KO mice, pre-and post-visual experience, using channelrhodopsin-2-assisted circuit mapping (CRACM). We have discovered that the strength of the connectivity from LM to the superficial layer II/III of V1 decreased in WT mice after the visual experience but did not change in Fmr1 KO mice. In contrast, the synaptic connections

from LM to the deep layer V of V1 were stronger after visual experience in Fmr1 KO compared to WT mice. Interestingly, some of the synaptic properties of the feedback projections in Fmr1 KO mice appeared to improve following visual experience, such as the synaptic E/I and the paired-pulse ratios as a measurement of STP. Our findings provide first measurements of the inter-areal synaptic connectivity before and after visual experience in WT and Fmr1 KO mice and suggest that visual training may potentially serve as a promising therapeutic intervention for ASD.

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Poster

P642. Ingestive Behavior: Central Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P642.01

Topic: F.09. Food and Water Intake and Energy Balance

Support: ERC Consolidator Grant 772994
German Research Foundation Project-ID 431549029 – SFB 1451
German Research Foundation Project-ID 233886668 - GRK1960

Title: Neuronal dynamics in the lateral hypothalamus determine the hierarchy of competing needs

Authors: *A. PETZOLD[1,2], H. VAN DEN MUNKHOF[1,2], R. FIGGE[1,2], T. KOROTKOVA[1,2];
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Abstract: Animals must continuously coordinate multiple needs, such as hunger and thirst, and rank them against competing opportunities like mating. Despite a long-known crucial role of the lateral hypothalamus (LH) in the regulation of hunger and thirst, the neuronal mechanisms enabling the representation and orchestration of multiple innate behaviors are not yet understood.
Here, we report how two functionally orthogonal neural populations of the lateral hypothalamus (LH) encode competing rewards and enable their appropriate prioritization even against acute metabolic pressure. Using a combination of deep-brain Ca^{2+} imaging in freely behaving mice and cell type-specific activity manipulations, we show that both leptin receptor-expressing ($LepR^{LH}$) and neurotensin-expressing (Nts^{LH}) populations track individual food consumption, water consumption and social interaction to selectively and flexibly promote their prioritization, and to regulate distinct anticipatory and consummatory phases of need fulfilment.
We provide a mechanistic understanding how the complementary control of innate drives by distinct, cooperating neuronal populations enables the flexible fulfilment of orthogonal needs according to current opportunities and gated by physiological demands.
We gratefully acknowledge support by the ERC Consolidator Grant (772994, FeedHypNet, to T.K.) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, Project-ID 431549029 - SFB 1451, to T.K., 233886668 - GRK1960, to R.F.).

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Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH Grant DK105510
NSF Grant 1652060

Title: Characterization of the parasubthalamic nucleus (PSTN) as an appetite suppression center

Authors: J. KIM, **G. KROMM**, J. SPERBER, K. HAN, L. HEUER, M. NEWMAN, O. BARNHILL, S. LOOMIS, T. LEGAN, F. GULAMALI, *M. CARTER;
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Abstract: Food intake behavior is regulated by a network of appetite-inducing and appetite-suppressing neuronal populations throughout the brain. The parasubthalamic nucleus (PSTN), a relatively unexplored population of neurons in the anterior hypothalamus, has been hypothesized to suppress appetite because of its connectivity with other anorexigenic neuronal populations and the fact that these neurons express Fos, a marker of neuronal activation, following a meal. However, the individual cell types that make up the PSTN are not well characterized, nor are their roles in food intake behavior. Here we identify two distinct PSTN subpopulations, those that express tachykinin-1 ($PSTN^{Tac1}$ neurons) and those that express corticotropin-releasing hormone ($PSTN^{CRH}$ neurons), and use a panel of genetically encoded tools to show that $PSTN^{Tac1}$ neurons play a causal role in appetite suppression in mice. Both populations increase activity following a meal and in response to administration of the anorexigenic hormones amylin, cholecystokinin (CCK) and peptide YY (PYY). Optogenetic and chemogenetic stimulation of $PSTN^{Tac1}$, but not $PSTN^{CRH}$ neurons, is sufficient to reduce food intake. Furthermore, chemogenetic inhibition of $PSTN^{Tac1}$ neurons reduces the appetite-suppressing effects of amylin, CCK, and PYY. $PSTN^{Tac1}$ and $PSTN^{CRH}$ neurons project to distinct downstream brain regions, and stimulation of $PSTN^{Tac1}$ neural projections to the anorexigenic parabrachial nucleus is sufficient to reduce food intake. Taken together, these results reveal the functional roles and connectivity of the cell types that make up the PSTN, demonstrating an anorexigenic role for $PSTN^{Tac1}$ neurons in food intake behavior.

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Poster

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Topic: F.09. Food and Water Intake and Energy Balance

Support: NSF PATHS-UP EEC-1648451

Title: Organ specific, wireless optogenetic gastric implants for multiplexing interoception dynamics

Authors: *W. KIM[1], B. C. JARVIE[2], Z. KNIGHT[2], **S. PARK**[1];
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Abstract: Optogenetics also has the potential to transform the study of the peripheral nervous system, but the complex anatomy of the peripheral nervous system (PNS) poses unique challenges for the focused delivery of light to specific tissues. In principle, it is possible to target peripheral tissues with light by using a wired fiber optic that exits the animal via the back or rectum, analogous to the intracranial fiber optics commonly used in the brain. However, the abdominal visceral differs from the brain in that it lacks a stable interface for securing large fiber optics and preventing motion. An alternative approach is to implant a wireless probe that internalizes the light source, thereby bypassing physical constraints associated with fiber optic cables. Strategies for such wireless, radio frequency (RF)-powered devices have recently been described, but it remains a major challenge to achieve long-term, organ-restricted illumination without impeding normal behavior or physiology. Recently, we have developed a new class of implantable wireless devices and demonstrated their applicability to study the vagus nerve. This new wireless optogenetic implant delivers light to nerve endings from inside the stomach via a pre-curved tether. This intragastric light delivery enables illumination of stomach innervating nerves with much greater specificity than μLEDs affixed to the organ surface and allows for simultaneous/independent control of multi-channels in a single platform device. It could in principle be extended to study other organs such as intestine. The optogenetic implants maintained functionality up to 1 month *in vivo*. With this approach, we induced appetite suppression in Calca(calcitonin gene-related peptide)-Cre mice by activating vagal nerve endings in the stomach of a freely behaving animal. We used adult male mice (C57/BI6 background) for this experiment. Animal model demonstrations of their utility in optogenetic studies of viscerosensory neural pathways in Calca-Cre mice revealed novel research findings that activation of Calca neurons innervating non-stretch receptors can inhibit appetite. This suggests that our wireless gastric optogenetic implants can be used for the study of peripheral sensory pathways, and the proposed wireless device will create many opportunities for future work in optogenetics and related behavioral science.

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Poster

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Title: Using mesoscale imaging of neural activity to map circuits controlling food intake behavior and circuit reorganization following consumption of high-fat diet.

Authors: *T. B. OUELLETTE, K. M. S. O'CONNELL;
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Abstract: Neurons expressing agouti-related peptide (AgRP) in the arcuate nucleus of the hypothalamus (ARH) are central regulators of hunger and their activity reflects metabolic need. It has been shown that AgRP neuronal activity is rapidly modulated by sensory detection of food (Betley et al., 2015; Chen et al., 2016; Garfield et al., 2016) and that consumption of high-fat diet (HFD), even for brief periods, changes excitability of AgRP neurons (Wei et al., 2015), but the location of presynaptic afferents and mechanisms for this change in excitability remain largely uncharacterized. These unidentified presynaptic inputs may represent untapped targets for therapeutic intervention to address pathological overeating. Our limited understanding of CNS driven feeding behavior is in part due to having incomplete understanding of these circuits. Additionally, the impact of diet and obesity on plasticity within these circuits is largely unknown, further obstructing a clear understanding of the role of CNS dysfunction in diet-induced obesity (DIO). We hypothesize that diet-induced plasticity in presynaptic inputs to AgRP neurons contributes to aberrant sensations of hunger, futhering pathological overeating and the progression of DIO. In this study, we used an unbiased approach to fluorescently label neurons brain-wide using transgenic mouse lines: Ai14;Arc^{CreERT2} and Ai14;Fos^{CreERT2} (referred to as ArcTRAP and FosTRAP, respectively). In these mice, the immediate early gene (IEG) *Arc* or *Fos* (which are well-defined as molecular markers of neuron activity) drive expression of Cre recombinase following administration of 4-hydroxy-tamoxifen (4-OHT), thereby permitting the permanent labeling of activated neurons using Cre-dependent expression of the reporter tdTomato. Expression of *Arc* and *Fos* is not uniform across the brain, necessitating the use of two separate transgenic lines to observe activity in regions where one of the two is absent. In this study we compared activity patterns of both sexes during low or high metabolic need states (sated, or overnight fasted) and during a satiated state following 2 days of HFD consumption. This unbiased approach allows us to identify novel brain regions involved in the CNS response to metabolic need state, and observe large-scale circuit plasticity during development of DIO.

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Patrick B. and Eloise E. Wieland Fellow (KN)
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NSERC Discovery Grant RGPIN-2017-06272 (MJC)

Title: Projection targets of medial zona incerta neurons expressing tyrosine hydroxylase

Authors: *B. S. BONO[1], K. NEGISHI[2], M. PONCE[2], T. C. AKINBODE[1], E. MEJIA[2], D. P. SPENCER[1], K. S. SCHUMACKER[1], M. GUIRGUIS[1], Y. DUMIATY[1], C. H. MACKAY-DIETRICH[1], A. J. HEBERT[1], A. M. KHAN[2], M. J. CHEE[1];
[1]Dept. of Neurosci., Carleton Univ., Ottawa, ON, Canada; [2]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: The zona incerta (ZI) is a predominantly GABAergic hypothalamic region, but some ZI GABA neurons co-express dopamine. ZI GABA neurons are implicated in behaviors underlying fear, feeding, sleep, hunting, and motor control, and while GABA and dopamine may be released from the same neuron, it is not known if ZI dopaminergic signaling mediates functions similar to GABA. To elucidate the potential roles of dopaminergic signaling from the ZI, we identified the projection targets of ZI neurons expressing tyrosine hydroxylase (TH) in a *Th-cre* mouse line. We first validated the *Th-cre* mouse line via a *Th-cre;L10-Egfp* reporter mouse and by performing *in situ* hybridization for *Gfp* and *Th* mRNA, followed by immunohistochemistry for TH. We determined the colocalization of *Gfp* with either *Th* mRNA hybridization and/or TH immunoreactivity (TH-ir). Overall, about one quarter of *Gfp*-labeled cells co-expressed *Th* mRNA and TH-ir (26%) but the majority expressed *Th* mRNA only (62%). The remaining *Gfp* cells (10%) did not express TH-ir or *Th* mRNA, and this ectopic *Gfp* expression was more prominent towards the lateral ZI, defined as the region of the ZI lateral to the mammillothalamic tract and fornix. Interestingly, 96% of *Gfp* cells in the medial ZI co-expressed *Th* mRNA and a few medial ZI *Gfp* cells (4%) were ectopic. We therefore delivered a Cre-dependent adeno-associated virus (50-75 nl) encoding either tdTomato or mCherry over the medial ZI to label the fiber projections of medial ZI *Th-cre* or *Th-cre;L10-Egfp* neurons. In both cases, we observed widespread fiber projections from medial ZI TH neurons throughout the brain. The projection sites that expressed consistent labeling were within the bed nucleus of the stria terminalis, paraventricular nucleus of the thalamus, nucleus reunions, and the periaqueductal grey. Similarities between these two injection cases using different viruses and mouse lines may reflect robust projection targets of dopaminergic neurons in the medial ZI. However, we also noted brain region differences between these two injection cases with regards to the pattern and density of fiber projections; for example, in the lateral septum, anterior hypothalamic area, and superior colliculus. These may be ascribed to differences in injection volume or the transfection of *Th-cre* cells outside the medial ZI. Interestingly, the projection targets of medial ZI TH neurons are also consistent with the known roles of GABA ZI neurons. Given that *Th-cre* ZI neurons are also GABAergic, future work will determine if they may innervate downstream targets by GABA and/or dopamine release.

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Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH NIDDK 1R01DK124801
Singapore MOE2018-T2-1-065
Singapore MOE2017-T3-1-002

Title: Identification of a cerebellar satiation network

Authors: *A. Y. T. LOW[1], N. GOLDSTEIN[1], J. R. GAUNT[3], K.-P. HUANG[5], J. R. E. CARTY[2], N. ZAINOLABIDIN[4], A. YIP[4], J. Y. CHOI[2], H. S. T. HO[4], C. LENHERR[7], T. CH'NG[4], M. A. HALKO[8], R. O. BRADY, JR[9], L. HOLSEN[10], A. L. ALHADEFF[6], A. I. CHEN[11], J. BETLEY[2];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadephia, PA; [3]Nanyang Technological Univ., Signapore, Singapore; [4]Nanyang Technological Univ., Singapore, Singapore; [5]Monell Ctr., Philadephia, PA; [6]Monell Ctr., Philadelphia, PA; [7]King's Col. London, London, United Kingdom; [8]Neurol., Harvard Med. Sch. / Beth Israel Deaconess Med., Boston, MA; [9]Beth-Israel Deaconess Med. Ctr., Boston, MA; [10]Harvard Med. Sch., Boston, MA; [11]Scintillon Inst., San Diego, CA

Abstract: Maintaining an adaptive body weight requires integrating hunger signals and nutrient status to influence hedonic and metabolic needs. The cerebellum integrates external and internal sensory feedback to fine-tune functional outputs, and recent work has linked the cerebellum to motivated behavior. Therefore, we tested the hypothesis that food modulates cerebellar activity using whole-brain task-based fMRI. Activity in the deep cerebellum responds to food cues, and this activity is dysregulated in individuals that never experience satiation (Prader Willi syndrome patients). To better understand the neuronal subtype identity and function of the deep cerebellum in food intake regulation, we conducted single-nucleus RNA sequencing, activity-dependent gene expression analyses and neural manipulation studies in rodents. Transcriptomic profiling, targeted recombination in active populations strategy and *in situ* hybridization uncovered the molecular identity and spatial organization of neurons in the anterior deep cerebellar nuclei (aDCN) activated by food intake and intragastic infusion of nutrients. Chemogenetic activation of these aDCN neurons suppressed food intake. We next examined how aDCN activity influences feeding associated neural circuits. We found that dopamine signaling in the nucleus accumbens and not activity in the hypothalamic agouti-related peptide expressing neuron is modulated during aDCN mediated food intake reduction. Our findings suggest that food intake activates cerebellar output neurons leading to a surge of striatal dopamine that stops eating by attenuating the reward value of additional consumption. Taken together, our study reveals that cerebellar output neurons is a critical and evolutionarily conserved neural node that puts a "brake" on food intake to promote satiation.

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Topic: F.09. Food and Water Intake and Energy Balance

Support: ERC Consolidator Grant (HypFeedNet, to TK)
DFG (CRC1451, to TK)
RTG-NCA (GRK1960, to RF)

Title: Complementary regulation of innate behaviours by distinct cell populations in the lateral hypothalamus

Authors: *R. FIGGE[1,2], H. E. VAN DEN MUNKHOF[1,2], A. PETZOLD[1,2], T. KOROTKOVA[1,2];
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Abstract: The lateral hypothalamus (LH) integrates metabolic signals and maintains energy homeostasis by modulating feeding through an intricate interplay between a neurochemically and functionally diverse neural populations. Our research is focused on GABAergic cell populations in the LH, which regulate multiple innate behaviours. Specifically, we investigated molulation of consumptive and exploratory behaviours by leptin receptor-expressing (LepR) and neurotensin-expressing (Nts) neurons in the LH. Using opto- and chemogenetics, as well as subsecond unsupervised analysis of behaviour using Motion Sequencing (MoSeq), in sated and food-deprived mice, we found that these cell populations exert opposite effects on social interaction. Further, LepR and Nts neurons complementary regulate feeding, drinking, and locomotion in a state-dependent way. Our study reveals neuronal mechanisms of adaptive need fulfillment in the presence of multiple natural rewards.

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Poster

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Topic: F.09. Food and Water Intake and Energy Balance

Title: The Impact of Acetylcholine on Basolateral Amygdala Macrocircuits

Authors: *E. K. TANTRY[1], J. ORTIZ-GUZMAN[2], M. KOCHUKOV[3], B. R. ARENKIEL[4];
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Abstract: Neural circuits governing food intake have been widely studied. However, our current understanding hinges on a binary hypothalamic neuronal model that fails to address more adaptive feeding behaviors underpinning variable environmental conditions. Previous work in our lab posits an extra-hypothalamic circuit involving the cholinergic-rich diagonal band of Broca (DBB) and the valence encoding basolateral amygdala (BLA). To further analyze this circuit, we used a projection-defined approach to characterize the cellular composition of the BLA. We utilized a stereotactic frame for bilateral injections of channelrhodopsin and tdTomato containing viruses into the DBB,

and either the nucleus accumbens (NAc) or the lateral hypothalamic area (LHA), respectively. The latter regions were selected due to their established involvement in regulating food intake. We determined projection profiles of BLA cells using channelrhodopsin assisted circuit mapping (CRACM) and optogenetics, and found that the majority of neurons projecting to the LHA exclusively possess fast-acting nicotinic synapses, whereas most neurons expressing slow-acting muscarinic synapses project exclusively to the NAc. The contrasting nature of these receptors indicates that there are more dynamic neural regions involved in orchestrating complex hedonic feeding behaviors.

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Poster

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Program #/Poster #: P642.09

Topic: F.09. Food and Water Intake and Energy Balance

Support: R01GM128209

Title: Elucidating the neural circuit that balances sugar and water ingestion in Drosophila melanogaster

Authors: *A. J. GONZALEZ-SEGARRA, K. E. SCOTT;
Univ. of California, Berkeley, Berkeley, CA

Abstract: All organisms need to acquire nutrients from their environment to survive. In particular, water and sugar ingestion are vital to sustain many metabolic needs. Ingestion of sugar and water is tightly regulated by internal signals, such as thirst, hunger, and satiety, to maintain homeostasis. Although generally considered separately, interactions between these internal nutrient signals are important to coordinate competing needs. Recent studies have identified four neurons called Interoceptive Subesophageal zone Neurons (ISNs) in *Drosophila melanogaster* that respond to endogenous hunger and thirst signals to oppositely regulate sucrose and water ingestion. Upon activation, ISNs increase sucrose ingestion but decrease water ingestion. While the key molecular pathways that lead to ISN activation have been identified, it is still unknown how ISN activity translates to a behavioral response. To examine how competing needs are coordinated by the nervous system, we identified and characterized the neural circuit downstream of the ISNs. Using a genetic approach for trans-synaptic circuit tracing, we labeled approximately 30 candidate downstream neurons. To gain genetic access to these neurons, we compared them to a novel neuron collection that labels single cell-types in the Subesophageal Zone and identified 30 candidate postsynaptic neurons based on neurite proximity to the ISNs. A behavioral activation screen was performed on these candidate neurons to determine their involvement in feeding, which yielded 4 candidate postsynaptic neurons which are involved in sucrose and water ingestion. Interestingly, activation of some of these neurons altered both sugar and water ingestion, while other neurons only altered sugar ingestion or water ingestion. Further functional imaging experiments, where we optogenetically activate the ISNs and measure candidate downstream neuron activity, are needed to

determine if these neurons are in fact postsynaptic to the ISNs. This study will provide insight into how the nervous system organizes competing internal needs to drive opposing behavioral responses.

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Poster

P689. Human Emotion and Disease

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Topic: G.04. Emotion

Support: NIH Grant R25 NS 80686
1 SC MH 109349

Title: Is respiratory sinus arrhythmia a marker for stress and anxiety during a stressor?

Authors: *M. KHAITOVA[1], B. FAN[2,1], S. MYRUSKI[3], Q. LIN[1], T. A. DENNIS-TIWARY[1,2]; [1]Hunter Col. - The City Univ. of New York, New York, NY; [2]The Grad. Ctr. - The City Univ. of New York, New York, NY; [3]The Pennsylvania State Univ., University Park, PA

Abstract: Anxiety disorders are the most common mental health diagnosis, and have been linked to reduced capacity to regulate the stress response. Respiratory sinus arrhythmia (RSA) reflects heart rate variability due to respiration changes, and reflects parasympathetic nervous system (PNS) activity. Suppressed RSA is associated with decreased PNS activity and represents an adaptive physiological response to stress, as the sympathetic nervous system engages during a stressor to help individuals cope. Few studies, however, have investigated associations between RSA suppression measured during a standardized lab stressor and behavioral signs of anxiety. This study aims to examine these associations by measuring self-reported anxiety, RSA, and behavioral indices of anxiety during a standardized lab stressor, the Trier Social Stress Test (TSST). The TSST has been shown to increase cortisol levels and heart rate in previous research. Participants self-reported anxiety symptoms, then completed the TSST, while electrocardiogram (ECG) was simultaneously recorded. Anxious behaviors were coded from videotaped TSST observations. RSA suppression during stressor versus baseline was quantified from ECG data, with more negative scores indicating greater suppression. Anxiety severity was measured using the Hamilton Anxiety Rating Scale (HAM-A). We tested the hypothesis that individuals with high versus low anxiety severity will show reduced RSA suppression during the TSST, which in turn will predict increased frequency of anxious behaviors. This research is exploratory. Anxiety level and anxious behaviors during the TSST were not significantly correlated, $r(98) = -.030$, $p = .768$. Similarly, anxiety level and RSA suppression during the TSST were not significantly correlated, $r(96) = -.031$, $p = .761$. The moderation analysis using regression revealed a trend, $\Delta R^2 = .0461$, $F(1, 87) = 4.2191$, $p = .0430$, albeit in a direction opposite to that hypothesized: those reporting greater anxiety severity evidenced fewer anxious behaviors during the TSST when they showed low levels of RSA suppression. Findings highlight the need for additional examinations of the associations between physiological and behavioral responses during a stressor among anxious individuals.

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Poster

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Topic: G.04. Emotion

Support: CONACYT CF-2020-6390.

Title: State-trait anxiety and State-trait depression in Mexican twins

Authors: *T. V. ROMÁN-LÓPEZ[1], X. J. LÓPEZ-CAMAÑO[1], Z. X. ESPINOSA-VALDÉS[2], E. I. ORTEGA-MORA[2], U. CABALLERO-SÁNCHEZ[2], E. CHIU-HAN[1], D. RAMÍREZ-GONZÁLEZ[1], O. ALDANA-ASSAD[3], E. GONZÁLEZ-LÓPEZ[2], A. POLO-ROMERO[2], C. GUILLERMO-FLORES[2], S. A. PRADEL-JIMÉNEZ[2], A. TAPIA-ATILANO[2], D. ZENTENO-MORALES[2], M. RENTERÍA[4], A. MEDINA-RIVERA[3], A. E. RUIZ-CONTRERAS[2], S. ALCAUTER[1];
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Abstract: Monozygotic (MZ) and dizygotic twin studies estimate the variability in a trait is due to environmental or genetic factors, this is known as heritability. Specifically, the heritability of traits as anxiety has been estimated around 7.4% for the population of European ancestry and 14% in Latin-American population living in the United States, which suggests that each population must be studied in a specific manner and that it is not possible to directly translate results between populations. The aim of this study was to correlate symptomatology of anxiety and depression in MZ and DZ Mexican twins, as a first step to calculate the heritability of these traits in a Mexican population. A sample of 108 (n=42 MZ pairs and n=12 DZ pairs) twins answered (through the website of the Mexican Twin Register, TwinsMX https://twinsmxofficial.unam.mx/) the State-Trait Anxiety Inventory (STAI) and 100 (MZ n=39 pairs; DZ n=11 pairs) of them, the State-Trait Depression Inventory (STDI). These instruments allow evaluating the state, defined as how a person currently feels, it is a measure of the feelings at the time of evaluation, and it can be understood as a transient measure. On the other hand, the trait describes how people usually respond to day-to-day life, which implies a more stable set about her/his cognition and behavior; this measure is related with temperament. As a result of this study was observed a significant correlation for Anxiety-Trait in MZ twins ($r_s=0.57$; $p<0.01$), but not in DZ ($p=0.75$). By contrast, for Anxiety-State there were no significant results for MZ ($p=0.054$) nor DZ ($p=0.76$). Meanwhile, for Depression-Trait there was a significant correlation for MZ ($r_s= 0.58$; $p<0.01$) but not for DZ twins ($p = 0.37$). For Depression-State, there was a significant correlation for both MZ ($r_s= 0.52$; $p<0.01$) and DZ ($r_s = -0.78$; $p<0.01$). Trait results for Anxiety and Depression, in MZ twins, but not in DZ, suggest that this symptomatology is probably associated with greater genetic contribution. Nevertheless, the results for state for anxiety and depression are still not conclusive, a greater sample will be necessary to improve statistical estimations,

including the heritability index. Overall, this study shows the necessity of having twin data in the Mexican population to strengthen the knowledge of mental health traits, such as anxiety and depression symptomatology.

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Poster

P689. Human Emotion and Disease

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Program #/Poster #: P689.03

Topic: G.04. Emotion

Support: CONACYT Grant (EAM 931445Y AMR 1008095)
PRODEP (TCLL UV-PTC-898)

Title: Differences between affective-cognitive empathy and overload in informal caregivers of patients with chronic diseases

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Abstract: It is known that patients with chronic diseases present physical and psychological affections, these complications can also affect informal caregivers (IC) directly and indirectly, generating changes in the quality life, care overload, cognitive and affective alterations, etc. This can occur at the initial time of diagnosis or during the disease, so it is relevant to know the variations that IC can present. The objective of this work was to identify the differences between the levels of empathy and overload in three IC groups of patients with cancer, psychiatric and lupus. A comparative, observational and cross-sectional study was carried out, with a sampling by convenience; where a total of 116 IC participated, 37 from the “Centro Estatal de Cancerología *Dr. Miguel Dorantes Mesa*”, 26 of the “Instituto Veracruzano de Salud Mental *Dr. Rafael Velasco Fernández*” and 53 at the “Hospital de Especialidades *Antonio Fraga Mouret* La Raza”. The Davis Interpersonal Reactivity Index (IRI), the Zarit Caregivers Burden Interviews (ZBI) and the Reading the Mind (RME) tests were applied. For statistical analysis, independent samples were taken with Mann-Whitney U test and intragroups were compared with the Kruskal-Wallis test, using the SPSS program. The results show a majority participation of women (71.6%), there were no differences between sex. Differences were found in RME ($p = 0,003$), where IC of patients with lupus obtained higher scores compared to those of cancer, also in IRI-Perspective Taking scale ($p = 0.048$) IC with psychiatric patients obtained higher scores compared to those with lupus, and finally at ZBI ($p = 0.030$) IC of patients with

lupus obtained higher scores compared with IC of cancer. It concludes that there are differences between IC according to the type of disease of the patient. So, it is pertinent to implement prevention and catalytic strategies for IC in patients with chronic diseases.

Disclosures: A. Caballero Velarde: None. **A. Montiel Rivera:** None. **E. Acosta-Mari:** None. **S. Zamora-Lugo:** None. **R.L. Castillo Lopez:** None. **T. Cibrian-Llanderal:** None.

Poster

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Topic: G.04. Emotion

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Title: Weaker resting-state ventromedial PFC-amygdala connectivity is associated with mindfulness meditation induced depressive mood reductions

Authors: *L. KHATIB[1], V. OLIVA[1], G. RIEGNER[1], G. POSEY[3], J. DEAN[1], J. BAUMGARTNER[1], Y. JUNG[4], R. KRAFT[3], J. BIRENBAUM[2], F. ZEIDAN[1];
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Abstract: Negative mood is associated with stronger functional connectivity between brain mechanisms supporting low-level affective reactivity (amygdala) and self-related affective processing [ventromedial prefrontal cortex (vmPFC)]. Mindfulness meditation, a practice premised on sustaining non-reactive attention to the present moment, reduces acutely evoked stress, anxiety and pain through greater PFC recruitment. Mindfulness also reliably reduces amygdalar activity in the presence of a stressor. However, it remains unclear if and how brief mindfulness training reduces dysphoric mood. The proposed study employed fMRI to examine if mindfulness-induced reductions in depressive mood would be associated with vmPFC-amygdala resting state functional connectivity.
Forty healthy participants were randomized to four, 20-minute sessions of mindfulness meditation training or book listening (n=20/group). The Center for Epidemiological Depression (CES-D) scale was administered before and after respective trainings. Resting state fMRI scans were acquired after completion of the interventions. Participants were instructed to "rest with eyes closed" during continual innocuous 35°C stimulation to the right calf (Medoc, Inc).
A 2 (group) X 2 (pre vs. post-intervention) ANOVA (SPSS v26) examined if mindfulness training produced greater reductions in depressive mood when compared to the controls. Within and between-group seed based functional connectivity analyses [FSL (Center for FMRIB, University of Oxford, Oxford, UK); randomise] between the bilateral amygdala (xyz coordinates right = 26, 0, -22; left = -24, -4, -18) and vmPFC (xyz = 36, -1, -14) were conducted. Residualized CES-D scores were then entered as

regressors to test if mindfulness-induced depression changes were associated with amygdala-vmPFC connectivity and if this relationship differed between groups.
Brief mindfulness training significantly reduced depressive mood (-15%) when compared to the book-listening regimen (+23%; $p < .05$, $\eta = .10$). The relationship between dysphoric mood changes and vmPFC-amygdala connectivity varied by group ($p < .05$). Mindfulness meditation-related reductions in depressive mood were associated with weaker vmPFC-amygdala resting state connectivity in meditators ($p < .05$) but not controls ($p = .55$). We provide novel evidence that 4 days of mindfulness training improves depressive mood. Further, at rest, lower depressive mood was associated with weaker vmPFC-amygdala connectivity and suggests that mindfulness may enhance psychological resilience to dysphoria in healthy individuals by reducing affective self-related appraisals.

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Poster

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Program #/Poster #: P689.05

Topic: G.04. Emotion

Title: Detrended fluctuation and coherence under emotional burnout formation (Exhaustion stage)

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Abstract: The neurophysiological mechanisms of emotional burnout remain insufficiently studied. It was found that EEG changes during burnout differ from biomarkers of depression and chronic fatigue syndrome. To establish the EEG markers of burnout was our aim. 182 volunteers, first-third year students from the Taras Shevchenko National University of Kyiv aged 18 to 24 years participated in this study. The EEGs were recorded during the resting state (3 min, closed eyes condition) monopolarly using EEG 23-channel system Neurocom. To establish EEG correlates of emotional burnout during rest state we used a special software written in Python 3.6 to implement Power Spectral Density calculation, the interhemispheric and intrahemispheric average coherence and Detrended Fluctuation Analysis (DFA). We analyzed separate artifact-free EEG segments in all frequency bands from 0.2 to 45 Hz. Psychological testing was performed before the registration of EEG. To determine the formation of emotional burnout Boyko's "Syndrome of emotional burnout" Inventory was used. The Exhaustion phase of emotional burnout was formed in 13 participants, and it was under development in 47 participants. In background EEG activity during the development of the exhaustion variations in EEG spatial synchronization were observed in low- and high-frequency EEG components. Development of exhaustion includes breaking of parietal-occipital links (alpha2,3-subbands) and formation of interhemispheric prefrontal, anterior frontal, and frontal links (alpha1,2-subbands). There were interruptions of coherence in the beta1 (interhemispheric frontal-frontal and parietal-parietal links) and beta2 subbands (right interhemispheric frontal link). DFA describes the long-term temporal correlations in the cortex, which are involved in

different aspects of brain functioning. We detected a high resting state DFA scaling exponent values (up to 0.90-0,95) under exhaustion development in the theta1 (left prefrontal area), theta2 (right frontal area), alpha3 (posterior regions), beta2 (left temporal region). Obtained values of DFA exponent and average coherence suggest the exhaustion formation is accompanied by the changes in visual and verbal processing, emotional processes (discretion and analysis).

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Poster

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Program #/Poster #: P689.06

Topic: G.04. Emotion

Support: Jordan Elizabeth Harris Foundation

Title: Emotional Conflict Processing in Adolescents with Epilepsy: A Pilot Magnetoencephalography Study

Authors: F. K. E. KING[1,2], M. S. PERRY[3], C. PAPADELIS[2,1,4,5], *C. M. COOPER[2,6,1];
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Abstract: Introduction: Comorbid psychological disorders are common in patients with epilepsy. Issues in emotion processing are postulated to underlie psychological disorders, yet they remain understudied in epilepsy research and clinical care. The goal of this exploratory study is to assess emotion conflict processing in epilepsy. We hypothesized that adolescents with epilepsy would exhibit a blunted response to emotional conflict both in behavior and brain function compared to typically developing (TD) individuals. **Methods:** Six adolescents with epilepsy and nine age- and gender-equivalent controls (aged 10-18) underwent a magnetoencephalography recording (MEG, 306-channel VectorView system) during an emotional face-word Stroop task. Images of faces were presented with emotion words written across them that were either congruent or incongruent with the facial expression. Response times were calculated by congruency. Event-related fields (ERFs) were calculated across a period of 1000 ms before and after motor response by group, condition (i.e., congruent, incongruent), and for the difference field (i.e., incongruent-congruent). Global Field Power (GFP) was estimated for sensors covering different brain regions. Minimum Norm Estimates (MNE) were estimated per condition and group. Additionally, depression severity was assessed using the 9-item Patient Health Questionnaire and investigated in relation to response times and MEG findings. **Results:** TD participants responded faster for congruent than incongruent stimuli ($t = 5.5$, $p < .05$). Contrarily, participants with epilepsy had similar response times across conditions ($t = 2.2$, $p > .05$). GFP revealed an over activation in the left temporal lobe from 0 ms to 200 ms post-response for patients with epilepsy, compared to TD individuals ($F = 7.6$, $p < .05$). MNE localized this activation to the left inferior temporal lobe. Depression severity was positively correlated to emotion conflict response time ($r = .5$; $p < .05$) and GFP values in the left temporal lobe ($r =$

.6; $p < .05$). **Discussion:** This preliminary study is the first to report potential blunted emotion conflict processing in an adolescent epilepsy sample using MEG. Differences in post-response activity in the left temporal lobe may be related to differences in post-response monitoring or conflict adaptation processes in epilepsy. Extending research on depression and emotion processing, the relationships between emotion conflict processing and depression level in the current study may suggest depression to play a modifying role in the ability to react to and regulate emotional conflict in those with epilepsy.

Disclosures: F.K.E. King: None. **M.S. Perry:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Encoded, Stoke, Zogenix, Ovid. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Zogenix. F. Consulting Fees (e.g., advisory boards); Encoded Therapeutics, Stoke Therapeutics, Zogenix, Greenwich Biosciences, Taysha. **C. Papadelis:** None. **C.M. Cooper:** None.

Poster

P689. Human Emotion and Disease

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Program #/Poster #: P689.07

Topic: G.04. Emotion

Title: Neighborhood safety is associated with anxiety symptoms and variation in emotion processing neurocircuitry in children

Authors: *B. BORG, H. MARUSAK;
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Abstract: While the literature has long established the relationship between the environment and mental health, less is known about the neural correlates underlying these associations. Emotion-related disorders, such as anxiety, commonly begin during childhood and adverse environments, such as living in dangerous neighborhoods, can increase risk for anxiety. Moreover, how children perceive their environment is a determinant for their overall health. This study aims to understand the relationships among perceived neighborhood safety, anxiety, and emotion processing neurocircuitry in a large, demographically diverse sample of children. The current study used cross-sectional baseline survey and functional magnetic resonance imaging (fMRI) data from 11,878 9-year-old children from the Adolescent Brain Cognitive Development study (48% female; 65% White, 15% Black). Children self-reported on their neighborhood safety using the Youth Neighborhood Safety/Crime Survey. Child anxiety was estimated using the Child Behavior Checklist. The primary neuroimaging outcome variables were blood oxygen-level dependent response in emotion processing brain regions of interest (ROIs) during an emotional n-back task: amygdala, hippocampus, dorsal anterior cingulate cortex (dACC), and the insula. We estimated neural response via mean beta weights in each ROI to (1) threatening v. neutral faces, (2) positive v. neutral faces, and (3) overall response to emotional faces. Regression models examined whether neighborhood safety predicted anxiety symptoms and neural response in ROIs, and if neural responses, predicted anxiety. Overall, lower neighborhood safety was associated with greater anxiety

symptoms in children. Children living in less safe neighborhoods also demonstrated greater left amygdala and right hippocampus reactivity to emotional faces and to positive faces, and lower dACC and insula reactivity to emotional faces. Lower insula reactivity was also associated with higher anxiety, but insula reactivity did not mediate the association between neighborhood safety and anxiety. Given the role of the amygdala and hippocampus in emotion reactivity, and the dACC and insula in top-down emotion regulation, lower neighborhood safety may be associated with greater emotion reactivity and poorer top-down regulation. These results demonstrate that neighborhood safety predicts anxiety and variation in emotion processing neurocircuitry in children. These findings also have public health implications and future interventions aiming toward neighborhood safety may be a promising approach for improving mental health and moderating neurodevelopment in children.

Disclosures: B. Borg: None. **H. Marusak:** None.

Poster

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Topic: G.04. Emotion

Support: MOST 108-2634-F-002-022
MOST 107-2420-H-002-031-RE2

Title: The neurophysiological markers of social anxiety

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Abstract: Social anxiety involves excessive fear and anticipation of social situations. The identification of the associated yet reliable neurophysiological signatures may facilitate early detection and prevention of the potential risk resulted from this symptom. This study adopted the well-established Trier Social Stress Test to induce psychosocial anxiety, in which participants were requested to perform a self-presentation speech that would be subsequently evaluated. Simultaneously, participants' (n=19) magnetoencephalography activities were recorded and anxiety levels was assessed using the State Anxiety Inventory (SAI)**.** As revealed from the SAI scores, participants' anxiety levels increased from the baseline to the task instruction stage and then slightly dropped during the task preparation stage. By exhaustively examining the common social anxiety-related biomarkers reported in previous literature, we observed a significant relation, across the above three stages, between the behavioral SAI scores and the delta/theta power over the frontal location, the alpha/low beta (14-20 Hz) power over the frontal/parietal locations or the frontal alpha power asymmetry. These findings reveal multifaceted and complex neural patterns that mediate social anxiety.

Disclosures: T. Hsu: None. **T. Huang:** None. **S. Hsu:** None.

Poster

P689. Human Emotion and Disease

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Program #/Poster #: P689.09

Topic: G.04. Emotion

Title: Affective components of a preclinical fibromyalgia model

Authors: *C. ARGENBRIGHT[1], C. A. SALCIDO[2], T. AGUIRRE[1], P. FUCHS[1];
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Abstract: Fibromyalgia (FM) is a highly represented pain disorder that is well understudied. FM animal models have provided knowledge surrounding the biological mechanisms of FM through the replication of physical symptoms, but often forego assessment of emotional comorbidities like anxiety. The purpose of this study was to investigate the efficacy of an acidic saline preclinical model of FM in replicating anxiety-like behaviors of approach/avoidance, while also assessing pregabalin in alleviation of FM-related pain affect. In a sample of 48 female rats, decreased mechanical thresholds for acidic saline compared to controls were found, suggesting model efficacy. Further, mechanical thresholds increased with the administration of pregabalin, indicating efficacy in treating FM related pain. Escape/avoidance behavior data revealed FM condition with a saline control treatment showed increased escape/avoidance behavior. There were, however, no differences between conditions in measures of velocity or distance travelled within the open field (OF) paradigm. As expected, animals reared more at baseline OF measures, than at post-injection 1 and post-treatment, but there were no differences observed in rearing behavior between conditions. These results indicate that while the acidic-saline model of FM was effective in lowering mechanical thresholds, it may not be as efficacious in replicating typical anxiety behavior in an OF paradigm.

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Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Program #/Poster #: P784.01

Topic: H.03. Decision Making

Support: European Research Council Consolidator Grant IndDecision – 865474

Title: Investigating the neural mechanisms of interval timing using electroencephalography.

Authors: *H. MCCONE[1,2], J. S. BUTLER[4,3], R. G. O'CONNELL[1,2];
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Abstract: Accurately reproducing time intervals in the range of hundreds of milliseconds to seconds is critical for everyday human behaviours such as playing music and sport. To probe the neural mechanisms underlying interval reproduction in this range, we recorded electroencephalography (EEG) while participants completed a time interval reproduction task. We examined two EEG signatures: the centro-parietal-positivity (CPP), which is an established signature of sensory evidence accumulation during perceptual decisions, and the Contingent Negative Variation (CNV), which is a fronto-central negative potential that is linked to anticipation and temporal decision making. The data used for the analyses were from nine students (5 female) with a mean age of 21 years (range: 19-23 years). The task consisted of two parts. In the first part of each trial, participants were presented with a time interval represented by a single, continuous auditory tone and were instructed to estimate its duration. Following a brief gap of variable duration, participants were presented with a short cue tone and reproduced the time interval by clicking a mouse button at the time they estimated the interval had elapsed. We found that participants' response times increased with interval duration and deviated from veridical towards the mean of the underlying time interval distribution. To examine the relationship between the EEG signatures and response times, we separated trials within participants, within interval conditions, into three response time bins and computed within participant average waveforms for each response time bin. We found that the slope of the CNV in the lead up to response significantly varied across response time bins (F (2,16) = 6.94, p = .006). Additionally, a linear mixed effects model indicated that single-trial estimates (5794 trials) of CNV slope significantly predicted response time independent from interval duration (standardized b = 0.07, 95% CI = [0.05, 0.09], p < 0.001), with a shallower CNV slope leading to a longer response time. By contrast, we did not find a gradually building positive CPP prior to response, or at any other point in the task. These findings suggest that variations in time reproductions are related to variations in CNV slope prior to response. The CNV may represent a motor plan for reproducing intervals or an urgency signal that emphasises the need to respond before a certain point in time. The absence of the CPP suggests that its role in decision making may be contingent on external sensory input and does not extend to internal representations of evidence such as the passing of time.

Disclosures: H. McCone: None. **J.S. Butler:** None. **R.G. O'Connell:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Program #/Poster #: P784.02

Topic: H.03. Decision Making

Title: Cognitive effort exertion enhances electrophysiological responses to rewarding outcomes

Authors: *M. BOGDANOV[1], H. RENAULT[1], S. LOPARCO[2], A. WEINBERG[1], R. OTTO[1];
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Abstract: A body of recent work has examined many of the neural mechanisms underlying cognitive effort-related discounting of anticipated rewards. However, studies investigating whether prior effort exertion increases or decreases the subjective value of obtained rewards have reported inconsistent findings. Here, we provide a more nuanced account of how cognitive effort affects subsequent reward processing in a novel task designed to assess effort-induced modulations of the Reward Positivity (RewP), an event-related potential characterized by larger responses to monetary gains than to losses. To probe individual differences, we also measured participants' effort discounting rates and RewP responses in absence of effort manipulations. We found that RewP amplitudes for both gains and losses were significantly elevated in trials requiring more versus less cognitive effort, suggesting that people ascribed more value to high-effort outcomes. Time-frequency analysis revealed that these effects were mirrored in delta band activity, but not in theta band activity. Examining individual differences, we found that participants who are more tolerant of cognitive effort exertion did not exhibit the canonical gain/loss difference in the delta band after low effort exertion, possibly suggesting that these participants experience reward received from easy tasks as less valuable. Together, our findings provide evidence that cognitive effort exertion can increase the subjective value of subsequent outcomes and further suggest that individual differences in effort sensitivity may modulate this effect.

Disclosures: M. Bogdanov: None. **H. Renault:** None. **S. LoParco:** None. **A. Weinberg:** None. **R. Otto:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Topic: H.03. Decision Making

Support: IRC GOIPG/2017/1093

Title: The influence of priors in encoding and accumulating sensory evidence in a decision-making task

Authors: *K. WALSH[1], D. P. MCGOVERN[2], R. G. O'CONNELL[1];
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Abstract: In recent years, there have been significant efforts to better understand how sensory expectations influence perceptual processing. Yet, many questions remain about the stages of information processing that exploit sensory priors and the mechanisms that best capture their influence on decision formation. Traditionally, priors have been represented in decision-making models with static biases in the rate of accumulation (drift biases). However, some have proposed that these biases may change dynamically across the duration of a trial. Here, we sought to address this question, using EEG to capture distinct electrophysiological signatures of three fundamental stages of perceptual decision-making: the encoding of sensory evidence, evidence accumulation, and motor preparation. Over the course of 4-6 sessions, subjects (n = 12) performed a two-alternative contrast discrimination task, consisting of discrete trials featuring two superimposed leftward- and rightward-tilted gratings, which gradually changed in

relative contrast. The task incorporated task-informative cues, designed to establish a prior expectations about the upcoming stimulus, and pulses of sensory evidence delivered at variable onsets. This allowed us to detect differences in the influence of prior-consistent and prior-violating sensory evidence at different stages of the decision-making process. Priors were found to influence both behavioural and neurophysiological indices of this process. Current analyses seek to clarify if these effects result from constant or dynamic biases shaping decision formation.

Disclosures: K. Walsh: None. **D.P. McGovern:** None. **R.G. O'Connell:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Topic: H.03. Decision Making

Support: W911NF-10-2-0022

Title: Dissociating neural mechanisms of recognition memory and decision criterion using dense sampling fMRI

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Abstract: When making a recognition memory judgment, individuals must determine whether the familiarity strength of an item surpasses the decision criterion to identify it as previously studied (‘old’) or novel (‘new’). Since recognition judgments encompass both memory *and* decisional processes, it is difficult to dissociate neural mechanisms associated with each. In a dense sampling fMRI study within a single individual, we systematically manipulated discriminability and decision criteria at four levels each to better dissociate activity underlying familiarity, the criterion, or both. During study phases the participant viewed a series of scene images that either appeared one, three, six, or nine times to modulate discriminability at test. A payment manipulation modulated the criterion at test, where the participant earned four cents for a correct response, lost either one or eight cents for a critical error, but received no penalty for a noncritical error. In the conservative criterion conditions incorrect ‘old’ responses represented the critical errors, whereas incorrect ‘new’ responses served as critical errors in the liberal criterion conditions. This created a fully crossed four discriminability by four criterion design in which the 16 test conditions appeared in separate test blocks (e.g. the lowest discriminability and most conservative criterion condition consisted of 20 old images studied once and 20 new images, where incorrect ‘old’ responses resulted in an eight cent penalty). The participant conducted the full task during fMRI scanning on 31 consecutive days, to obtain enough power to assess how each manipulation affects frontoparietal activity within an individual. In whole-brain analyses comparing old versus new responses in each test condition, we found widespread frontoparietal regions that became more active as the decision criterion became more conservative (e.g. anterior insula, dorsolateral prefrontal cortex, and superior parietal lobule) or more liberal (e.g. angular gyrus and medial prefrontal cortex), independent of the discriminability condition. In contrast, changes in discriminability revealed spatially sparser increases

in frontoparietal activity as memory performance increased, such as anterior regions of the dorsolateral prefrontal cortex. Most of the widespread frontoparietal activity observed in the old versus new response contrast is attributable to the decision criterion. Whole-brain fMRI analyses appear to be rather insensitive to changes in discriminability when controlling for the decision criterion.

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Poster

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Program #/Poster #: P784.05

Topic: H.03. Decision Making

Support: NIH Grant 5R01MH122513

Title: Probing sensory evidence accumulation and decision-related signals using human intracranial EEG

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Abstract: Making choices on the basis of perceptual information involves a dynamic flow of events that includes (but is not limited to) encoding the sensory input, evaluating the sensory evidence in favor of the options, and performing the appropriate action. Single-unit recordings in non-human primates have characterized neural activity across frontoparietal regions supporting the formation of perceptual choices through a process of evidence accumulation over time. In humans, scalp EEG work has identified neural signals consistent with this process, however the generators of these signals are not yet clear. Human intracranial EEG provides a unique opportunity to study the time-resolved unfolding of neural activity with increased spatial precision, and to therefore capture the heterogeneity of decision-related neural responses and disentangle their underlying sources. Here, we recorded data from presurgical epilepsy patients implanted with intracranial electrodes while they performed one or more of three possible perceptual decision tasks. A visual speeded response task asked participants (N=18) to judge the direction (up vs. down) of random-dot motion stimuli and report their choice with a button press. To probe for stimulus-independent choice related activity, we used an auditory analogue of this task where participants (N=15) discriminated the dominant pitch (high vs. low) of mixed tone auditory stimuli. Finally, to evaluate decision related signals that might arise independently of motor requirements, a subset of participants (N=8) performed a version of the visual direction discrimination task whereby choices were reported vocally after a randomized delay. Using a data-driven dimensionality reduction approach, we were able to identify functionally dissociable task-correlated components in the neural activity that showed unique temporal dynamics, spatial distribution, and relationship with decision behavior, in line

with a cascade of neural events supporting the decision process, and consistent with previous observations in the non-human primate brain. Our results highlight the complementary value of iEEG to scalp EEG and invasive animal studies to investigate the neural substrates of perceptual decision making.

Disclosures: S. Gherman: None. **N. Markowitz:** None. **E. Espinal:** None. **A.D. Mehta:** None. **R.G. O'Connell:** None. **S. Kelly:** None. **S. Bickel:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Program #/Poster #: P784.06

Topic: H.03. Decision Making

Support: 1U19NS107609-01

Title: Distinct frequency bands synchronize distributed feedback tuned neuronal populations in the human brain

Authors: *I. SKELIN[1], H. ZHANG[2], M. R. PAFF[3], E. A. BUFFALO[5], R. T. KNIGHT[6], J. LIN[4]; [2]Biomed. Engin., [1]Univ. of California Irvine, Irvine, CA; [3]Univ. of California, Irvine, Orange, CA; [4]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [5]Univ. of Washington, Seattle, WA; [6]Univ. of California Berkeley, Berkeley, CA

Abstract: Adaptive behavior requires utilization of action outcome feedback, which could be present at the level of neuronal populations, reflected in the high-frequency activity (HFA; 70-200 Hz). The Wisconsin Card Sorting Task (WCST) contains 12 possible rules, across 3 different dimensions (color, shape and texture), with unpredictable rule switching. This experimental model is suitable for investigating the neural and behavioral dynamics underlying feedback signaling during rapid rule acquisition and switching. We recorded intracranial electroencephalographic (iEEG) signal from the temporal and frontal lobe in 16 subjects undergoing pre-surgical evaluation of epileptic foci, during performance on WCST (32 datasets; 983 electrodes). The HFA feedback tuning (HFA significantly associated with trial outcome) was present in 12.4% of local populations, distributed across all the recorded structures (amygdala, hippocampus, orbitofrontal and anterior cingulate cortices). Next, we assessed the noise correlations between the feedback-tuned electrode pairs and found significantly higher noise correlations during the time periods when HFA in both populations contained feedback information. Finally, we hypothesized that HFA noise correlations are driven by low-frequency synchrony. To test this hypothesis, we computed the Spearman correlations between the pairwise noise correlation time-courses and low-frequency connectivity (phase-locking value; PLV) for the feedback-tuned populations. PLV dynamics was significantly associated with noise correlations in two distinct, feedback-dependent bands: beta range (25-30 Hz) during correct and ~2 Hz during incorrect trial feedback periods. These results provide evidence for outcome-based oscillatory mechanisms integrating distributed feedback information in the human brain.

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Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Topic: H.03. Decision Making

Support: Marie Skłodowska-Curie Grant No 842143
European Research Council Consolidator Grant No 865474
Wellcome Trust Grant No 219572/Z/19/Z

Title: EEG signatures of decision formation in motion direction estimation

Authors: *E. A. CORBETT[1], P. L. SMITH[2], H. MCCONE[1], S. KELLY[3], R. G. O'CONNELL[1]; [1]Trinity Col. Inst. of Neurosci. and Sch. of Psychology, Trinity Col. Dublin, Dublin, Ireland; [2]Melbourne Sch. of Psychological Sci., Univ. of Melbourne, Melbourne, Australia; [3]Sch. of Electrical and Electronic Engin., Univ. Col. Dublin, Dublin, Ireland

Abstract: In perceptual decisions with continuous outcomes, response variability may be influenced by categorical biases as well as attentional fluctuations. Here we investigated whether directional biases and trial-to-trial variability in accuracy were reflected in EEG signatures of decision formation in a random-dot-kinematogram direction estimation task. Six participants reported the perceived direction of motion from 18 stimulus directions spanning 360º using a joystick. Two levels of coherence of the dot motion stimulus were interleaved, and modulated at a frequency of 15Hz generating a steady-state visual motion evoked potential (SSVMEP) in the EEG signal reflecting the strength of sensory evidence encoding. We also measured the centroparietal positivity (CPP), thought to reflect the evidence accumulation process. Both the SSVMEP (466 ms post-stimulus) and CPP (200-333 ms) were strongly modulated by coherence (linear mixed effects (LME) models with random intercepts for participants, excluding minority of trials with errors > 120º in all EEG analyses; both $p<.001$). The SSVMEP ($p=.01$) and CPP ($p=.045$) signals were both significant predictors of response accuracy (LME model with fixed effects for coherence, CPP and SSVMEP, with random intercepts).
Participants' responses displayed varying amounts of idiosyncratic directional biases. We jointly fit individuals' response angles and response times with the circular diffusion model, including a mixture component with a zero-drift process in low coherence trials to account for encoding failures. We accounted for directional variation through stimulus biases using the similarity-choice method of Smith et al (2020), in which the drift rate is the vector sum of the encoded metric (true stimulus direction) and categorical (participant-favoured directions) representations of the stimulus. We then averaged the SSVMEP and CPP for each direction and coherence level to examine their relationships with the directional drift rate estimates. Drift rate was a significant predictor of the CPP ($p=.001$, LME model with fixed effects for coherence and drift rate, with random intercepts), but not the SSVMEP ($p=.49$). Taken together, these results suggest that while directional biases may be reflected in neural processes of evidence accumulation, the modulation of the sensory-level SSVMEP signal reflects trial-to-trial influences on response accuracy unrelated to directional biases.
Smith, Saber, Corbett & Lilburn (2020). Modeling Continuous Outcome Color Decisions With the Circular Diffusion Model: Metric and Categorical Properties. Psychol. Rev. 127-4, 562-590.

Disclosures: E.A. Corbett: None. **P.L. Smith:** None. **H. McCone:** None. **S. Kelly:** None. **R.G. O'Connell:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Program #/Poster #: P784.08

Topic: H.03. Decision Making

Support: Irish Research Council

Title: Neurally informed insights into speed-accuracy adaptations in older adults

Authors: *C. JUDD, J. DULLY, E. A. CORBETT, R. G. O'CONNELL;
Trinity Col. Inst. of Neurosci., Trinity Col. Dublin, Dublin, Ireland

Abstract: When instructed to prioritise speed over accuracy in decision making, older adults tend to make smaller adjustments to their choice behaviour compared to younger adults. Behavioural modelling suggests this may be due to less pronounced adjustment of decision bounds across conditions and a general preference for a more cautious response style. However, this work has relied on standard models which overlook important algorithmic elements and adjustments that have been identified in recent neurophysiological research. The current study aims to leverage neurally-informed modelling to investigate aging's effects on speed-accuracy adaptation. 30 older adults and 30 young adult controls completed a random dot-motion task, while electrical brain activity was recorded through EEG. Neural data indicated significantly greater pre-stimulus motor preparation in the young group which was not present in the older group ($F(1)=7.571$, $p=0.008$). A cross-over effect of condition on sensory processing signals was also observed, with higher sensory encoding signal amplitudes (SSVEP) under speed pressure in older adults, while the signal was stronger under accuracy pressure in the young group ($F(1,56)=9.672$, $p=0.003$). Concurrent drift-diffusion modelling indicated age differences in the setting and dynamic adjustment of decision bounds. This work is using neural signals to constrain model parameters, seeking to reconcile the two data streams to create a parsimonious and biologically grounded model of the impact of ageing on speed-accuracy adaptations in older adults.

Disclosures: C. Judd: None. **J. Dully:** None. **E.A. Corbett:** None. **R.G. O'Connell:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Topic: H.03. Decision Making

Support: Center of Biomedical Research Excellence grant P20GM103645 from the National Institute of General Medical Sciences

Title: Two distinct patterns of EEG activity emerge during value-based choice, neither related to evidence accumulation

Authors: *R. FRÖMER[1], M. R. NASSAR[2], B. V. EHINGER[3], A. SHENHAV[1];
[2]Metcalf Hall, [1]Brown Univ., Providence, RI; [3]Univ. of Stuttgart, Stuttgart, Germany

Abstract: Research into value-based choice and its neural correlates often centers on a unitary process subsuming the accumulation of evidence about one's options until a choice is made. The centro-parietal positivity (CPP) is one putative index to this evidence accumulation process. At odds with a unitary view, our previous fMRI research suggests two distinct forms of evaluation during value-based choice: (1) overall appraisal of one's options, and (2) comparing between those options for the current choice. Here we test whether these processes are also temporally dissociable, with appraisal-related processes tied to the time one's options appear and choice-related processes tied to the time a decision is made. In light of this dissociation, we reevaluate the CPP as an index of evidence accumulation.We recorded EEG while participants (N = 39) made choices between consumer goods, previously rated individually. Afterward, participants rated their overall appraisal (liking) of each set, how anxious they felt making the choice, how confident they were in this choice. Using PCA, we reduced the dimensionality of measures to two components, broadly indexing variance associated with the appraisal of items (e.g. overall value and set appraisal) and choice between items (e.g. value difference and confidence). We used those components as regressors for stimulus- and response-locked EEG activity.As predicted, activity locked to the onset of the stimuli correlated with our appraisal-related PC, and activity locked to (and preceding) the response with our choice-related PC. Neither activity pattern was consistent with canonical indices of evidence accumulation. However, we show that typical CPP evidence accumulation patterns can emerge artificially as stimulus and response locked effects occur closely in time. Confirming this, we demonstrate in an independent dataset that signatures of evidence accumulation commonly observed in the CPP vanish when accounting for such overlap through joint modeling of stimulus and response-locked activity. Our results provide further evidence that neural activity during value-based choice does not reflect a unitary choice process. Neither of the spatiotemporally distinct patterns associated with appraisal and choice conformed with canonical signatures of evidence accumulation. They might instead reflect affective and metacognitive appraisals of one's options and (latent) choice. Our findings call for caution when interpreting neural correlates of choice value, a critical re-examination of putative EEG evidence accumulation signals, and for taking a broader, more integrative perspective on value-based choice.

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Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Program #/Poster #: P784.10

Topic: H.03. Decision Making

Support: NIH NIMH R01MH119086

Title: Representations of the subjective value of cognitive effort

Authors: *G. E. STEWARD, V. S. CHIB;
Johns Hopkins Univ., Baltimore, MD

Abstract: Many of our daily tasks require us to evaluate how cognitively effortful they feel. We often use these effort judgements to prioritize tasks -- which to take on, and which to leave for another day. Despite the ubiquity of cognitive effort judgement, it is not well understood how we make decisions involving cognitive effort at the levels of brain and behavior. We used a combination of functional magnetic resonance imaging and a behavioral decision-making task for prospective cognitive effort, in the form of working-memory, to understand how healthy human participants represent the subjective nature of cognitive effort in the brain.
We had participants make choices as to whether to undergo a low-effort cognitive task for $1 or a variable higher-effort cognitive task for variable reward while undergoing an fMRI scan. The cognitive effort task took the form of the N-Back working memory task, with increasing N representing increasing working memory load and increasing cognitive effort. The choice paradigm used was designed to be robust, with considerations for balanced order randomization and choice difficulty over time.
We found that participants probability of acceptance of the more effortful option increased with increasing reward and decreased with increasing effort level. We found that individuals varied the point at which they began accepting high effort options for reward, indicative of individual differences in subjective valuation of cognitive effort. Subsequent analysis will examine brain regions with activity associated with participants subjective preferences for cognitive effort and reward.

Disclosures: G.E. Steward: None. **V.S. Chib:** None.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

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Topic: H.03. Decision Making

Support: NSERC Discovery Grant RGPIN-2020-05577
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Title: Widespread gamma suppression in exploratory decision-making

Authors: *K. JUREWICZ[1], S. KOENIG[2], R. MCGOVERN[2], M. C. PARK[2], D. P. DARROW[2], B. EBITZ[1], A. B. HERMAN[2];
[1]Univ. de Montréal, Montreal, QC, Canada; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: In complex and changing environments, the best option is not always known in advance or stable over time. Under these circumstances, organisms have to balance two goals: exploiting options

with a known, good value versus exploring alternatives that might turn out better. Exploring and exploiting require such different computations that we might expect to see large changes in brain activity between periods of exploration and exploitation, but we have only recently developed methods to clearly differentiate these goal states. Here, we examined neural activity across distributed intracranial recordings while humans made both exploratory and exploitative choices.
Ten epileptic patients performed a sequential decision-making task, choosing between three available options whose values changed gradually and independently over trials. A hidden Markov model (HMM) was used to model exploration and exploitation as the latent states underlying behavior, which allowed us to label choices as exploratory or exploitative. The patients contributed signals from over 1000 subdural electrocorticographic (ECoG) and/or depth electrodes, distributed across a wide range of brain regions, with the most dense coverage of prefrontal, temporal, and (para)hippocampal regions.
Exploration produced widespread suppression of local field potential power in the gamma band (~60-120 Hz), when compared to exploitation state. Gamma suppression was identified in most of the recording electrodes and was sustained throughout the trial, across decision-making and reward-processing epochs. This effect was highly specific to the gamma band and could not be explained by the lower reward rate in explore than exploit trials.
Gamma oscillations index the intensity of local neuronal activity and widespread differences in gamma local field potentials have been previously identified in cognitive tasks, with higher gamma activity when mnemonic demands are higher. In this context, the profound whole-brain gamma suppression we observed in exploration could suggest that distributed information maintained for exploitative choices is less available during exploration. This could facilitate the discovery of new options through overcoming historical biases.

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Poster

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Support: This work was partly supported by a joint grant from the John Templeton Foundation and the Fetzer Institute. The opinions expressed in this publication are those of the author(s) and do not necessarily reflect the views of the JTF or the FI.

Title: Does the timing of a decision cue based on neural activity modulate the decision outcome? A real-time EEG study

Authors: *M. SCHULTZE-KRAFT, H. STEINRÜCK, J.-D. HAYNES;
Bernstein Ctr. for Computat. Neurosci. Berlin, Berlin, Germany

Abstract: The relationship between voluntary, spontaneous motor decisions and preceding neural activity has been studied for decades, yet the question whether this relationship is causal remains debated. In

humans, movements executed at freely chosen time points ("when" decisions) are preceded by a negativation of the electroencephalogram (EEG) over motor areas, the so-called readiness potential (RP) (Shibasaki & Hallett, 2006). Similarly, when people are instructed to decide whether to execute a rapid or a delayed movement at an externally cued time point ("whether" decisions), rapidly executed movements are preceded by signals similar to RPs (Filevich et al., 2013). This suggests that neural signals preceding spontaneous movements and those preceding cued, free-choice rapid movements are closely related. Using a novel experimental paradigm, we tested whether the presence of such RP-like events (RPLEs) at the time of a free-choice cue in a motor task has an effect on the subsequent decision. In an initial experimental stage, we instructed participants (N=18) to perform self-paced movements in single trials and trained a brain-computer interface (BCI) on the recorded RPs. In the main experimental stage, participants were presented with a visual cue in each trial and instructed to spontaneously decide to quickly execute a movement, or not to move. The cues were elicited in real-time by the BCI either upon detecting the presence or the absence of an RPLE in the ongoing EEG. We hypothesized that participants would decide more often to execute a movement when the decision cue was elicited by an RPLE than when no RPLE was present. We found no evidence for an effect of EEG signals at the time of the cue on participants' decisions. This negative result can have several reasons. First, although offline analyses show that the EEG preceding the two types of cues indeed reflected the presence or absence of RPLEs, the accuracy of a BCI in detecting RPLEs in real-time is limited by the noisy nature of EEG. Second, it could be that the similarity between EEG signals preceding "when" and "whether" decisions is spurious. Finally, RPLEs may simply not modulate the outcome of "whether" decisions. Future advancements of our real-time paradigm will help disambiguate these findings.

Disclosures: M. Schultze-Kraft: A. Employment/Salary (full or part-time):; Bernstein Center for Computational Neuroscience Berlin, Charité - Universitätsmedizin Berlin, Berlin, Germany, Berlin Center for Advanced Neuroimaging, Charité - Universitätsmedizin Berlin, Berlin, Germany. **H. Steinrück:** None. **J. Haynes:** A. Employment/Salary (full or part-time):; Bernstein Center for Computational Neuroscience Berlin, Charité - Universitätsmedizin Berlin, Berlin, Germany, Berlin Center for Advanced Neuroimaging, Charité - Universitätsmedizin Berlin, Berlin, Germany, Clinic of Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany, Department of Psychology, Humboldt Universität zu Berlin, Berlin, Germany, Cluster of Excellence Science of Intelligence, Technische Universität Berlin und Humboldt Universität zu Berlin, Germany.

Poster

P784. Neural Mechanisms of Decision-Making and Cognitive Processes in Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P784.13

Topic: H.03. Decision Making

Title: Neuronal mechanisms of dynamic social competition

Authors: *Y. JIANG, M. L. PLATT;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: People naturally engage in social interactions involving competition or negotiation in which they continuously update mental models of other agents. To understand the neurobiology of these dynamic interactions, we studied humans and monkeys playing a virtual competitive soccer game in which the numbers of moves and counter-moves were unconstrained. This game combined a classic zero-sum matching penny scheme with a timing game by requiring players to optimize both movement sequence and temporal control of their final move to win. Using this game we uncovered a wide range of strategic performance in humans that was correlated with various socio-cognitive traits including mentalizing capacity. Remarkably, performance of monkeys was well within the human distribution in all facets. Next, we recorded neuronal activity in macaque mid-superior temporal sulcus (mSTS), the putative simian homolog of the human temporo-parietal junction (TPJ)--a brain area engaged in strategic social interactions guided by mentalizing. Two distinct neuronal populations with different tonic firing rates and residing within different depths in the mSTS showed opposing activity patterns throughout the virtual soccer game. One population encoded self over opponent movements during gameplay, and encoded loss over win after gameplay. The second population encoded opponent moves during gameplay and win over loss after gameplay. Both populations retained information about trial history and behaved similarly when monkeys played attacker or defender. Together, these activity patterns are well-suited to support the complex, dynamic interactions between players in this game, and by extension natural pairwise social interactions. To test this idea, we inactivated mSTS with muscimol, and observed a significant decrease in players' strategic flexibility and responsiveness as a result. These findings suggest mSTS evaluates strategies to fit the current social context and endorse the hypothesis that it is the primate homolog of human TPJ.

Disclosures: Y. Jiang: None. **M.L. Platt:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Program #/Poster #: P788.01

Topic: H.03. Decision Making

Support: T32-MH115886
R01-MH112688

Title: Identification of functional subdivisions within the rodent medial prefrontal cortex during decision making

Authors: G. W. DIEHL, A. D. REDISH;
Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Anatomical work has long identified heterogeneity within the rodent medial prefrontal cortex (mPFC) suggesting distinct subdivisions of anterior cingulate (ACC), prelimbic (PL), and infralimbic (IL) cortices. However, it remains unknown if these anatomical differences are reflected functionally, or how multiple functional subregions may interact in support of behavior.
We trained rats to perform a complex economic decision making task (Restaurant Row) that required

multiple cognitive processes such as sensory descrimination, value assessment, and cognitive override, which have been closely associated with the mPFC. We used silicon probes to record ensemble activity from the full dorso-ventral extent of the mPFC during behavior and precisely localize each unit. This experimental approach allowed us to monitor neural activity patterns across multiple portions of the mPFC simultaneously during decision making to directly test for the existence of functional subdivisions and interactions between them.
Leveraging the precise anatomical information afforded by silicon probes, we developed a novel analytic approach that related functional activity patterns across pairs of mPFC cells according to their specific positions along the mPFC dorso-ventral axis. This analysis revealed distinct functional domains with the mPFC and allowed us to define independent subregions. The boundaries between these subregions closely matched anatomical data, providing a direct link between the functional and anatomical domains. Integrating functional and anatomical profiles yielded four distinct subregions, Acc, IL, and dorsal (dPL) and ventral (vPL) prelimbic cortex. All four subregions exhibited unique but complementary activity profiles. ACC and dPL were involved in active decision making with dPL providing a general decision signal and ACC signalling an override of the default choice. vPL and IL provided more state based signals, either marking transition points in the task (vPL) or maintaining and updating information about the current state (IL).
Finally, examination of network interactions revealed that functional connectivity within mPFC is graded, with the strength of influence dissipating with increasing anatomical distance. Followup ensemble analysis between subregions pointed to the existence of two complementary modes of information transfer: A strong connectivity that relayed information stepwise across adjacent regions from dorsal to ventral mPFC, and a weaker, longer range connectivity from ventral to dorsal mPFC which may provide updates about changes to task conditions for consideration in future decisions.

Disclosures: G.W. Diehl: None. **A.D. Redish:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Program #/Poster #: P788.02

Topic: H.03. Decision Making

Support: R01-MH112688

Title: Optogenetic manipulation of the rodent medial prefrontal cortex disrupts the transition from deliberative to procedural decision processes on a delay discounting task

Authors: A. E. MCLAUGHLIN, K. SEELAND, A. SHEEHAN, *A. D. REDISH;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Rats show a preference for smaller, immediate rewards over larger, delayed ones, a phenomenon known as delay-discounting. Rats were trained on a spatial delay discounting task (Papale et al 2012 CABN) where they repeatedly faced two choices while running laps on a figure-8 maze: a smaller-sooner reward offered immediately or a larger-later reward offered after a variable delay that

increased in time (+1s) each lap it was selected and decreased each lap it wasn't (-1s).
Well-trained rats typically show three behavioral phases: investigation, characterized by alternation between options, titration, characterized by a repeated preference for one side or the other (adjustment laps) which titrates the delay to a preferred delay, and exploitation, characterized by alternation between options which holds the delay constant. These phases can be identified by changes in behavioral characteristics such as path stereotypy, pause and re-orient behavior at choice points (vicarious trial and error, VTE), and changes in adjustment and alternation laps, suggesting these phases are indicative of transitions between deliberative and procedural decision processes. The medial prefrontal cortex (mPFC) has been identified as a central component in the mediation between these decision-making processes. 15 rats underwent in-vivo optogenetic manipulation of the mPFC during the spatial delay discounting task. Comparisons between rats with active (n=8, AAV5-CaMKIIa-ChR2-mCherry) and inactive (control, n=7, AAV5-CaMKIIa-mCherry) virus revealed a significant deficit in the active group's ability to transition to automated, procedural decision processes. Both groups learned the task equally well after transfection, but before the experimental phase in which light activated the optogenetic receptors; however, differences appeared with extended exposure to the task after light administration. Interestingly, we did not find trial-by-trial changes due to light delivery, but instead found long-term changes that arose after the first delivery of light to the transduced rats. Control rats showed developing procedural responses as they gained experience with the task, but active rats did not, continuing to express adjustment laps throughout each session. Active animals also exhibited fewer instances of VTE compared to the control group after the first delivery of light to mPFC. These results suggest that VTE may be an important component in learning to transition from deliberative to procedural decision modalities and that this transition may be mediated in part by the medial prefrontal cortex in rats.

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Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Topic: H.03. Decision Making

Support: T32-MH115886
R01-MH112688

Title: Distinct representations across the medial-to-lateral rodent orbitofrontal cortex in an economic decision-making task

Authors: *P. J. CUNNINGHAM, G. W. DIEHL, A. D. REDISH;
Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: The rodent orbitofrontal cortex (OFC) plays a diverse role in value-based decision making. Emerging evidence suggests functional heterogeneity along the medial-to-lateral axis of the OFC. We examined information-processing from the medial (MO), ventral (VO), and lateral (LO) subregions simultaneously while rats made value-based decisions in the Restaurant Row (RRow) neuroeconomic

task.
Rats serially encountered four “restaurants” offering distinctly flavored food delivered after a randomly chosen delay (ranging from 1- 30 s) to earn their daily food intake within a one-hour time budget. Each restaurant contained an offer zone (OZ) and a wait zone (WZ). Entry into the OZ triggered a tone indicating the delay to reward for that offer. In the OZ, rats could either “accept” the offer by entering the WZ or “skip” it by proceeding to the next restaurant. In the WZ, the delay to reward counted down and rats could either wait through the delay and earn reward (“earn”) or leave the WZ prior to earning reward (“quit”). Neural ensembles were recorded simultaneously from MO, VO, and LO with 3 silicon probes each as rats (n=5) made value-based decisions in RRow.
We found dissociable information processing in LO, VO, and MO ensembles. LO firing increased in the moments preceding reward delivery, whereas VO and MO firing decreased after reward delivery. Despite these contrasting firing patterns, each subregion contained information about the currently offered reward type at reward delivery time. VO ensemble firing differentiated skip/accept decisions in the OZ by increasing firing rate only when a skip decision was made. Indeed, VO ensembles contained more mutual information about the current OZ decision (accept vs. skip) than LO or MO ensembles. This result suggests that VO ensembles represent accept/skip OZ decisions at the decision moment more than LO and MO ensembles. In contrast, LO ensemble firing rate differentiated quit/earn decisions by increasing prior to leaving the restaurant only when a quit decision was made. These results suggest that accept/skip and quit/earn decisions depend on different evaluation processes which are likely mediated by VO and LO respectively.
Finally, VO ensemble firing increased when leaving a restaurant regardless of whether the rat left by quitting the WZ, or by proceeding to the next restaurant after post-reward lingering. This result suggests that VO ensembles likely participate in deciding to leave a reward-associated location to search for reward elsewhere. Overall, these results suggest distinct information-processing characteristics across the medial-to-lateral OFC at various learning and decision moments in a neuroeconomic task.

Disclosures: P.J. Cunningham: None. **G.W. Diehl:** None. **A.D. Redish:** None.

Poster

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Program #/Poster #: P788.04

Topic: H.03. Decision Making

Support: NIH R01EY0190141
DOD VBFF

Title: Neuronal encoding in LIP during abstract categorical decisions based on multiple visual features

Authors: *P. MOGHIMI, A. A. SILVA, D. J. FREEDMAN;
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Abstract: Primates have a remarkable ability to group visual stimuli into arbitrary learned categories, which often involves integrating multiple features such as shape, motion and color. Previous studies have

shown that neurons in the lateral intraparietal area (LIP) of monkeys encode the learned category membership of visual stimuli, and that inactivation of LIP impairs category judgements. In previous studies of categorization in LIP, stimuli were typically categorized by a single visual feature—direction of motion. The current study asks whether LIP's role in categorization of visual motion is but one example of a more general role in visual categorization. We investigated whether and how neuronal populations in LIP participate in categorizing visual stimuli when categorical decisions require integrating two visual features—motion direction and color. We trained one monkey to perform a double-feature categorization task where it was required to assign a random-dot motion stimulus into one of two categories based on both their direction of motion and color. Each trial began with fixation, after which an array of colored, coherently moving dots appeared. After 700ms, two targets appeared, each associated with one category. The animal indicated category of the stimulus by making a saccade to one of the two targets. Six motion directions (36° apart) and six colors (ranging from red to yellow) were combined to generate a set of visual stimuli, and a category boundary was defined which required the monkey to take into account both features in order to categorize the stimulus. During the task, we recorded from LIP in 16 sessions, and completed preliminary analysis of 41 single units from four sessions. The monkey's accuracy was 83% for conditions away from the category boundary and 64% for conditions close to the category boundary on included sessions. We used three-way nested ANOVA ($p=0.05$) to assess selectivity of each neuron for both features and the abstract category of the stimulus. A majority (30/41) of LIP neurons were selective for at least one of two features (14 and 16 neurons selective for direction of motion and color, respectively). Interestingly, five neurons were selective for both features, suggesting integrative encoding of the two features. Two neurons were category selective, of which one was selective for both features and one was not selective for either feature. These results indicate that LIP neurons integrate multiple features to perform this categorization task. Ongoing work is examining the nature of stimulus and categorical representations in LIP during this task, to gain insight into how integrative representations support the animal's decisions.

Disclosures: P. Moghimi: None. **A.A. Silva:** None. **D.J. Freedman:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Program #/Poster #: P788.05

Topic: H.03. Decision Making

Support: HHMI
NIH Grant NS113113
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Title: Distinct roles of the superior colliculus and the lateral intraparietal area in decision formation and termination

Authors: *G. M. STINE, E. M. TRAUTMANN, D. JEURISSEN, M. N. SHADLEN;
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Abstract: Many decisions arise through an accumulation of evidence to a terminating threshold. Previous work has shown that the lateral intraparietal area (LIP) represents the accumulation of evidence when monkeys make decisions about the direction of random dot motion (RDM) and express their decision with an eye movement. However, LIP is interconnected with several other brain regions that also display decision-related activity, such as the superior colliculus (SC). SC and LIP are strongly interconnected and share several functional similarities, including subsets of neurons that display spatially selective, persistent activity. Whether SC's role in the decision process is similar to or fundamentally different from that of LIP is unclear.

We used newly-developed, primate neuropixels probes and v-probes to record simultaneously from retinotopically-aligned populations of neurons in LIP and SC as a monkey performed a reaction-time, RDM task. LIP neurons represented the accumulation of noisy motion-evidence on single trials (e.g. drift-diffusion). In contrast, SC neurons did not reflect evidence accumulation—including neurons with persistent activity in a memory-guided saccade task (i.e. prelude neurons). SC neurons generated an all-or-none burst of activity immediately preceding the saccade. In addition, single-trial analyses revealed that this saccadic burst was often preceded by non-saccadic bursts of activity, which were not apparent in trial-averages. Both types of bursts were associated with a sharp increase in LIP activity. Saccadic bursts tended to occur when LIP had also achieved a higher level of firing rate, suggesting that the conjunction of a sharp increase and elevated activity in LIP facilitates a burst in SC large enough to generate a saccade.

We hypothesized that this saccadic burst terminates the decision process. Consistent with this, we found that unilateral inactivation of SC induced (1) a coherence-dependent increase in reaction times for contralateral choices, (2) an ipsilateral choice bias, and (3) an increase in overall sensitivity, the combination of which is diagnostic of a higher terminating threshold for contralateral choices. Recordings in LIP during SC inactivation showed a prolonged build-up of activity, further suggesting that commitment to a contralateral choice required more accumulated evidence. We conclude that LIP and SC play fundamentally different roles in the decision process—LIP represents the accumulation of evidence whereas SC is involved in implementing the decision threshold—and we pose a novel neural mechanism for terminating an ongoing decision process.

Disclosures: G.M. Stine: None. **E.M. Trautmann:** None. **D. Jeurissen:** None. **M.N. Shadlen:** None.

Poster

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Topic: H.03. Decision Making

Support: NIH Grant NS113113
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HHMI

Title: Neuropixel recordings in macaque area LIP reveal drift-diffusion dynamics on single trials

Authors: *N. A. STEINEMANN[1], G. M. STINE[1], E. M. TRAUTMANN[1], A. ZYLBERBERG[1], M. N. SHADLEN[1,2];
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Abstract: The concept of a dynamic firing rate, *r(t)*, is elemental to principles of computational systems neuroscience. Yet it is elusive, or latent, because single neurons produce spikes separated by silent interspike intervals. *r(t)* is thus estimated by averaging across repetitions, on the assumption that the neuron is a member of a larger population that represents r(t) on a single trial. With few exceptions, such populations have been inaccessible to electrophysiology, either because they lie deep in sulci or because they are intermingled among a heterogeneous population. This is especially problematic for the study of stochastic dynamic processes, such as decision making, where a decision variable, *V(t)*, is itself stochastic. On a trial i, $V_i(t)$ is thought to represent the cumulative sum of random samples—the momentary evidence, x_t—as in discrete drift-diffusion. Averaging across repetitions renders only a ramp: a line with slope $\langle x \rangle$, termed the drift rate. The diffusion component of $V_i(t)$ is latent. Two monkeys indicated the net direction of dynamic random dots by making a saccadic eye movement to a left or right choice target when ready. We recorded simultaneously from 54-191 neurons in the lateral intraparietal area (LIP) using high density, multichannel, primate neuropixel probes (IMEC/HHMI-Janelia). We focused on groups of 7-18 neurons (sample-population) with response fields that overlap a common choice target. We hypothesized that these neurons are a subset of a larger population that represents the animal's decision variable, $V_i(t)$. We found that mean firing rates from sample populations, $S_i(t)$, approximate drift-diffusion processes on single trials. (1) The variance of S(t), across trials, increases linearly over time. (2) Values of $S_i(t)$ at the beginning of the decision are correlated with decision outcome (choice and response time), consistent with temporal integration, and (3) this correlation is nullified when controlling for sample-population activity at later time points, consistent with the Markov property of diffusion. (4) When the decision ends with an eye movement to the choice-target in the common response field, $S_i(t)$ achieves a stereotyped level 50-100 ms before saccade initiation, consistent with the hypothesis that decision termination is accomplished via a threshold applied to . The observation of diffusion dynamics on single trials provides direct support for a neural mechanism long suspected to underly perceptual decisions arising through evidence accumulation.

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Poster

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Program #/Poster #: P788.07

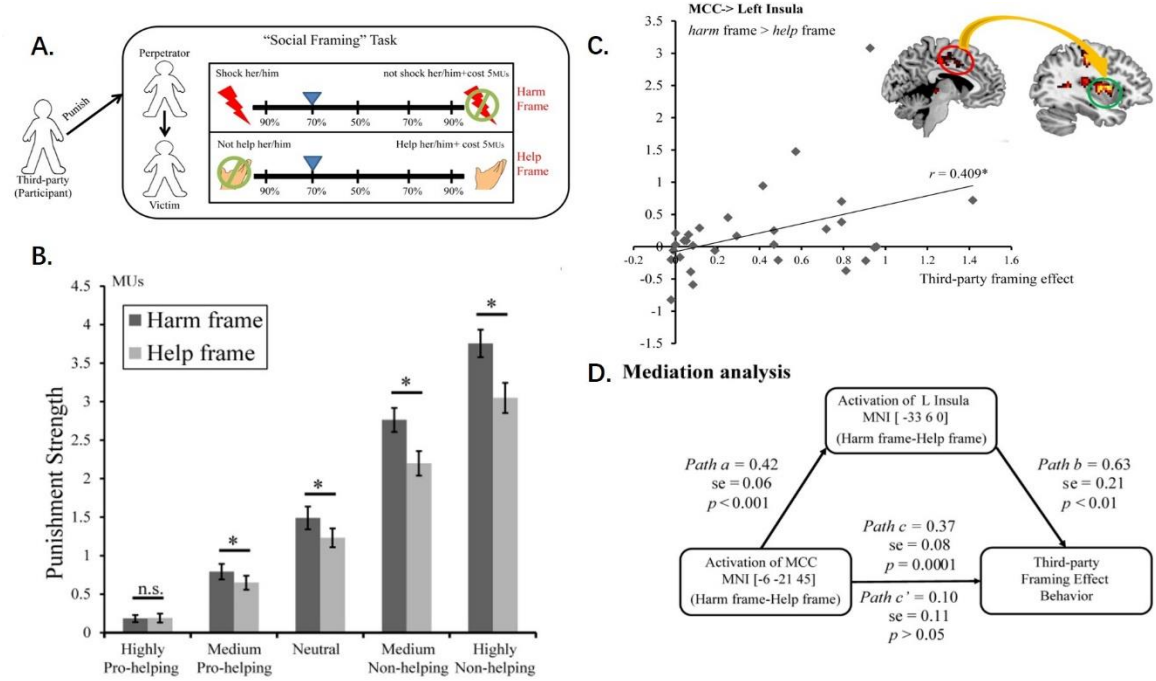
Topic: H.03. Decision Making

Support: National Natural Science Foundation of China:31871109
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Title: To blame or not? Modulating third-party punishment with the framing effect

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Abstract: People as third-party observers, without direct self-interest, may punish norm violators to maintain social norms. However, third-party judgment and the follow-up punishment might be susceptible to the way we frame (i.e., verbally describe) a norm violation. We conducted a behavioral and functional magnetic resonance imaging (fMRI) experiment to investigate the above phenomenon, which we call "third-party framing effect". Our task design combined the "social framing" task with third-party punishment. Participants observed an anonymous perpetrator deciding whether to keep her/his economic benefit while exposing a victim to a painful shock(described as "shocking others" in harm frame condition and "not helping others" in the help frame condition), then they had a chance to punish that perpetrator at their own cost. Our results showed that the participants were more willing to execute third-party punishment under the harm frame compared to the help frame, manifesting as a framing effect. In Behavioral Experiment, self-reported anger toward perpetrators mediated the relationship between empathy toward victims and the framing effect. In fMRI Experiment, we found that the mid-cingulate cortex (MCC), and insula were both significantly sensitive to the main effect of frame; the functional connectivity between these regions could significantly predict the framing effect size. Also, insular activation mediated the relationship between mid-cingulate cortex activation and the framing effect. Overall, this study reveals that third-party punishment is susceptible to decision frames, which may help understand why moral standards and moral actions could be flexible and relativistic. Besides, our findings may broaden the understanding of the framing effect in general.



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Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Topic: H.03. Decision Making

Support: R01 MH080318
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Title: The effect of topology on adaptive strategies that arise from a conflict between deliberative and procedural decision-making.

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Abstract: Prior research suggests that decision-making arises from a conflict between systems driven by dissociable neural circuits. Navigation studies reveal that deliberative strategies are characterized by pause-and-re-orientation behaviors (vicarious trial and error, VTE) and hippocampal (HC) goal-directed representations, while procedural responses are characterized by regularity in paths taken (path stereotypy) and dorsolateral striatal (DLS) task-bracketing (increased firing at the start and end of ballistic trajectories).
To examine the role of environmental structure on the balance between these decision-making strategies, we re-analyzed previous data from a contingency-switching task, taking into account a new measure of topological complexity, which quantifies the difficulty of the central path. This new measure uses an abstract representation of the task space to calculate its graph entropy, which quantifies the structural feature of the environment (Mugan and MacIver, 2020).
The task consisted of a spatial maze with a changeable central path that led to a high cost choice point (CP). Three different reward contingencies were used: turning left for reward at CP, turning right for reward at CP, or alternating choices. The reward contingency changed roughly half way through the session. Neural ensembles (n = 50 sessions) were recorded from DLS (6 rats) or HC (5 rats). The proportion of VTE events per session increased with central path and topological complexity. Neurophysiological correlates of deliberative decision-making also changed with environmental complexity. In HC, theta cycles were more symmetric in environments with high central path complexity. These theta cycles included more time spent in the ascending phase of the theta cycle—hypothesized to contain nonlocal representations. Both sharp wave ripple (SWR) overall rate and individual duration increased with central path complexity. SWRs have been implicated in planning, consolidation, and the mental exploration of navigational possibilities. More complex environments likely require a higher cognitive memory load, which could lead to more and longer SWRs. In contrast, path stereotypy decreased with central path and topological complexity, consistent with theories that environmental complexity slows the development of procedural automation. Task-bracketing effects (preferential firing in DLS at the start and end of a lap), emerged more slowly in environments with complex central paths. These data suggest that rats are more likely to use deliberative decisions in environments with more topological complexity.

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Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Program #/Poster #: P788.09

Topic: H.03. Decision Making

Title: A two-step decision task to measure confidence in economic choices

Authors: *K. M. ROTHENHOEFER[1], W. R. STAUFFER[2];
[2]Neurobio., [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Decision confidence is the belief that a choice is correct. This concept has been widely used to perform psychometric measurements of confidence in perceptual judgements. However, the application of confidence measures to economic choices is more challenging because 'correct' and 'incorrect' are not well defined. To address this limitation, we modified a recently published, two-step choice task that showed confidence in the first judgment was used as a prior in the second judgment (Lisi, Mongillo et al. 2021). In our version of the task, the first decision was an economic choice and we applied first- and second-order stochastic dominance (FOSD and SOSD, respectively) rules to the animals' utility function to categorize the choices as better or worse. The second decision was a perceptual judgment about the net direction of motion in a Random Dot Kinetogram (RDK). We trained NHPs that better choices were followed by motion stimulus to the right, whereas worse economic choices were followed by motion stimulus to the left. When the monkey indicated the correct direction of motion, it was rewarded with the amount chosen in the economic decision, otherwise it received no reward. Because monkeys rarely choose worse options, we masked the stimuli during the economic choice; we only revealed both options after the choice was made. On half the trials, by design, the animal chose the better option, and on the other half the worse option. In preliminary data, we observed an effect of the first (economic) choice on the second (perceptual) choice. When the difference between the reward options was large, for example when selecting between 0.75 and 0.15 mls, the monkeys indicated the correct motion, right or left, on the second choice with greater than 95% accuracy. However, when the difference was smaller, for example between 0.55 and 0.35 mls, the behavior diverged. When the animal chose the better option, it correctly indicated rightward motion >95% of the time. When it chose the worse option, on the other hand, it correctly indicated leftward motion only ~55% of the time. The different performance on the RDK stimulus - for lower value choices - was not value based: the animal performed much better when the outcome was 0.15 mls than when it was 0.35 mls. Rather, their psychophysical judgements appeared highly dependent on the value differences between the options in the economic choice. Further testing is underway to explore this paradigm, but the preliminary results are consistent with the notion that the confidence in the economic choice was used as a prior in the perceptual judgment. If confirmed, this task will provide a method to measure the trial-by-trial confidence in economic choices.

Disclosures: K.M. Rothenhoefer: None. **W.R. Stauffer:** None.

Poster

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Topic: H.03. Decision Making

Support: NIMH grant DP2MH113095

Title: Rhesus macaques demonstrate economic deliberation in the 'knapsack task'

Authors: *T. HONG[1,2,3], W. STAUFFER[3,4,5,6,7];
[1]Program in Neural Computation, [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [3]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [4]Syst. Neurosci. Ctr., [5]Dept. of Neurobio., [6]Ctr. for Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [7]The Brain Inst., Pittsburgh, PA

Abstract: Value optimization is a defining principle of economic choices. To uncover the psychological and neural processes underlying value optimization, we developed a behavioral task based on the 'knapsack problem'. Given several items, each with a value and weight, the objective of the knapsack problem is to maximize value within a specified weight limit. We adapted the knapsack task for non-human primates (NHPs), by equating weights with juice reward values. We presented the animal with multiple items - visual cues that each predicted a different sized reward. The animal could select any subset of the items by using a touchscreen. In each trial, the animal received the total reward value of the chosen subset, unless the chosen subset exceeded the virtual knapsack size limit, in which case no reward was provided. Task performance was higher when a virtual knapsack displayed on the screen to provided visual feedback on the value of chosen items. The animal performed well above chance and achieved at least 75% of the optimal reward value on approximately half of all trials. We defined each unique set of items as an 'instance,' and we estimated the difficulty of instances according to the number of feasible solutions. Crucially, the performance was sensitive to instance difficulty: the selected subsets were closer to optimal on easier instances, compared to more difficult ones. Response time showed the same trend: the animal took longer to choose the total subset on difficult instances, and took longer on individual selections when the probability of exceeding the limit was higher. Selection-by-selection analysis revealed that the animals employed a 'satisficing' threshold and, moreover, that threshold was lower when the instance was more difficult. Finally, as the instances became more difficult, the chosen solutions became more stable. This increased stability observed on difficult trials suggests an underlying algorithm for value optimization. Overall, these results lay the foundation for uncovering behavioral algorithms for optimal reward seeking and their neural implementation.

Disclosures: T. Hong: None. **W. Stauffer:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Topic: H.03. Decision Making

Support: Berkeley Fellowship for Graduate Study

Title: Assessing the influence of reward and attention on value-based decision-making

Authors: *N. T. MUNET[1], L. A. MECKLER[1], Z. BALEWSKI[1], J. D. WALLIS[1,2];
[1]Helen Wills Neurosci. Inst., [2]Dept. of Psychology, Univ. of California, Berkeley, Berkeley, CA

Abstract: During decision-making, attention is a powerful mechanism to select which option to evaluate and filter out irrelevant information about alternatives. However, just as attention can influence value computations, the reverse is also true: attention paradigms often use reward to manipulate attentional allocation, demonstrating that value can guide attention. This raises the question of how attention and value computations dynamically interact to guide decision-making processes. Prior work from our lab shows that value-encoding ensembles in orbitofrontal cortex (OFC) alternate between encoding the value of chosen or unchosen options during a value-guided choice task. This serial encoding of option values may reflect attentional filtering of OFC's inputs, or it may serve as a basis for value-guided attention as value information is transmitted from OFC to attention-related regions in lateral prefrontal cortex (LPFC). To distinguish these possibilities, we trained macaques on a task that combined attention and value-based decision-making paradigms in interleaved blocks, allowing us to potentially train attention and value decoders on prefrontal ensemble activity and examine how these processes interact. Here we present a behavioral analysis of the attention and value-based decision-making components of our task, which validate the task's suitability for dual-decoding experiments. In value-based decision-making blocks, we fit subjective value models to stable choice behavior and found that the amount and probability of reward are integrated with similar weights to yield abstract subjective values for each option. To investigate how these subjective values are learned, we fit reinforcement learning (RL) models to choices as animals learned to map novel stimuli onto a set of nine unique reward contingencies. Model comparison showed that animals learn novel stimulus-outcome associations quickly and efficiently, in a manner that can be approximated with a model-free RL algorithm. Moreover, we found that animals treat reward information similarly on free and forced choice trials, supporting previous evidence that subjective value generalizes between free and forced trials. On attention blocks spatial cuing yielded a robust attentional effect on change detection accuracy and reaction times. Together, our results confirm the distinct effects of reward and attention on overt choice behavior and validate our task's suitability for future decoding experiments that will analyze the relationship between neural signals of attention and value during decision-making.

Disclosures: N.T. Munet: None. **L.A. Meckler:** None. **Z. Balewski:** None. **J.D. Wallis:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Topic: H.03. Decision Making

Support: NIH Grant 5R01MH117763-03

Title: Interhemispheric orbitofrontal communication during value-based choice

Authors: *T. W. ELSTON, Z. Z. BALEWSKI, J. D. WALLIS;
Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: Contralaterality describes how sensory and motor functions pertaining to one half of the body are carried out by the opposite half of the brain. For example, the left hemisphere's motor cortex controls the musculature of the right side of the body. Here, we asked whether pre-choice, deliberative processing in the orbitofrontal cortex (OFC) of monkeys making value-based choices would also exhibit lateralization. Once monkeys learned to decide between options varying in both the amount and probability of yielding a juice reward, we lowered multiple, multi-channel probes bilaterally into OFC, allowing us to record from up to 240 neurons simultaneously. Our behavioral task was explicitly designed for a decoding approach. We included single-picture, forced choice trials to ensure that all value levels were regularly sampled and used these trials to train linear discriminant classifiers, one for each hemisphere, in each session. We tested our decoders on both a held-out set of forced-choice trials and free-choice (two picture) trials. We found that when the more valuable option was on the left, the right OFC carried information about the value that would be chosen earlier than the left OFC (and vice versa). This effect depended on the animal deliberating between two options: we found no evidence of lateralized value processing during forced choice trials. Interestingly, the time-courses of the decoder states in each hemisphere became correlated during pre-choice deliberation, suggesting that deliberative choice may involve coordination between the hemispheres. In support of this view, we found a spectral signature of lateralized value processing in the local field potential: increased alpha-band (8-14Hz) interhemispheric coherence was associated with lateralized value processing. We found that alpha coherence was elevated during free (as compared to forced) choice trials. This effect was also evident at single-trial resolution: individual trials with more lateralized responses in ensemble decoding were associated with greater alpha coherence. These results suggest a previously unappreciated role for interhemispheric coordination during value based choice and potentially reveal alpha coherence as a mechanism facilitating that coordination.

Disclosures: T.W. Elston: None. **Z.Z. Balewski:** None. **J.D. Wallis:** None.

Poster

P788. Neural Mechanisms of Perception, Cognition, and Decision-Making II

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Program #/Poster #: P788.13

Topic: H.03. Decision Making

Title: Fast decision representation in caudate nucleus during value-based choices

Authors: *Z. BALEWSKI[1], E. B. KNUDSEN[2], J. D. WALLIS[3];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Helen Wills Neurosci. Inst., [3]Univ. of California Berkeley, Berkeley, CA

Abstract: Decades of research in humans and animals have identified brain regions and circuits critical to value-based decision making. However, the dynamics of value computation are difficult to study because the decision process is opaque and varies from trial to trial. In this experiment, we decoded choice

behavior at the level of single trials in a two alternate forced choice task. We identified fast, stereotyped value signals in the head of the caudate nucleus (CdN), in contrast with the variable value representations found in orbitofrontal cortex (OFC). We hypothesize that these signals reflect parallel value processes that both contribute to the ultimate choice. We trained two monkeys on unique juice reward outcomes predicted by 16 pictures. The subjects freely viewed pairs of pictures and used a lever to choose between them. Both performed the task with high accuracy but relatively slow response times (RT; subject 1: 666 ms, subject 2: 454 ms). We performed large-scale acute single-unit recordings simultaneously in the head of the caudate nucleus (CdN) and the orbitofrontal cortex (OFC), averaging 27 (subject 1) and 103 (subject 2) units from each region per session. We observed strong prediction of choice direction from the CdN population using a linear decoder trained on firing rates in sliding time windows. Prediction strength peaked around 180 ms after trial onset. While the strength of the peak correlated with picture value and RT, the timing of the peak was independent of RT. This fast signal was also highly correlated with the timing and direction of the first saccade, which was overwhelmingly directed to the chosen picture. These observations are consistent with fast, automatic value processing. In contrast to the stereotyped dynamics of CdN, the value representation in OFC appeared to be idiosyncratic across trials. We successfully replicated our previous results (Rich & Wallis, Nat Neuro 2016), which showed that OFC representation flip-flopped between the pair of available picture values over the course of an entire trial and was predictive of response time. We found no evidence that the OFC representation was influenced by eye movements or CdN population dynamics. Representations in both regions predicted choice behavior but were not correlated with each other. Important open questions remain about how and when distributed value signals like these are integrated into motor actions.

Disclosures: Z. Balewski: None. **E.B. Knudsen:** None. **J.D. Wallis:** None.

Poster

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Program #/Poster #: P788.14

Topic: H.03. Decision Making

Support: NSF DGE 1752814

Title: Neural mechanisms of hidden state inference

Authors: *C. FORD[1], J. D. WALLIS[2];
[1]Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA; [2]Univ. of California Berkeley, Berkeley, CA

Abstract: Understanding the world requires making inferences about the hidden causes, or belief states, generating our observations. Converging evidence from rodent, human, and computational models suggests that the orbitofrontal cortex (OFC) represents these states by contextualizing relevant information. The hippocampus (HC) may also contribute to this process by representing a cognitive map of the current task environment, linking observations, actions, and outcomes. Given their strong anatomical and functional connections, OFC and HC likely work together to drive inferential learning and decision-making behavior. However, the neural mechanisms of these processes remain unknown. Here,

we trained a male monkey (Macaca mulatta, 6.5 years old, 10.8 kg) on a probabilistic reversal learning task where state inference is required for optimal choice behavior. Reversals were triggered by meeting a set of learning criteria. On average, he triggered 18 reversals per session (n = 6), and was able to quickly detect and adapt to state changes, informing decisions on trials where reward contingencies had not yet been directly experienced. Given this evidence that he acquired a working knowledge of task structure, we simultaneously recorded single-unit neuronal activity from OFC (n = 287) and HC (n = 418) during task performance to examine how task state representations are stored, updated, and used to drive decision-making. The majority of units we acquired across both OFC and HC were sensitive to task state, implicating both regions in state inference. To analyze neural state representations with single-trial resolution, we trained a linear discriminant analysis (LDA) algorithm to classify task state for each trial, given activation patterns in OFC or HC synced at different trial events. We observed that, while task state can be decoded in HC across an entire trial, it can only be reliably decoded in OFC after choice options are visible. This suggests that state representations stored in HC are passed to OFC during decision-making, where they are ultimately used to guide behavior.

Disclosures: C. Ford: None. **J.D. Wallis:** None.

Poster

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Topic: H.03. Decision Making

Support: NIMH R01-MH117763
NIMH R01-MH121448

Title: Replay events in primate hippocampal neurons encoding an abstract cognitive map

Authors: *E. B. KNUDSEN, J. D. WALLIS;
Univ. of California, Berkeley, Berkeley, CA

Abstract: The ability to learn the relationships that govern and mediate interactions with the world is a key component of flexible behavior. In rodents, representation of physical spaces takes the form of a place map, encoded by place neurons in the hippocampus. Consolidation of prior routes or mental rehearsal of prospective routes are supported by replay events, temporally-compressed sequential activations of the place neurons that tile the space. In primates, we recently found that abstract spaces are also instantiated in hippocampal neurons. These ‘value place’ neurons map the cognitive dimensions defined by a value-based learning task. Although human work has hinted at replay-like phenomena in non-invasive neural signals, whether value place neurons participate in replay events during cognition remains an open question. We investigated hippocampal neuronal activity collected from two monkeys making decisions within a value space defined by the reward probabilities of three visual stimuli for evidence of replay.
We first found that sharp wave ripples (SWRs), high (150-300 Hz) frequency oscillations in the local field potential that coordinate prospective and retrospective activity, tended to occur predominantly

during two task epochs: when subjects were fixating a central target prior to the onset of visual stimuli, and when subjects received the outcome of their choice. We investigated SWRs for the presence of replay-like activity by correlating pairs of value place neurons recorded simultaneously. During the fixation epoch, forward ordered correlations were roughly twice as prevalent as reverse ordered, consistent with subjects anticipating the expected value of the choice options. During the outcome epoch, forward and reverse ordered events were more evenly balanced. We also observed differences in the prevalence of forward and reverse replay across the course of the value trajectory, with forward replay more prevalent when the animal begins moving through the value space, and reverse ordered events more common during the later stages of the traversal. Together, these results provide the first direct evidence of the compressed sequential activation of hippocampal neurons encoding the relational structure of a cognitive parameter, and furthers the idea that a representational cognitive map, instantiated at the level of individual hippocampal neurons, enables sophisticated flexible behaviors.

Disclosures: E.B. Knudsen: None. **J.D. Wallis:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.01

Topic: H.06. Social Cognition

Support: NIH R01MH101130
NIH R01AG061200
UofSC ASPIRE
UofSC SOM RDF Award
UofSC SPARC
NSF GRFP

Title: The Role of PDE11A4 in Social Isolation-Induced Changes in Intracellular Signaling and Neuroinflammation

Authors: *K. PILARZYK[1], M. P. KELLY[2], L. D. PORCHER[1], R. FARMER[1];
[1]Univ. of South Carolina- Sch. of Med., Columbia, SC; [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Phosphodiesterase 11A (PDE11A), an enzyme that degrades cyclic nucleotides (cAMP and cGMP), is the only PDE whose mRNA expression in brain is restricted to the hippocampal formation. Previously, we showed that chronic social isolation changes subsequent social behaviors in adult mice by reducing expression of PDE11A4 in the membrane fraction of the ventral hippocampus (VHIPP). Here we seek extend these findings by determining 1) if isolation-induced decreases in PDE11 require chronic social isolation or if they occur acutely and are sustained long-term, 2) if isolation-induced decreases occur uniquely in adults (i.e., not adolescents), and 3) how the loss of PDE11A4 signaling may increase neuroinflammation. We find that both acute and chronic social isolation decreases PDE11A4 expression in adult but not adolescent mice. This decrease in PDE11A4 is specific to the membrane compartment of the VHIPP, as it does not occur in either the cytosolic or nuclear compartment of the VHIPP nor in any

compartment of the dorsal HIPP. The effect of social isolation on membrane PDE11A is also selective in that PDE2A and PDE10A expression remain unchanged. Isolation-induced decreases in PDE11A4 expression appear to be functional as social isolation elicited changes in PDE11A-relevant signal transduction cascades (i.e., decreased pCamKIIα and pS6-235/236) and behavior (i.e., increased remote long-term memory for social odor recognition). Interestingly, we found that isolation-induced decreases in membrane PDE11A4 correlated with increased expression of interleukin-6 (IL-6) in the cytosolic fraction, suggesting pro-inflammatory signaling for this cytokine. This effect on IL-6 is consistent with the fact that *Pde11a* deletion increased microglia activation, although it left astrocytes unchanged. Together, these data suggest that isolation-induced decreases in PDE11A4 may alter subsequent social behavior via increased neuroinflammatory processes in adult mice.

Disclosures: K. Pilarzyk: None. **M.P. Kelly:** None. **L.D. Porcher:** None. **R. Farmer:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.02

Topic: H.08. Learning and Memory

Title: Serotonin 1B/1A receptor activation impairs behavioral flexibility in C57BL/6J mice

Authors: B. OLIVER, A. PAHUA, M. BURDETTE, S. SANCHEZ, P. FLORES, *D. AMODEO; California State Univ. San Bernardino, San Bernardino, CA

Abstract: Obsessive compulsive disorder (OCD) is defined as insistent urges, persistent thoughts, and/or repetitive behaviors that are difficult to inhibit. Pharmacologically induced alterations to the serotonergic system have been shown to directly induce OCD-like behaviors (Shanahan et al., 2009; Ho et al., 2015). The serotonin 1B/1A receptor (5-HT1B/1A) agonist RU24969 has been shown to induce OCD-like behaviors in rodents (Ho et al., 2015; Shanahan et al., 2009; Woehrle et al., 2013), in addition to inducing working memory deficits (Woehrle et al., 2013). Several studies examining increased 5-HT1B/1A activation use relatively high doses of RU24969, usually between 1 to 10 mg/kg (Ho et al., 2015; Shanahan et al., 2009; Thompson & Dulawa, 2019; Woehrle et al., 2013). OCD symptoms include excessive habit formation that can inhibit goal-directed learning (Gillan & Robbins, 2014) and behavioral flexibility (Grutter & Pitteger, 2017). The current study examines the effects of systemic 5-HT1B/1A receptor agonist RU24969 (vehicle, 0.01, 0.1 or 1.0 mg/kg) treatment on behavioral flexibility using a spatial 80:20 probabilistic reinforcement reversal learning task. Before acquisition, all mice were treated with vehicle. Before the reversal phase, mice were injected with RU24969 and the reinforcement contingencies were reversed to examine how many trials were required for mice to reach learning criterion. Learning criterion was met when mice made six consecutive correct choices. As previously demonstrated, all groups performed similarly on acquisition of the initial spatial discrimination. On reversal, female mice treated with 1.0 mg/kg RU24969 required significantly more trials to reach criterion. Instead, all doses (0.1, 0.1 & 1.0 mg/kg) of RU24969 significantly increased trials needed to reach reversal learning criterion. This impairment was driven by a specific increase in perseverative type errors, suggesting RU24969 treatment impaired the ability to initially inhibit the previously learned

spatial discrimination. Further analysis shows that RU24969 did not increase trials per minute, demonstrating that RU24969 was not sedative. In sum these findings indicate that acute systemic 5-HT1B/1A receptor activation significantly impaired reversal learning performance.

Disclosures: B. Oliver: None. **A. Pahua:** None. **M. Burdette:** None. **S. Sanchez:** None. **P. Flores:** None. **D. Amodeo:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.03

Topic: H.08. Learning and Memory

Title: Effects of pharmacological substances on long term potentiation in rodent hippocampal slices: an ex vivo model of episodic-like memory.

Authors: *K. WALKER[1], E. ESNEAULT[1], T. FRERET[2], C. ROUX[1];
[1]Porsolt S.A.S., Le-Genest-Saint-Isle, France; [2]Univ. de Caen Normandie, Caen, France

Abstract: Memory capacity relies on adaptive and long-term modifications in synaptic strength, a process known as synaptic plasticity. NMDA-dependent long-term potentiation (LTP) is a form of synaptic plasticity, considered to be the main support for memory processes. Hippocampal formation plays a key role in the memory process and was historically the first brain region where LTP experiments were performed.
Our study aims to evaluate the effects of well-known pharmacological substances, to investigate the memory process on LTP recordings. Both pro- and a-mnesic agents were investigated. D-AP5, an NMDA-antagonist, and scopolamine, a muscarinic antagonist, were used as LTP blockers. The pro-cognitive agent Rolipram was used as an LTP enhancer.
Transverse hippocampal slices were obtained from male Wistar rats. Extracellular recordings were performed at the apical dendritic layer of the CA1 area. Field excitatory postsynaptic potentials (fEPSPs) were elicited by electrical stimulation of afferent Schaeffer collaterals located in the *stratum radiatum*. A Theta-burst stimulation protocol was used to mimic naturally occurring brain oscillations observed during spatial learning tasks. fEPSPs were recorded for 15 min for baseline levels and another 60 min after induction of LTP.
D-AP5 (50 and 100µM) prevented the induction of LTP, while the LTP magnitude remained unchanged with scopolamine treatment (10µM), when compared to control slices. Conversely, the LTP magnitude was significantly enhanced when Rolipram (0.1µM) was added to the perfusion bath.
These results highlight the potential to modulate LTP by pharmacological substances acting at different synaptic levels inducing and/or maintaining LTP. D-AP5 is commonly used to assess NMDA-dependent features of LTP. Rolipram, through inhibition of type 4 phosphodiesterase, leads to an increase of cAMP, a key regulator of the signaling cascade involved in the persistence of LTP. Here we show that pro-cognitive properties of a substance could be linked to LTP enhancement. While scopolamine is considered the gold standard to induce memory deficits in rodents, the weak cholinergic tone in hippocampal slices may explain the absence of an observed effect.

These results suggest that LTP recordings represent a reliable tool for predicting the effects of new molecules on memory-related electrophysiological features. This model is also useful for providing new insights into the mechanisms underlying the effects that are observed in pre-clinical cognitive tests.

Disclosures: K. Walker: None. **E. Esneault:** None. **T. Freret:** None. **C. Roux:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.04

Topic: H.08. Learning and Memory

Support: CNPq Grant 306777/2016-9
CNPq Grant 307022/2019-6

Title: Involvement of the medial prefrontal cortex in fear memory reconsolidation impairments induced by cannabidiol in rats

Authors: *H. BAYER[1], C. A. J. STERN[2], F. TROYNER[1], L. GAZARINI[3], F. S. GUIMARAES[4], L. J. BERTOGLIO[1];
[1]Pharmacol., Federal Univ. of Santa Catarina, Florianopolis, Brazil; [2]Pharmacol., Federal Univ. of Parana, Curitiba, Brazil; [3]Pharmacol., Univ. Federal do Mato Grosso do Sul, Tres Lagoas, Brazil; [4]Pharmacol., Sch. Med. Ribeirao Preto-Usp, Ribeirao Preto, Brazil

Abstract: Fear memories can be attenuated by targeting their reconsolidation, which is differentially regulated by medial prefrontal cortex (mPFC) subregions. The major non-psychotomimetic component of the Cannabis plant, cannabidiol (CBD), can disrupt fear memory reconsolidation through cannabinoid type-1 (CB1) receptor signaling in the brain. Here we aimed to investigate whether CBD-induced reconsolidation impairments involve the activation of CB1 receptors in the anterior cingulate (AC), prelimbic (PL), and infralimbic (IL) cortices. Adult male Wistar rats were fear conditioned in context A. A brief context A re-exposure was performed on the next day to induce memory labilization, then animals were infused with vehicle (VEH) or the CB1 receptor antagonist AM251 into the AC, PL, or IL cortex and systemically treated with VEH or CBD. Animals were re-exposed to conditioned Context one day later (Test A) to assess the potential pretreatment and treatment effects on memory reconsolidation. In experiment 1 (n = 9-12/group), CBD-treated animals presented less freezing time than controls during Test A (VEH/VEH: 77 ± 6%; VEH/CBD: 51 ± 4%). CBD effects were prevented by AC cortex CB1 receptor antagonism (AM251/VEH: 82 ± 5%; AM251/CBD: 80 ± 7%). In experiment 2 (n = 8-9/group), PL cortex CB1 receptor antagonism prevented the CBD effects on reconsolidation (VEH-VEH: 85 ± 4%; VEH/CBD: 43 ± 7%; AM251/VEH: 72 ± 6%; AM251/CBD: 74 ± 7%). In experiment 3 (n = 8-9/group), CB1 receptor blockade in the IL cortex also prevented CBD effects (VEH-VEH: 70 ± 6%; VEH/CBD: 42 ± 9%; AM251/VEH: 78 ± 5%; AM251/CBD: 66 ± 6%). In experiment 4 (n = 7-11/group), we sought to determine wheter CBD injections in different mPFC subregions can mimic the effects of systemic treatment. Animals treated with CBD intra-AC or intra-PL presented less freezing during test A than controls (AC-VEH: 70 ± 9%; AC-CBD: 48 ± 4%; PL-VEH: 82 ± 5%; PL-CBD: 45 ± 6%), whereas intra-

IL CBD treatment didn't produce effects compared to controls (IL-VEH: 70 ± 9%; IL-CBD: 62 ± 8%). Present results suggest that activation of CB1 receptors along the mPFC dorsoventral axis is necessary for the impairing effects of CBD on memory reconsolidation. Furthermore, CBD infusion into the AC or PL cortex is sufficient for mimicking the systemic effects of CBD on reconsolidation.

Disclosures: H. Bayer: None. **C.A.J. Stern:** None. **F. Troyner:** None. **L. Gazarini:** None. **F.S. Guimaraes:** None. **L.J. Bertoglio:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.05

Topic: H.08. Learning and Memory

Title: Acquisition of extinction requires microglia activity in adult rats

Authors: *R. BUENAOBRA, N. FERRARA, A. ROSENKRANZ;
Rosalind Franklin Univ. of Med. and Sci., Grayslake, IL

Abstract: Title: Acquisition of extinction requires microglia activity in adult rats**Authors:** Reggie, Nicole C. Ferrara, & J. Amiel Rosenkranz**Dept/Inst:** Cellular and Molecular Pharmacology/RFUMS Anxiety and stress-related disorders induced by trauma are characterized by maladaptive fear responding as a result of dysregulated associations between predictive aversive stimuli and the aversive event. This often results in a loss of context-appropriate emotional responding, which can be treated with exposure therapy. The mechanisms underlying exposure therapy are similar to extinction learning, where fear responses can be reduced through repeated presentations of the associated conditional stimulus (CS) in the absence of the aversive stimulus. A new memory, extinction memory, results from extinction learning and is then in competition with the fear memory for behavior. While this approach to reducing fear has many benefits, fear responding can return in circumstances outside of the context in which extinction was learned, known as renewal. Therefore, there is great therapeutic potential for understanding the processes through which renewal occurs to minimize the return of fear following extinction. There are several brain regions that interact and are essential for encoding fear and extinction processes, such as the prefrontal cortex, amygdala, and ventral hippocampus. During extinction, prefrontal cortical activity driven by the ventral hippocampus can reduce amygdala activity, ultimately resulting in a lower fear response. There are many factors that can regulate neuronal activity in this circuit to permit extinction and one relatively understudied are microglial cells, the resident immune cells of the CNS. Microglia participate in neural inflammation and regulate synaptic activity in various immune states that change with stress exposure. Here, we investigated the way in which microglia contribute to the behavioral and neural process of extinction. Our data demonstrate that suppression of microglia with minocycline prior to extinction diminish fear response to the CS and results in heightened fear during a renewal test. Ongoing work is investigating the relationship between microglia activity during extinction and activity in extinction circuitry. These results suggest that there is a relationship between fear extinction and renewal and microglia, where activation of microglia can in turn regulate fear inhibition.

Support: NIMH R01 MH118237Theme: Cognition and behaviorSubtheme: Animal cognition and behaviorTopic: XXXKeywords (5): amygdala, hippocampus, extinction, renewal

Disclosures: R. Buenaobra: None. **N. Ferrara:** None. **A. Rosenkranz:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.06

Topic: H.08. Learning and Memory

Support: NIMHANS - NIMH/Proj/BNS/00555
SERB, DST, India - ECR/2015/000545; CRG/2020/005229

Title: Development and characterization of a rat model of post-finasteride syndrome

Authors: *A. AHIRE, R. SASIBHUSHANA, K. MRUDULA, B. SHANKARANARAYANA RAO; Natl. Inst. of Mental Hlth. and Neuro Scie, Bengaluru, India

Abstract: Development and Characterization of a Rat Model of Post-Finasteride Syndrome R. Sasibhushana, Ashutosh Ahire, K. Mrudula, B. S. Shankaranarayana Rao, **B.N. Srikumar**Department of NeurophysiologyNational Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, IndiaEmail: kumarasri@nimhans.ac.in
The enzyme 5α-Reductase (5α-R) catalyzes the formation of dihydroxytestosterone, which is involved in male pattern hair loss and benign prostatic hyperplasia. Finasteride inhibits 5α-R and is used to treat both these conditions. Several clinical studies show that chronic finasteride treatment induces persistent depression, suicidal thoughts and cognitive impairment. The neurobiological mechanisms underlying the effects of finasteride are not clearly understood. In an effort to address this, we are developing an animal model of finasteride-induced depression and cognitive dysfunction. We subjected male/female rats to repeated finasteride administration over a period of 7 or 10 days. We evaluated depression, anxiety and cognitive function in several paradigms. Repeated finasteride administration resulted in increased immobility in the forced swim test, decreased grooming in the splash test, decreased open arm exploration in the elevated plus maze and impaired social interaction. Further, the antidepressant effect of fluoxetine was diminished following finasteride administration. Memory was impaired in the radial arm maze task and cognitive flexibility in the attentional set-shifting task was also decreased following finasteride administration. When the allopregnanolone levels were examined in the frontal cortex and hippocampus, we observed a decrease following finasteride administration. Finasteride administration (100mg/Kg, s.c.) also significantly decreased AChE activity in the frontal cortex and hippocampus. In summary, our results indicate that repeated finasteride administration induces treatment-resistant depression-like behavior, co-morbid with anxiety and cognitive dysfunction, potentially through cholinergic and neurosteroid mechanisms. These results provide insights into the involvement of neurosteroids in depression and cognitive function and has potential for development of novel therapeutics to treat neuropsychiatric diseases.**Keywords:** finasteride, treatment-resistant depression, anxiety, finasteride, neurosteroid, cognition

Acknowledgements: Finasteride gift sample was kindly provided by Dr. Reddy's laboratories and this work is supported by research grants from NIMHANS and SERB, DST, Govt. of India. RS and KM were supported by fellowships by CSIR and NIMHANS, respectively.

Disclosures: A. Ahire: None. **R. Sasibhushana:** None. **K. Mrudula:** None. **B. Shankaranarayana Rao:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.07

Topic: H.08. Learning and Memory

Support: CAPES 001
FAPESP

Title: The effects of Ouabain treatment on adult hippocampal neurogenesis

Authors: *A. M. M. ORELLANA[1], N. M. S. PORT´S[1], J. A. LEITE[2], J. A. M. NETO[1], C. SCAVONE[1], E. M. KAWAMOTO[1];
[1]Pharmacol., Univ. of São Paulo, São Paulo, Brazil; [2]Dept. of Pharmacol. - Inst. of Biomed. Sci., Federal Univ. of Goiás, Goiânia, Brazil

Abstract: Neurogenesis is a very complex process that provides the integration of new functional neurons into developed brain circuitry. This process occurs mostly in two brain regions that have a permissive neurogenic microenvironment. In this neurogenic niche, stem cells coexist with differentiated astrocytes that secrets support factors for the maintenance and development of new neurons, adult neurons and other cell types. Furthermore, the proximity to endothelial cells facilitates the contact of stem cell clusters with signal transduction modulators such as mitogens (EGF, bFGF, IGF), morphogens (Wnt, Shh, Notch, Eph), and neurotrophins (BDNF), among others. Although the entire process of neurogenesis is not yet fully understood, at least in the hippocampus it seems to be important for the formation and maintenance of functional hippocampal circuitry and thus for memory and learning. It has been proposed that Ouabain (OUA), a cardiotonic steroid, in non-inhibitory concentration, can bind to Na,K-ATPase and trigger many signaling pathways. A previous study reported that, in rat hippocampus, OUA could activate signaling pathways such as CREB, Wnt/β-catenin and NFκB in neurons, increasing BDNF levels, hippocampal neuronal dendritic branching and leading to a spatial long-term memory improvement in rats. Therefore, the main purpose of this study is to verify whether OUA affects hippocampal adult neurogenesis. Methods: Newborn Wistar rats from both genders were purchased from the Animal Facility at Institute of Biomedical Sciences, USP. Their hippocampus were used for the primary culture of neural precursor cells (NPCs). The protocol was approved by the Ethics Committee from University of São Paulo (CEUA 74/2017). Immediately after being plate, cells were exposed for 7 days to medium (DMEM/F12, supplemented with B27, bFGF 10 ng/mL e EGF 10 ng/mL, penicillin and streptomycin 10%) containing OUA 10 nM or aCSF (Control). Neurospheres developed during this period. After neurospheres dissociation, NPCS were plated and maintained for more 7 days with aCSF or OUA 10 nM in the medium

(DMEM/F12, supplemented with B27, penicillin/streptomycin 10% and NGF 20 ng/mL) to start differentiation. Immunofluorescence, flow cytometry, viability assays and Western Blot were performed, all with samples from 6 independent cell cultures. Results: Preliminary results suggest that: (i) OUA 10 nM is not toxic for NPCs; (ii) OUA didn´t alter the NPCs´proliferation rate and (iii) OUA increases immature neurons percentage in the culture after 14 days, compared to control.

Disclosures: A.M.M. Orellana: None. **N.M.S. Port´s:** None. **J.A. Leite:** None. **J.A.M. Neto:** None. **C. Scavone:** None. **E.M. Kawamoto:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P853.08

Topic: H.08. Learning and Memory

Support: Wellcome Trust grant HMR01180

Title: Tropomyosin-related kinase B receptor agonism rescues the long-term spatial memory impairment seen in mice lacking new oligodendrocytes

Authors: *F. HEATH, H. JOHANSEN-BERG;
Wellcome Ctr. for Integrative Neuorimaging, Univ. of Oxford, Oxford, United Kingdom

Abstract: Myelin in the central nervous system (CNS) is produced by oligodendrocytes (OLs) and the adult rodent brain retains the ability to produce new myelinating OLs through the differentiation of oligodendrocyte precursor cells (OPCs). The ability to produce new myelinating OLs is important for learning and memory, with recent evidence suggesting that disrupting oligodendrogenesis leads to behavioural impairments in long-term spatial memory. Further, there is growing evidence that brain derived neurotrophic factor (BDNF) may have a pro-myelinating effect in the CNS. However, whether the influence of BDNF on processes of myelination has any impact for learning and memory is unclear. Here we investigated the effect of BDNF tropomyosin-related kinase (Trk) B receptor agonist 7,8-dihydroxyflavone hydrate (DHF) administration on spatial learning and memory via newly formed OLs. Mice with a conditional knock-out of OPC myelin regulatory factor ($MyRF^{-/-}$) were tested in the Morris water-maze (MWM). $MyRF^{-/-}$ mice and their hemizygous siblings ($MyRF^{-/+}$) underwent seven days of MWM training. Immediately following each training session they were systemically administered DHF or vehicle. The long-term memory of the mice was assessed 28-days later. Following behavioral testing histology was undertaken to stain for anti-adenomatous polyposis coli clone CC1 and 5-ethynyl-2' -deoxyuridine (EdU). GFAP-TK mice that have inhibited adult neurogenesis were also tested in the MWM under the same conditions as the MyRF mice. We found, using analysis of variance, that long-term spatial memory was impaired in $MyRF^{-/-}$ mice compared with $MyRF^{-/+}$ and that systemic administration of DHF immediately following training rescued this memory impairment. We also found that DHF administration during training partially rescued the number of $EdU^{+}/CC1^{+}$ cells in the corpus callosum. The memory of the GFAP-TK mice was unaffected, suggesting this finding is not associated with adult neurogenesis. In

conclusion, these findings show that newly formed oligodendrocytes are required for long-term spatial memory consolidation and that this effect is facilitated by BDNF signaling via TrkB receptors.

Disclosures: F. Heath: None. **H. Johansen-Berg:** None.

Poster

P853. Cognitive Disorders: Pharmacology I

Location: Virtual Only

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Program #/Poster #: P853.09

Topic: H.08. Learning and Memory

Support: NIH T32GM108563 (L.R.S.)
NIH 1U01DA041632 (T.J.G)
Jean Phillips Shibley Endowment (T.J.G.)
Penn State University (T.J.G.).

Title: Inbred mouse strains differ in adolescent ethanol-induced learning deficits

Authors: *L. R. SEEMILLER, L. R. GOLDBERG, T. J. GOULD;
Penn State Univ., University Park, PA

Abstract: Ethanol impairs learning and memory, and these effects can be greater among adolescents. This study investigated how other factors, specifically genetic background and sex, may influence learning outcomes after ethanol exposure in adolescent mice. Adolescent (PND 38 +/- 3) male and female inbred mice from different strains were treated with saline or ethanol (1.5 g/kg) 15 minutes prior to fear conditioning training. Contextual and cued fear retention were tested one day later. Blood ethanol content (BEC) was also assessed 15 minutes after 1.5 g/kg ethanol treatment to investigate the role of ethanol metabolism in strain differences. We found significant effects of drug and strain on contextual learning. Analysis of BEC data suggested that these effects were not likely related to strain differences in ethanol metabolism. Overall, we demonstrated that genetic background contributes to differences in contextual learning after ethanol administration to adolescent mice.

Disclosures: L.R. Seemiller: None. **L.R. Goldberg:** None. **T.J. Gould:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.01

Topic: H.08. Learning and Memory

Support: NSF Grant IOS1754869

NIH Grant R01 NS118606
U.S.-Israel Binational Science Foundation (BSF) Grant 2017624

Title: Neural correlates of success and failure to swallow foods that may act as reinforcers of Aplysia feeding

Authors: *J. P. GILL[1], H. J. CHIEL[2], A. J. SUSSWEIN[3];
[1]Biol., [2]Biology, Neurosciences, Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [3]Bar-Ilan Univ., Ramat-Gan, Israel

Abstract: *Aplysia* that try and fail to swallow food learn that the food is inedible, and subsequently respond less to that food. By contrast, *Aplysia* that successfully consume food learn that the food is edible, and later respond more to the food. Lip stimulation inducing bites but no attempts to swallow has no long-term consequences.
To provide insight into how animals differentiate success and failure to swallow, and bites initiated by lip stimulation, extracellular nerve recordings coupled with video recordings of feeding behaviors were obtained in freely behaving animals while the lips of *Aplysia* were stimulated with food, and were fed edible and inedible foods. One possibility is that edible foods elicit attempts to swallow, whereas inedible foods elicit a mixture of swallows and rejection responses that push food out of the mouth. Swallowing and rejection are readily distinguished by different patterns of neural activity. However, inedible food overwhelmingly induced attempts to swallow, rather than rejection responses, with very occasional rejection responses observed.
Previous data have shown that the esophageal nerve (EN) has a role in learning that food is edible or inedible. In particular, bilaterally severing the EN blocks the ability to learn that food is inedible, and stimulation of one branch of the EN paired with lip stimulation acts as a positive reinforcer of feeding. Activity of the EN during successful and failed attempts to swallow was compared to activity in response to lip stimulation eliciting bites. Recordings from the trunk of the EN showed significant increases of large spike activity when animals successfully swallowed food, and significant decreases in activity when animals failed to swallow food, suggesting that increased activity is a correlate of successful swallowing, and decreased activity is a correlate of failure to swallow. During all types of feeding responses, EN activity decreased during retraction, with respect to activity during protraction, or during the interval between the end of retraction and the start of the next protraction, suggesting that EN activity during success or failure occurs in the seconds after swallowing, as a consequence of food entering or not entering the gut.

Disclosures: J.P. Gill: None. **H.J. Chiel:** None. **A.J. Susswein:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.02

Topic: H.08. Learning and Memory

Title: Functional dissection of recurrent feedback signaling within the mushroom body network of the Drosophila larva

Authors: *R. LYUTOVA-HRISTOVA;
Univ. of Regensburg, Regensburg, Germany

Abstract: Behavioral adaptation to environmental changes is crucial for animals' survival. The prediction of the outcome of one owns action, like finding reward or avoiding punishment, requires recollection of past experiences and comparison with current situation, and adjustment of behavioral responses. The process of memory acquisition is called learning, and the *Drosophila* larva came up to be an excellent model organism for studying the neural mechanisms of memory formation. In *Drosophila*, associative memories are formed, stored and expressed in the mushroom bodies. In the last years, great progress has been made in uncovering the anatomical architecture of these brain structures, however there is still a lack of knowledge about the functional connectivity.
Dopamine plays essential roles in learning processes, as dopaminergic neurons mediate information about the presence of rewarding and punishing stimuli to the mushroom bodies. In the following work, the function of a newly identified anatomical connection from the mushroom bodies to rewarding dopaminergic neurons was dissected. A recurrent feedback signaling within the neuronal network was analyzed by simultaneous genetic manipulation of the mushroom body Kenyon cells and dopaminergic neurons from the primary protocerebral anterior (pPAM) cluster, and learning assays were performed in order to unravel the impact of the Kenyon cells-to-pPAM neurons feedback loop on larval memory formation.
In a substitution learning assay, simultaneous odor exposure paired with optogenetic activation of Kenyon cells in fruit fly larvae in absence of a rewarding stimulus resulted in formation of an appetitive memory, whereas no learning behavior was observed when pPAM neurons were ablated in addition to the KC activation. I argue that the activation of Kenyon cells may induce an internal signal that mimics reward exposure by feedback activation of the rewarding dopaminergic neurons. My data further suggests that the Kenyon cells-to-pPAM communication relies on peptidergic signaling via short neuropeptide F and underlies memory stabilization.

Disclosures: R. Lyutova-Hristova: None.

Poster

P856. Invertebrates: Learning and Memory I

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Topic: H.08. Learning and Memory

Support: Texas Comprehensive Research Fund

Title: Aversive massed training in Aplysia uncouples normally co-expressed behavioral changes by inducing long-term feeding suppression in the absence of long-term sensitization

Authors: R. T. MUELLER, M. L. WAINWRIGHT, *R. MOZZACHIODI;
Life Sci., Texas A&M Univ. Corpus Christi, Corpus Christi, TX

Abstract: Following exposure to aversive stimuli, an organism budgets its behaviors by enhancing defensive responses and reducing appetitive behaviors. In response to aversive training, *Aplysia* co-expresses sensitization of defensive withdrawal reflexes and feeding suppression across different training protocols and with common temporal domains (Acheampong et al. 2012; Shields-Johnson et al. 2013). However, a recent regimen of prolonged food deprivation was shown to uncouple the above training-induced behavioral changes, with sensitization prevented and feeding suppression still expressed but attenuated (Mac Leod et al. 2018). These findings raised the question of whether other protocols could induce feeding suppression in the absence of sensitization. Therefore, in this study, we examined whether massed training, which does not induce long-term sensitization (LTS; Wainwright et al. 2002), could still induce long-term feeding suppression (LTFS) at 24 h, compared to a multiple-day spaced training, which leads to the co-expression of LTS and LTFS (Mac Leod et al. 2018). Both protocols consist of 16 trials, each made of 10-s trains of electrical shocks to the animal's body wall. However, the delivery pattern is remarkably different: in spaced training, 4 trials are delivered per day (30-min inter-trial intervals) for 4 consecutive days, whereas in massed training, 16 trials are administered every 30 min in one day. Four groups of 10 animals each were utilized: massed-trained (M-T), massed-untrained (M-UT), spaced-trained (S-T), and spaced-untrained (S-UT). The untrained animals were handled as the trained animals but did not receive any shock. To remain blind to the condition of the animals, the experimenter was kept unaware of their training history. For each group, the duration of the defensive tail-siphon withdrawal reflex and the number of bites in response to a food stimulus were measured prior to (pre-test) and 24 h after the conclusion of aversive training (post-test). Statistical significance was determined using the Kruskal-Wallis test followed by the Student-Newman-Keuls post-hoc comparisons (Mac Leod et al. 2018). Results revealed that both S-T and M-T animals expressed LTFS at 24 h. Notably, LTFS in the M-T group was statistically indistinguishable from LTFS measured in the S-T group, thus, indicating that LTFS was fully expressed in the M-T animals, even in the absence of LTS. These findings indicate that massed training is another protocol that leads to the expression of feeding suppression in the absence of sensitization, suggesting that these behavioral changes may act independently from one another and may be modulated by different mechanisms.

Disclosures: R.T. Mueller: None. **M.L. Wainwright:** None. **R. Mozzachiodi:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.04

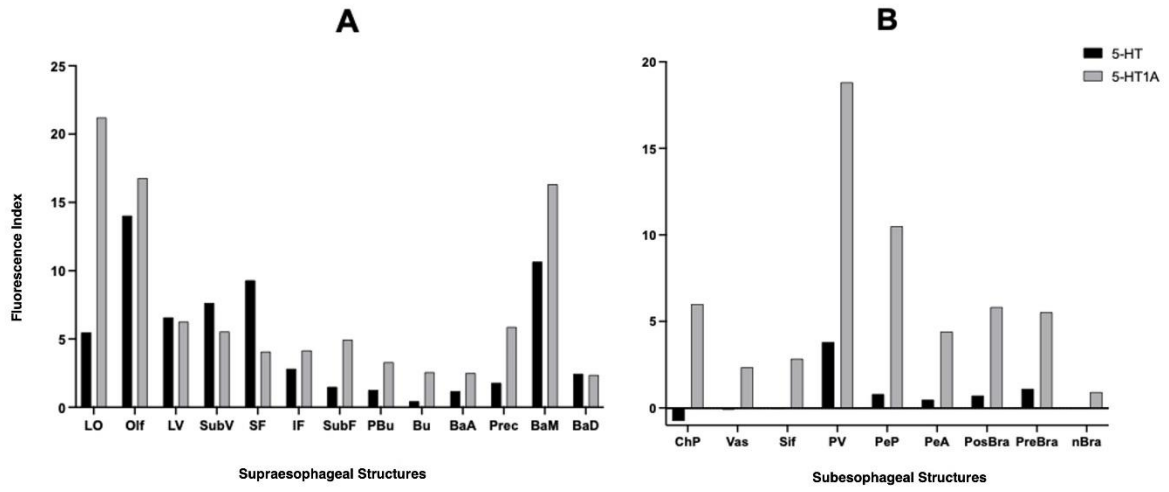
Topic: H.08. Learning and Memory

Support: PAPIIT IN 306 918
PAPIME PE 306 318

Title: Characterization Of Serotoninergic Pathways In The Brain Of Octopus maya

Authors: *P. GARCÍA-ANDALUZ, H. SÁNCHEZ-CASTILLO, D. GONZÁLEZ-NAVARRETE, F. VERGARA OVALLE;
UNAM, Mexico City, Mexico

Abstract: Serotonin (5-HT) is a highly conserved neurotransmitter among species and its study has been considered crucial for understanding the physiological mechanisms underlying behavior and cognition. Importantly, research on physiologically distant species from mammals like invertebrates has strongly contributed to the overall perspective of 5-HT's role in an organism but also has presented an opportunity to study the evolutionary development of complex nervous systems and the emergence of cognition. Even though the presence of 5-HT has been previously identified in the brain of octopuses, its mechanism and role on cognition hasn't been described yet. Therefore, in this study, we evaluated the presence and distribution of 5-HT and its receptor 5-HT1A in the brain of Octopus maya. Through an immunolabeling technique, we were able to observe 5-HT and 5HT1A-like immunofluorescence (Inf) in the optic, olfactory, vertical, sub-vertical, superior frontal, inferior frontal, sub-frontal, posterior buccal, buccal, anterior basal, precommissural, medial basal, dorsal basal, palliovisceral, posterior pedal, anterior pedal, post-brachial and, pre-brachial lobes; as well as 5HT1A-like Inf in the posterior chromatophore, vasomotor, and siphon lobes and brachial nerve. These results show a possible conserved participation of 5-HT on information integration, learning, memory, axonal regeneration, inhibitory modulation of neurotransmitters, and homeostatic regulation of vertebrates and some invertebrate animals. Hence, this is the first direct evidence of the presence of a serotonergic receptor and a possible underlying mechanism for synaptic plasticity in the octopod nervous system.



Porcentual normalization of the Fluorescence Index. Abbreviations: Optic, Olfactory, Vertical, Subvertical, Superior Frontal, Inferior Frontal, Subfrontal, Buccal, Posterior Buccal, Anterior Basal, Precommissural, Dorsal Basal, Medial Basal, Posterior Chromatophore, Vasomotor, Siphon, Palliovisceral, Posterior Pedal, Anterior Pedal, Post-brachial, Pre-brachial, Brachial Nerve.

Disclosures: P. García-Andaluz: None. **H. Sánchez-Castillo:** None. **D. González-Navarrete:** None. **F. Vergara Ovalle:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.05

Topic: H.08. Learning and Memory

Support: NINDS Grant R01 NS092716
NIDA Grant R25 DA033674
NSF Grant DGE-1633213

Title: Effects of Injury on Nociceptive Operant Conditioning

Authors: J. DOHN[1], J. HOYNOSKI[1], ***B. BURRELL**[2];
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Abstract: The capacity to learn to avoid damaging or potentially damaging stimuli represents an important component of nociception. The goal of this project is to observe how prior injury affects nociceptive operant conditioning. In *Hirudo verbana* (medicinal leech) 40 needle pokes (25 gauge needle) were delivered to the posterior sucker at one minute intervals. Initially, the animal's response to these stimuli were reflexive withdrawals, but repeated stimulation the magnitude of these reflexes diminished and were replace by preemptive evasion behaviors. These evasion behaviors consisted of hiding the posterior sucker under the rest of the body or locomotion to avoid the needle poke. Prior injury to the posterior sucker on the same day as training (Day 1) enhanced nociceptive operant conditioning in *Hirudo* in two ways. First, there was an increase in level of locomotion-based evasion compared to non-injured animals. A second difference was that injured animals required fewer stimuli (pokes) to transition to evasion behaviors, indicating rapid/more efficient conditioning. In non-injured *Hirudo*, 34% required >20 pokes to begin evasion behaviors with the remaining animals requiring <20 pokes. In injured *Hirudo*, 100% required <20 pokes to reach evasion criterion (in fact the all animals tested required <15 pokes). In animals that underwent operant conditioning 7 days after injury no change in the level of evasion behaviors was observed compared to non-injured animals. However, these injured animals again required fewer stimuli to begin evasion behaviors, with 83% requiring <20 pokes to reach criterion. These findings suggest that prior injury can facilitate learning to avoid further nociceptive stimuli. The enhancement on Day 1 likely represents a sensitization effect, while the enhancement observed on Day 7 may represent a form of priming. The mechanisms that contribute to this sensitization vs. priming effect may have implications in the study of chronic pain.

Disclosures: J. Dohn: None. **J. Hoynoski:** None. **B. Burrell:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.06

Topic: H.08. Learning and Memory

Support: HFSP RGP0042/2019-102
Israel Science Foundation 1928/15
U19 NS104653
U24 NS109102-01
NIH 1U01NS108637

Title: Insight into the connectome of the learning and memory network of the Octopus

Authors: F. BIDEL[1], Y. MEIROVITCH[2], R. SCHALEK[2], L. XIAOTANG[2], A. YANG[2], D. BERGER[2], A. PELEG[2], A. SHAKED[1], T. FLASH[3], J. LICHTMAN[2], *B. HOCHNER[1];
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Abstract: The vertical lobe (VL) in the *Octopus vulgaris* brain is a major structure involved in learning and memory. The VL demonstrates a robust activity-dependent NO-mediated LTP (Turchetti-Maia et al 2018), which is important in memory acquisition (Shomrat et al 2008). Our anatomical knowledge of the VL considerations is limited to the work of Young and Gray in the 1940-70's. To better understand the computational functions of the VL, the current study used volume electron microscopy (EM) to produce the first detailed synaptic-level wiring diagram of VL. The VL was fixed, serially sliced at 30 nm, imaged with a Scanning Electron Microscope at 4 nm per pixel and aligned into a traceable 3D image stack (260x390x30µm). Based on morphology, connectivity, and EM profiles, we have identified new components of the VL circuitry and provide detailed descriptions of 7 key cellular components (only 3 were previously characterized). The synaptic outputs of axons from the Superior Frontal Lobe (SFL), forming the main input to the VL, were reconstructed. This showed that the VL is segregated into two distinct interconnected feedforward networks that utilize two distinct populations of interneurons: a very large (~$22X10^6$) population of non-bifurcating simple amacrines (SAM) that are highly selective as they receive only one SFL input via an extremely large SFL synapses, and a newly identified, much smaller population (~$500X10^3$) of bifurcating complex amacrines (CAM), which integrate synaptic inputs from multiple SFLs and neighboring SAMs. Both the SAMs (likely excitatory, cholinergic) and CAMs (conceivably inhibitory) converge on the dendritic processes of the VL large efferent neurons (LNs). We also describe an overlay of two extrinsic highly organized modulatory systems which are likely involved in reward/punishment signaling (Shomrat et al 2010). While the organization of the SAMs in a feedforward fan-out fan-in organization is similar to other feedforwarded classification/association networks, the parallel CAM integrates global activity (SFLs+SAMs) and may provide an inhibitory input for balancing the excitatory SAMs inputs. Another surprising result is the unprecedented way in which "sensory features" are represented at the $22x10^6$ one-to-one SFL-to-SAM monosynaptic connections. As this synaptic structure undergoes LTP we suggest that SFL-to-SAM connection has an exclusive role as a "temporary memory-module". Overall, our results demonstrate morphological and network wiring novelties that have evolved independently in octopuses to subserve their highly advanced learning and memory.

Disclosures: F. Bidel: None. **Y. Meirovitch:** None. **R. Schalek:** None. **L. Xiaotang:** None. **A. Yang:** None. **D. Berger:** None. **A. Peleg:** None. **A. Shaked:** None. **T. Flash:** None. **J. Lichtman:** None. **B. Hochner:** None.

Poster

P856. Invertebrates: Learning and Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P856.07

Topic: H.08. Learning and Memory

Support: FONCyT PICT 2016-1875
UBA-UBACYT 2018 20020170100119BA

Title: Network Ca^{2+}-activity correlation of memory reactivation in a mushroom body-like brain center of the crab Neohelice granulata

Authors: *F. J. MAZA[1], F. J. URBANO[1,2], A. DELORENZI[1,2];
[1]IFIByNE-CONICET-Universidad de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina;
[2]Dept. de Fisiología, Biología Mol. y Celular, FCEN-UBA, Ciudad Autónoma de Buenos Aires, Argentina

Abstract: High order brain centers play key roles in sensory integration and learning. In arthropods, although much is known about insect high-order associative centers, the mushroom bodies, much less is known about the putative equivalent structures in crustaceans, the hemiellipsoid bodies. Getting both structural and physiological evidence to support the hypothesis that crustaceans possess structures equivalent to the mushroom bodies that play a role in associative memories has proved challenging. In the true crab Neohelice granulata, this high order brain center exhibits, for instance, dopaminergic innervation and elevated expression of proteins necessary for memory processes (Maza et al. 2020, doi 10.1002/cne.24960). Moreover, plasticity in hemiellipsoid bodies` neuronal activity reflects, in the short term, the context dependent attribute of memory (Maza et al. 2016, doi 10.1073/pnas.1612418113). The Neohelice memory paradigm consists in a long-term, context-specific, decrease in the escape response toward an iterative visual danger stimulus presentation. We used in vivo calcium imaging to test whether crab hemiellipsoid bodies' neuronal activity is associated with memory reactivation in the long-term (24 h after training). Long-term training effects were tested by presenting the reminder known to trigger the reconsolidation process (a shift in setup illumination in the training context) and, next, the visual danger stimulus. We found hemiellipsoid bodies' spontaneous activity, which does not differ between trained and naïve animals (n=5-6). However, after the training-context presentation, the trained animals disclosed an increase in the event rate, suggesting memory reactivation changes the activity state of the hemiellipsoid body. Similar to the behavioral changes, when animals were tested with the visual danger stimulus, trained animals showed a significantly lower evoked calcium transient. Results suggest that hemiellipsoid bodies play a role in contextual associative long term memory processes.

Disclosures: F.J. Maza: None. **F.J. Urbano:** None. **A. Delorenzi:** None.

Poster

P877. Relational and Spatial Learning

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.01

Topic: H.10. Human Learning and Cognition

Support: IBS-R015-D1
NRF-2019M3E5D2A01060299
NRF-2019R1A2C1085566
NRF-2021R1A6A3A13044260

Title: A neuromarker of narrative comprehension abilities in constructing causal structures

Authors: *J. PARK[1,2], H. SONG[4], W. SHIM[1,2,3];
[1]Ctr. for Neurosci. Imaging Research, IBS, Suwon-si, Korea, Republic of; [2]Dept. of Biomed. Engin., [3]Dept. of Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon-si, Korea, Republic of; [4]Dept. of Psychology, Univ. of Chicago, Chicago, IL

Abstract: Narrative comprehension requires a process of extracting information from individual events and inferring their coherent causal structures. In this study, we examined the neural signatures that predict individual differences in each comprehension process and characterized the features of narratives that are critical for comprehension using a natural language processing (NLP) approach. After watching a movie consisting of temporally scrambled events in an fMRI scanner, subjects recounted the original story. In a separate behavioral experiment, a group-aggregate measure of the subjective degree of comprehension at each moment of the movie was obtained from an independent group of subjects. We computed individuals' comprehension scores for the amount of recalled information (content score) and the accuracy of reordering the temporal sequence of recalled events (ordering score) by comparing the similarity in the semantic content between the original movie annotations and each subject's recall using a topic modeling method (Heusser et al., 2021). We then developed a model to predict each individual's content and ordering scores based on whole-brain functional connectivity patterns (Shen et al., 2017). Separate predictive models were built based on two periods in the movie—the moments at which the group measure of the degree of comprehension was either high or low. We found that the functional connectivity patterns during movie watching could predict the content score, regardless of which moments of the movie were used for the model. In contrast, the ordering score could only be predicted when the functional connectivity patterns at high comprehension moments were used. To further examine the characteristics of narratives that are critical for comprehension, we estimated the coherence of each annotated sentence in a narrative using the pre-trained deep language model BERT (Devilin et al., 2018). We found that the degree of comprehension at each moment of the movie could be predicted by the narrative coherence between the current and past sentences, as estimated from the next sentence prediction task. Together, these results suggest that individuals' abilities to encode the semantic information of events and construct a coherent causal structure across them can be predicted differentially via large-scale functional connectivity. Our findings also suggest that the predictability of future events estimated from an NLP model can computationally characterize the causal relationships in narratives that are associated critically with human narrative comprehension.

Disclosures: J. Park: None. **H. Song:** None. **W. Shim:** None.

Poster

P877. Relational and Spatial Learning

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.02

Topic: H.10. Human Learning and Cognition

Support: NSF BCS 16302296

Title: The contributions of vision and body-movements to memory for locations in real-world environments

Authors: *A. MULLER[1], J. GARREN[2], M. PETERSON[1], A. EKSTROM[1];
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Abstract: Vision has long been associated with encoding and retrieving items from memory although its contributions to active navigation are unclear. Similarly, body movements are critical to learning spatial layouts though it is unclear how much they contribute to memory. This issue has been difficult to address due to constrains in virtual reality navigation experiments, a lack of free ambulation experiments in humans, and the difficulty of performing eye tracking in freely moving participants. The current research aimed to address these concerns by pairing mobile eye tracking with a navigation and memory task in a real-world environment. 17 participants stood stationary to encode the layout of 8 objects attached to the walls (4 objects on 2 walls) for 30 seconds. Then, they were either asked to remain still while the researcher removed the objects from the wall or they were guided around the room blindfolded and instructed to remove the objects. After the objects were collected, the participants placed the objects back in their original positions on the wall from either the same location as encoding or on the opposite side of the room. Placement error scores were calculated by comparing the positions of objects at encoding and replacement and converting those scores to error estimates in centimeters. A Friedman's test of differences among repeated measures was performed to assess differences in accuracy in our 4 conditions (walking condition: walking around the room to collect objects, remaining stationary while the research collects the object; replacement orientation: replace objects from same location as during encoding, replace objects from the opposite side of the room). We found a significant difference for the height of the placed object ($\chi 2(3) = 10.92$, $p = .01$). Post-hoc analysis using a Nemenyi-Wilcoxon-Wilcox all-pairs test revealed that placement error was significantly larger when participant did not walk around the room and replaced objects from the opposite than when participants did not walk around the room and replaced objects in the same location ($p = .002$). This was also true when comparing participants not walking around the room and replacing from the same viewpoint than when participants walked around the room and replaced objects from the opposite side of the room ($p = .04$). There were no significant differences in placement error among conditions for horizontal placement error ($\chi 2(3) = 6.20$, $p = .10$). Our finding suggest an advantage for body-movement (ambulation) in generalizing viewpoints. Future analyses will investigate how eye movements, particularly "scanpaths" contribute to memory from the same and different viewpoints.

Disclosures: A. Muller: None. **J. Garren:** None. **M. Peterson:** None. **A. Ekstrom:** None.

Poster

P877. Relational and Spatial Learning

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.03

Topic: H.10. Human Learning and Cognition

Support: Singapore Ministry of Health National Medical Research Council Open Fund - Individual Research Grant (NMRC/OFIRG/0043/2017)
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Singapore Ministry of Education Academic Research Fund Tier 3 (MOE2017-T3-1-002)
National Research Foundation, Singapore (Award Number: NRF2015-NRF-ISF001-2451)

Title: One-shot learning of paired associations by a reservoir computing model with Hebbian plasticity

Authors: *M. G. KUMAR[1], C. TAN[5], C. LIBEDINSKY[2], S.-C. YEN[3], A. Y. Y. TAN[4];
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Abstract: One-shot learning can be achieved by algorithms and animals, but how the latter do it is poorly understood as most of the algorithms are not biologically plausible. Experiments studying one-shot learning in rodents have shown that after initial gradual learning of associations between cues and locations, new associations can be learned with just a single exposure to each new cue-location pair. Foster, Morris and Dayan (2000) developed a hybrid temporal difference - symbolic model that exhibited one-shot learning for dead reckoning to displaced single locations. While the temporal difference rule for learning the agent's actual coordinates was biologically plausible, the model's symbolic mechanism for learning target coordinates was not, and one-shot learning for multiple target locations was not addressed. Here we extend the model by replacing the symbolic mechanism with a reservoir of recurrently connected neurons resembling cortical microcircuitry. Biologically plausible learning of target coordinates was achieved by subjecting the reservoir's output weights to synaptic plasticity governed by a novel 4-factor variant of the exploratory Hebbian (EH) rule. As with rodents, the reservoir model exhibited one-shot learning for multiple paired associations.

Disclosures: M.G. Kumar: None. **C. Tan:** None. **C. Libedinsky:** None. **S. Yen:** None. **A.Y.Y. Tan:** None.

Poster

P877. Relational and Spatial Learning

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.04

Topic: H.10. Human Learning and Cognition

Support: CIHR Project Grant (FRN 159492)

Title: Temporal Proximity Does Not Influence Behavioral Integration of Spatial Memories across Experiences in humans

Authors: *X. FANG[1], K. ALSBURY-NEALY[1,4], Y. WANG[2,5], S. A. JOSSELYN[5,2,1,3], P. W. FRANKLAND[5,2,1,3,6], M. L. SCHLICHTING[1], K. D. DUNCAN[1];
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Abstract: Linking memories across related experiences is crucial to the extraction of commonalities that can inform decision making in novel situations. Rodent work using fear conditioning (Cai et al., 2016; Rashid et al., 2016) has shown that memories are more likely to be integrated, as evidenced by the generalization of freezing behavior across contexts, when they are encoded close (within a few hours) as compared with far apart (>18 hours or one week) in time. Such behavioral generalization is a result of allocation of related memories to overlapping sets of neurons. However, the scope of this phenomenon is unclear; both whether temporal proximity—i.e., the length of delay between related experiences—similarly affects the integration of reward-motivated learning and whether it has a similar impact on human behavior as it does in rodents. Here, 134 participants searched for rewards in two similar virtual environments (created using OpenMaze; https://openmaze.ca), learning the rewarded zone of each in a separate session. Across environments, the two rewarded zones were adjacent to one another, making it possible to merge memories about reward locations. The delay between sessions was either 30 minutes, 3 hours, or 27 hours. We measured memory integration three days later by comparing search paths across similar environments. Based on previous rodent work, we hypothesized higher search path similarity—reflecting an integration of related memories into the same mental map—across similar environments experienced at shorter delays. We found that participants successfully formed spatial memories about reward locations by the end of each learning session. In the final test, while participants were most likely to search in the rewarded zone of each environment, we also observed evidence for integration: When participants searched in an incorrect location, they were more likely to search in the rewarded zone from the related environment as compared with a never-rewarded zone. Critically, however, Bayesian analysis yielded strong evidence that memory integration was not modulated by temporal proximity, in contrast to previous work. One possible explanation for this finding is that humans are more inclined to adopt strategic solutions, making their memories less sensitive to temporal proximity. While future work is needed to uncover the neural mechanisms contributing to such species differences, our findings provide preliminary evidence that species-specific mechanisms could underlie memory integration in certain tasks.

Disclosures: X. Fang: None. **K. Alsbury-Nealy:** None. **Y. Wang:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None. **M.L. Schlichting:** None. **K.D. Duncan:** None.

Poster

P877. Relational and Spatial Learning

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.05

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01 DC0161119

Title: The neural and cognitive markers of enhanced processing of asymmetric musical scales

Authors: *C. PELOFI[1], M. REZAEIZADEH[3], M. M. FARBOOD[2], S. A. SHAMMA[3];
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Abstract: Music is produced and enjoyed in every known human culture, past and present. Despite its rich diversity across cultures, musical systems exhibit recurrent features, and the extent to which these "universals" result from cognitive and neural constraints is still debated. Here, we focus on the asymmetry of scales, a robust universal feature (Savage et al., 2015) which corresponds to the fact that the discrete pitches used in melodies are separated by intervals of different sizes. This intervallic asymmetry has been posited to help orient listeners in a tonal space representation (Brown, 1981). Here we use a combination of behavioral and EEG measures to assess the cognitive benefits associated with asymmetry in scales. Melodies are generated using an artificial grammar based on a first-order Markov chain and derived from either an asymmetric or symmetric hexatonic (i.e. six-tone) scale. After an exposure phase presenting a corpus of melodies derived from the grammar, listeners' performances on detecting syntactic violation in a set of new melodies are measured behaviorally and contrasted for asymmetric and symmetric scales. Behavioral results demonstrate enhanced performances in detecting syntactic irregularities for melodies derived from the asymmetric scale. EEG results mirror these findings: ERPs associated with distinct probabilities of note transitions suggest that neural responses better encode the grammar of melodies of the asymmetric scale. Besides, a set of linear decoders trained on classifying neural processing of grammatical structure shows enhanced accuracy in the context of the asymmetric scale. By highlighting the cognitive underpinning of a music universal, this study provides an account of the trade-off between diversity and stability across musical cultures and opens a new avenue in the investigation of cross-cultural musical learning.

Disclosures: C. Pelofi: None. **M. Rezaeizadeh:** None. **M.M. Farbood:** None. **S.A. Shamma:** None.

Poster

P877. Relational and Spatial Learning

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P877.06

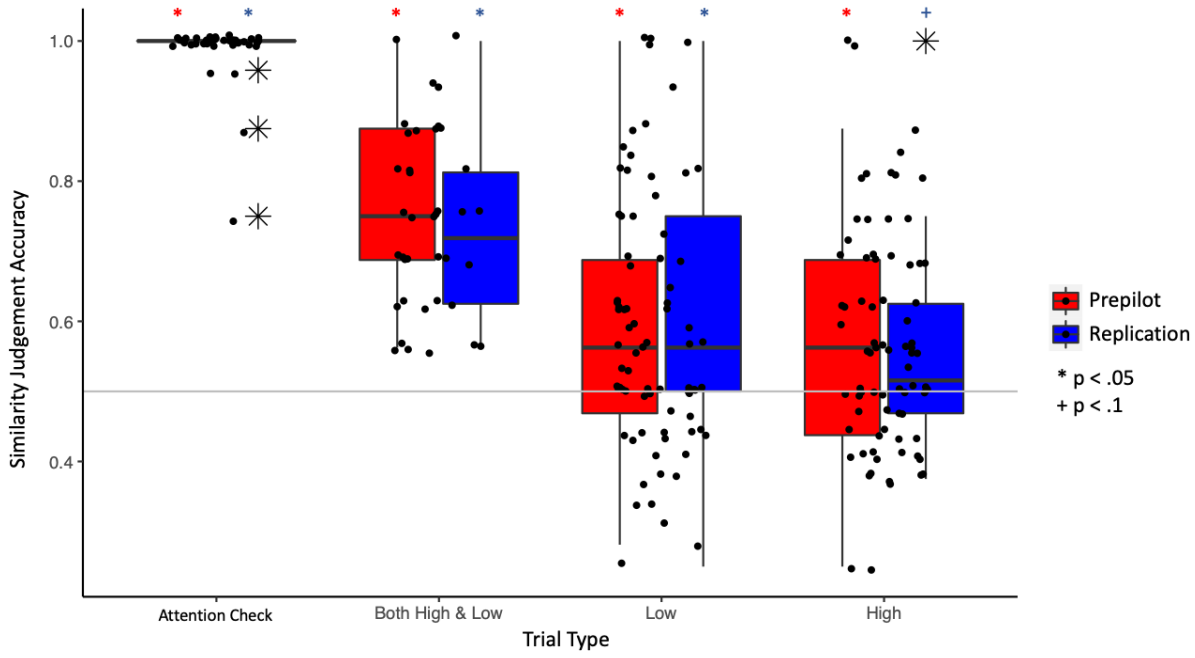
Topic: H.10. Human Learning and Cognition

Support: R01DC00920
F32MH123002

Title: Learning context-dependent temporal associations across time-scales

Authors: *C. M. SMITH, A. C. SCHAPIRO, S. L. THOMPSON-SCHILL;
Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: How does the brain encode temporal contingencies at different time-scales? A cortical hierarchy of sensitivity to order information at different time-scales has been observed using naturalistic paradigms (Hasson et al. 2015). We seek to develop a statistical learning paradigm that can be used to map cortical and hippocampal temporal gradients. Human participants (pilot N=32, replication ongoing) played a game similar to "whack-a-mole" in which they clicked on a target image when it appeared in one of 9 locations. The task was performed in 8 different contexts, differentiated by the background and target image. Across contexts, the order of locations where the target might appear changed systematically, at either a short or long time-scale. At a short time-scale we manipulated the order of pairs of locations in which the target appeared. At a longer time-scale, we manipulated the higher order set of locations that appeared in the first vs. second half of the game. Participants were periodically asked to predict the upcoming target location. They later performed similarity judgements comparing the games based explicitly on their order properties. Preliminary data suggest context dependent sensitivity to order information at both short and long time-scales. Figure shows that sensitivity to high and low level order information among good learners (separately assessed) is numerically above chance. To our knowledge, this is the first time it has been shown that humans can learn hierarchically nested order information at different time-scales in a statistical learning paradigm. Neural network modeling results and plans to collect fMRI and EEG data will be discussed.



Disclosures: C.M. Smith: None. **A.C. Schapiro:** None. **S.L. Thompson-Schill:** None.

Poster

P877. Relational and Spatial Learning

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Program #/Poster #: P877.07

Topic: H.10. Human Learning and Cognition

Title: Effects of presentation order on learning hierarchical structure

Authors: W. ALEXANDER, R. GALLAGHER;
Florida Atlantic Univ., Boca Raton, FL

Abstract: It is generally accepted that prefrontal cortex is organized along a hierarchical rostrocaudal abstraction gradient: caudal regions represent concrete task information, while rostral regions maintain information related to abstract rules and context. While the existence of an abstraction gradient is well-supported by empirical investigation, it is less clear how the information signaled by a stimulus is identified as being either concrete or abstract in the first place. A recent model of prefrontal cortex, the *Hierarchical Error Representation* (HER) model, suggests not only how hierarchically organized regions in prefrontal cortex interact to support behavior, but also how humans learn to identify abstract and concrete cues in the first place. According to the HER model, relative levels of abstraction amongst information sources are determined by their temporal proximity to a response as well as by the degree to which the cue on its own reduces uncertainty about identity of the correct response. A key prediction of the model is that manipulating the order in which structured information is presented produces differences in performance: learning rate and accuracy will increase when a cue that more effectively reduces response uncertainty is presented immediately prior to a response. We tested this prediction by having subjects perform a task in which they were required to learn the correct response to repeated sequences of two images. In one condition ('Concrete First'), stimuli that were more effective at reducing uncertainty about response identity were presented first, while in a second condition ('Abstract First'), these stimuli were presented immediately prior to a response. As predicted by the HER model, subjects learned more slowly and with lower terminal accuracy in the Concrete First condition. Drift-diffusion modeling of behavioral data aligned to the onset of the second cue shows that subjects integrated information more quickly in the Abstract First condition than in the Concrete First condition, consistent with a role for context information in modulating the processing of concrete information rather than directly driving behavioral responses. Taken together, these results provide additional insight into how hierarchically structured information is identified, represented, and used to inform behavior.

Disclosures: W. Alexander: None. **R. Gallagher:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

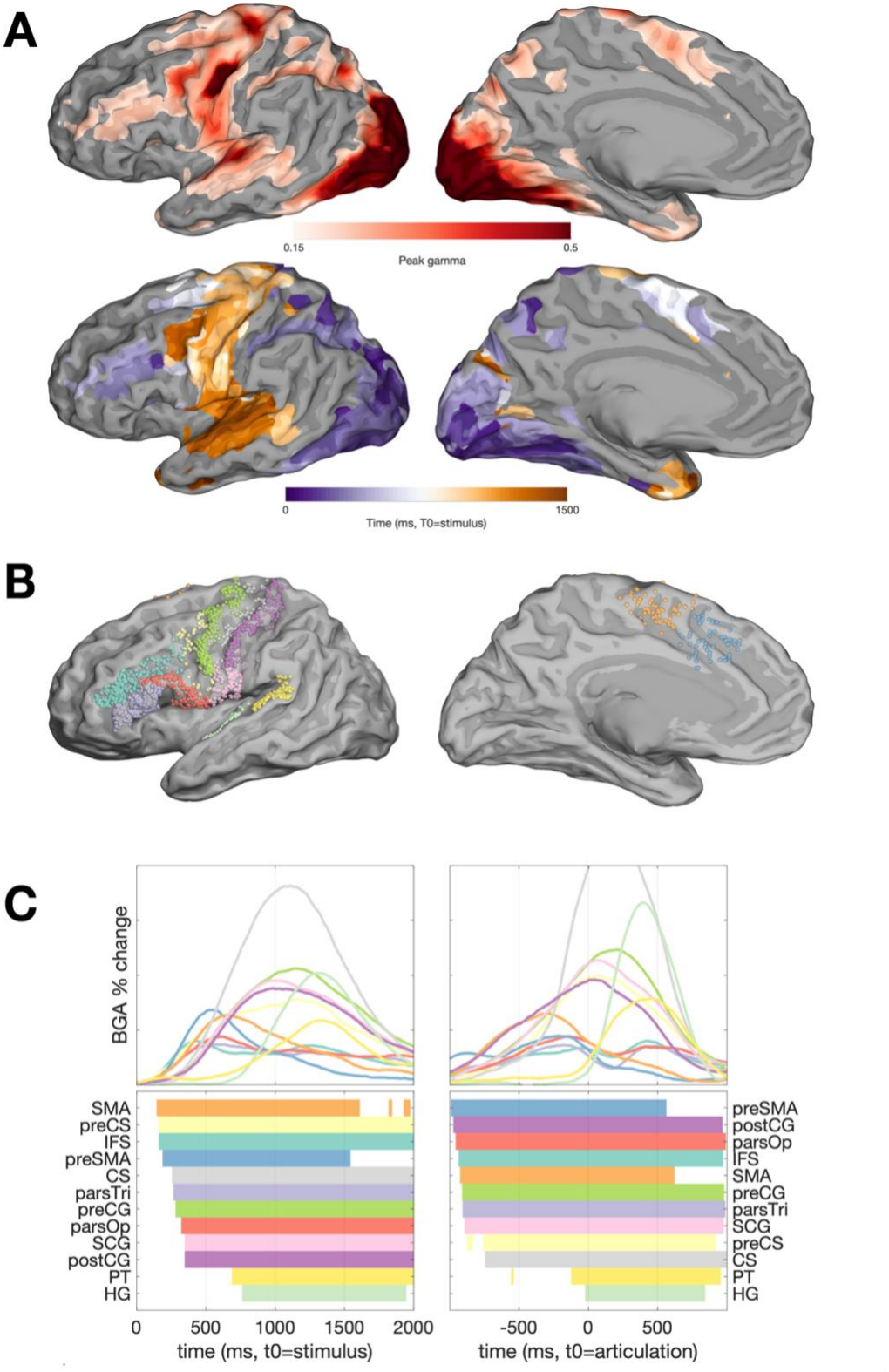
Program #/Poster #: P888.01

Topic: H.11. Language

Title: Supplementary motor area first predicts reaction time in stereotyped word articulation in large-scale intracranial EEG

Authors: *L. BULLOCK[1], K. FORSETH[1], N. TANDON[1,2,3];
[1]UT Hlth. Sci. Ctr. Houston, Houston, TX; [2]Texas Inst. for Restorative Neurotechnologies, Houston, TX; [3]Mem. Hermann Hosp., Houston, TX

Abstract: Intracranial recordings provide unparalleled insights into the dynamics of word production. However, these data are limited by sparse coverage of brain areas, and the derivation of a whole brain map of speech production is confounded by varied responses across individuals, along with the semantic, lexical, and phonological confounds intrinsic to the generation of a range of words. To control for this, we performed intracranial recordings in a large cohort (n = 134, 25,000+ electrodes) while they articulated a single multisyllabic word, 'scrambled' (average 66/person). Global mean broadband gamma activity (BGA), derived using a surface-based mixed-effects multilevel analysis (SB-MEMA), was used to create a 4D representation of cortical dynamics during production of this single-word. BGA changes in supplementary motor area (SMA), pre-SMA, precentral sulcus, and inferior frontal sulcus reached significance earliest, followed by central sulcus and IFG. To assess contributors to RT variability, we modelled it as a function of BGA across trials at time points across the pre-articulatory window. Activity in the SMA was the earliest predictor of RT, reaching significance just 250ms after stimulus onset. In contrast, activity in other early-onset ROIs, such as IFS and precentral sulcus, were not predictive of RT until 300ms after stimulus onset. In a final set of analyses, we use linear mixed-effects modeling of RT to show a priming effect: The second of two consecutive SCRAMBLED trials had a lower RT. We tested each active electrode in each ROI for BGA divergence between the two conditions. 13 of 637 recording sites showed a 'preference' for either the PRIMED or UNPRIMED conditions. Taken together with the finding that SMA predicts RT earliest, the sparse cortical effects we see suggest that RT decreases in the PRIMED condition may be primarily driven by SMA-mediated cortical-basal ganglia-thalamus loops, that are initiated sooner for PRIMED trials as they require a re-execution of a motor program. Overall, this work highlights the key role of the SMA in speech initiation and timing.



Disclosures: L. Bullock: None. **K. Forseth:** None. **N. Tandon:** None.

Poster

P888. Neural Circuits and Mechanisms III

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Program #/Poster #: P888.02

Topic: H.11. Language

Support: NSFC32071099 to XT
Natural Science Foundation of Shanghai 20ZR1472100 to XT
Program of Introducing Talents of Discipline to Universities, Base B16018 to XT

Title: Impaired monitoring on intact repreaentational function mediates auditory verbal hallucinations

Authors: *F. YANG[1,2], C. ZHANG[3], **X. TIAN**[4,2,1];
[1]Sch. of Psychology and Cognitive Science,East China Normal Univ., Shanghai, China; [2]NYU-ECNU Inst. of Brain and Cognitive Sci., Shanghai, China; [3]Shanghai Mental Hlth. Ctr., Shanghai, China; [4]Neural and Cognitive Sci., New York Univ. Shanghai, Shanghai, China

Abstract: Speech production requires efficient monitoring. Impairment in the monitoring functions may misattribute inner speech to stimulus induced perception and result in auditory verbal hallucinations (AVHs). We hypothesize that auditory representation can be induced by a motor signal (*efference copy, EC*) that contains detailed speaking contents; whereas motor signal (*corollary discharge, CD*) monitors and determines the source of internally induced auditory representation by the *EC* signal. Specific in patients with AVHs, *EC* that induces auditory representation is relatively intact but *CD* that monitors the induction process is impaired so that the internally evoked auditory responses are incorrectly attributed as externally induced and hence yields AVHs. To test our hypothesis, we carried out an electroencephalography (EEG) experiment with a delayed articulation paradigm. Nineteen schizophrenic patients with AVHs and sixteen schizophrenic patients without AVHs were instructed to make different types of preparation before speaking according to visual cues. One visual cue consisted of symbols that did not contain any linguistic information. Participants were asked to prepare to speak without knowing what to say *(general preparation GP* that would induce *CD).* Another visual cue was syllables. Participants were asked to prepare to speak a specific syllable *(specific preparation, SP* that would induce *EC).* Auditory syllables were presented during the last 400ms of each preparation stage to investigate the nature of the motor signals by testing how distinct preparation stages modulate the perceptual responses to the auditory probes. In both schizophrenic patients with AVHs and without AVHs, *general preparation* did not inhibit auditory neural responses, contrasting with suppression results in normal participants (Li, Zhu & Tian, 2020). The absence of inhibition during *general preparation* suggests the impairment of *CD* in patients. Whereas *specific preparation* modulated auditory representation but different between patients with and without AVHs. Specifically, in patients without AVHs, the modulation effect was consistent with normal participants where *specific preparation* enhanced auditory neural responses to the sounds congruent with what prepared. Whereas in patients with AVHs, the modulation was in an opposite direction as observed in normal participants, indicating the malfunctioned *CD* on monitoring the intact *EC*. These results suggest that the interplay of distinct
functional motor signals balances the computational demands between executing and monitoring the top-down mental operations.

Disclosures: F. Yang: None. **C. Zhang:** None. **X. Tian:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.03

Topic: H.11. Language

Support: R01 DC019354
R01 DC015260
Simons Collaboration on the Global Brain

Title: A speech planning circuit for interactive language use

Authors: *G. A. CASTELLUCCI[1], C. K. KOVACH[2], M. A. HOWARD, III[2], J. D. GREENLEE[2], M. A. LONG[1];
[1]Neurosci. Inst., NYU Langone Med. Ctr., New York, NY; [2]Neurosurg., Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: During conversation, people take turns speaking by rapidly responding to their partners while simultaneously avoiding interruption. Such interactions display a remarkable degree of coordination, as typical gaps between turns are ~200 ms - approximately the duration of an eyeblink. These response times are considerably shorter than those observed in simple word production tasks, indicating that speakers often plan their responses while listening to their partners. Although a distributed network of brain regions has been implicated in speech planning, the neural dynamics underlying the specific preparatory processes which enable rapid turn-taking are poorly understood. Here we use intracranial electrocorticography to precisely measure neural activity as participants perform interactive tasks, and we observe a distinct class of cortical dynamics associated with speech planning. We localize these preparatory responses to a frontotemporal circuit that is anatomically segregated from regions involved in speech perception and production, and we find the core of this network to be comprised of language-critical caudal inferior frontal cortex (i.e., 'Broca's region') and caudal middle frontal gyrus - a region not normally implicated in speech planning. Using a series of motor tasks, we then show that this planning network is selectively active when preparing speech but largely unrecruited when planning nonlinguistic orofacial and manual actions. Finally, we uncover planning-related circuitry in natural conversation that is nearly identical to the network mapped with our interactive tasks, and we find this circuit to be most active prior to participant speech during unconstrained turn-taking. Therefore, we have identified a speech planning network central to natural language generation during social interaction.

Disclosures: G.A. Castellucci: None. **C.K. Kovach:** None. **M.A. Howard:** None. **J.D. Greenlee:** None. **M.A. Long:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.04

Topic: H.11. Language

Support: CMLH Fellowship

Title: Leveraging brain encoding models to predict individual differences in behavior

Authors: *J. WILLIAMS[1], L. WEHBE[2,3];
[1]Computat. Biol., [2]Machine Learning, [3]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: To increase our understanding of the brain-behavior relationship we want to understand how individual differences in brain function are associated with differences in behavior. Recent neuroimaging studies have shown that individual differences in functional connectivity (FC) are predictive of behavior. FC tells us when two brain areas are connected and activated together. This is an important part of understanding which areas are interacting, and has allowed researchers to identify networks related to different cognitive processes (i.e., vision, language). However, this knowledge does not include what kind of information different areas are processing and passing to each other, which might also be predictive of individual differences in behavior. To better understand individual differences in processing information a complementary approach to FC is to identify where differences in information processing exist and what information is processed in these areas. Encoding models have enabled researcher to build complex maps of the information underlying processes such as vision or language. However, encoding models are typically used in studies with lots of data from a few participants, which would prevent them from leading to insights about individual differences. We propose a framework to leverage encoding models to identify individual differences in stimulus processing. We evaluate our framework on the fMRI blood-oxygen-level-dependent (BOLD) responses collected when 176 participants (104 female, age 22-37) watched an hour of naturalistic video clips, and when they performed a tightly controlled motor task for 7 minutes. This data was provided as part of the Human Connectome Project (HCP). We use encoding models, to estimate the BOLD response of each area from the stimulus features. We find that encoding model predictive performance, correlation between actual and encoding model predicted BOLD response, is feature-space and task specific. Next we interrogate the relationship between brain function and behavior, by using the individual differences in predictive performance to predict cognitive behavior measures in the HCP. We find that predictive performance predicts the vast majority (12/15) of cognitive behavior measure scores significantly higher than chance (one-sided permutation test, alpha = 0.05, FDR corrected), and that these predictive capabilities are feature-space and task specific. These results argue that encoding models can be a powerful tool for studying individual differences that is complementary to FC and can reveal specific differences in how brain areas process information and how these differences relate to behavior.

Disclosures: J. Williams: None. **L. Wehbe:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.05

Topic: H.11. Language

Support: NIH Grant NS098981

Title: Spatiotemporal brain dynamics of sentence reading

Authors: *O. WOOLNOUGH[1], E. MURPHY[1], P. S. ROLLO[1], C. DONOS[1], S. DEHAENE[2], N. TANDON[1];
[1]UTHealth, Houston, TX; [2]INSERM-CEA, GIF/YVETTE, France

Abstract: Reading a sentence entails inferring meaning from combinations of multiple lexical objects, allowing us to derive complex meaning. Studies of cortical activity underlying semantic and syntactic operations implicate inferior frontal gyrus (IFG) and middle temporal gyrus (MTG), yet the relative contributions of these regions to sentence comprehension remains controversial. We used direct intracranial recordings from IFG and MTG in the left hemisphere, in a large cohort, to map spatiotemporal neural correlates of multi-word semantics and sentence structure building. 29 patients undergoing implantation of intracranial electrodes for localising pharmaco-resistant epilepsy silently read Sentences, Jabberwocky sentences, Unstructured word lists, and Pseudoword lists, presented in rapid serial visual presentation. Broadband gamma activity (70-150Hz) was extracted from electrodes across the left hemisphere (n>2,500) and subjected to linear mixed effects modelling to dissociate the impact of sentence structure, word frequency and lexicality on recorded activation. Contrary to predictions from prior studies, we found that sentence structure did not lead to a simple monotonic increase in activation across the duration of the sentence, relative to word lists. Instead, we observed an initial suppression of activity for sentences, coinciding with formation of a phrase structure at word 2, followed by a progressive increase in activity along the rest of the sentence. This pattern was identical for electrodes in MTG, anterior IFG and medial frontal operculum. Ventral visual cortex, parietal cortex and posterior IFG did not show modulation by sentence structure. Lastly, a tuning to word frequency was observed across ventral occipitotemporal cortex, appearing earliest in mid-fusiform cortex, and preceding frequency tuned responses in IFG and traditional visual word form regions by around 200 ms. Our work suggests that the neural correlates of sentence structure comprehension. primarily care about an accumulation of semantic rather than syntactic information. Both IFG and MTG demonstrate comparable sensitivity to sentence structure. The IFG is sensitive to lexical properties of single words, subserving an item-specific representation, while MTG appears to be involved in the generation of abstract, structural inferences. Our work provides crucial insight into the integration of individual words into complex semantic concepts and highlights the critical need for large cohort studies of sentence processing utilising methods that provide high spatiotemporal resolution.

Disclosures: O. Woolnough: None. **E. Murphy:** None. **P.S. Rollo:** None. **C. Donos:** None. **S. Dehaene:** None. **N. Tandon:** None.

Poster

P888. Neural Circuits and Mechanisms III

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.06

Topic: H.11. Language

Support: NATS/NIH UL1 TR000445
U54 HD083211
NICHD/NIH R01 HD044073

Title: Prefrontal mediation of the reading and language network in first-grade predicts longitudinal reading comprehension growth

Authors: *K. ABOUD, A. N. BURGESS, L. CUTTING;
Vanderbilt Univ., Nashville, TN

Abstract: Early developmental predictors of long-term reading comprehension (RC) have primarily focused on behavioral and neural measures related to reading and language. However, recent studies have revealed that executive brain areas, such as the dorsolateral prefrontal cortex (dlPFC), play a critical role in in the integration of word and text reading processes. In the current study, we aimed to determine how executive versus reading and language network (RLN) connectivity patterns relate to early RC (first grade) and later RC growth (from second to third grade). We hypothesized that within-network RLN connectivity would be associated with RC at all time points, but executive interactions with the RLN would be particularly predictive of later RC growth. We examined n = 44 first graders as they read words in the MRI. We then employed a longitudinal design to examine first-grade neural predictors of RC growth in first, second, and third grades. Specifically, we were interested in the role of executive versus the RLN in early and later RC performance. Functional connectivity analysis revealed that first-grade coupling in the canonical RLN, but not executive areas, was significantly predictive of first-grade out-of-scanner RC ability. However, RC growth from second to third grade was predicted by RLN connectivity as well as left dlPFC mediation of within-network RLN coupling. These findings mirror previous studies on reading intervention that show similar executive mediation of the RLN as a significant pre-intervention predictor of reading intervention response. Our results reveal that early executive support of the RLN is a critical part of longitudinal RC development, suggesting that the development of an executive "scaffold" of reading processes may be an important component of early reading practice. Future studies should track executive-RLN interactions across development and bridge findings to inform intervention.

Disclosures: K. Aboud: None. **A.N. Burgess:** None. **L. Cutting:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.07

Topic: H.11. Language

Title: Higher order thinking and neuroplasticity

Authors: *M. ORKODASHVILI;
Vanderbilt Univ., Tbilisi, Georgia

Abstract: The paper looks into the influence of the so-called *higher order thinking* on the development of neuroplasticity in monolingual, bilingual and multilingual brains. *Higher order thinking* involves understanding of linguistic units and linguo-pragmatic means with non-literal meanings such as certain abstract notions (often of polysemantic nature), metaphors, and humor. The paper analyzes the effects of the recognition of abstract notions, metaphors, and humor in monolingual, bilingual and multilingual individuals on the development of their cognitive capacities. It is hypothesized that transferring, explaining and understanding abstract notions, metaphors, and humor across languages is more difficult than transferring, explaining and understanding simple and concrete concepts or actions (e.g. concrete nouns and verbs denoting simple actions). As a result of systematic mental exercise, subjects develop three important advantageous features of cognitive capacity: 1) quicker response time to understanding expressions and statements with non-literal meanings; 2) multitasking ability of understanding and reacting (or proacting) to simultaneous multiple tasks such as simultaneous translation and interpretation; and 3) quicker context anticipation. All three advantages indicate higher brain plasticity. The study so far has come to the following findings:a) bilinguals and multilinguals are 85-95 milliseconds quicker in recognizing and understanding non-literal meanings as opposed to monolinguals;
b) monolinguals are 45-55 milliseconds quicker understanding complex texts after being exposed to the metaphoric expressions for a while; c) subjects who have been exposed to metaphoric expressions and texts report the ability of performing two tasks at a time such as simultaneous translation in multiple languages more often than those who have not been exposed to such non-literal expressions; d) furthermore, in the process of reading a new text, the subjects who have been exposed to metaphoric expressions, anticipate the subsequent words, actions or concepts from the context with 78 % precision, as compared to those who have not been exposed to such expressions and who reveal only 22 % precision of anticipation.

Disclosures: M. Orkodashvili: None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.08

Topic: H.11. Language

Support: NIH Grant NIDCD-DC014279
NSF CAREER award
Pew Charitable Trusts, Pew Biomedical Scholars Program

Title: Distributed and joint representation of linguistic feature hierarchy in the human auditory cortex

Authors: *M. KESHISHIAN[1], S. AKKOL[2], J. L. HERRERO[3], S. BICKEL[2], A. D. MEHTA[2], N. MESGARANI[1];

[1]Columbia Univ., New York, NY; [2]Hofstra Northwell Sch. of Med., Manhasset, NY; [3]The Feinstein Inst. For Med. Res., Manhasset, NY

Abstract: How the human auditory cortex represents and transforms the sound pressure waveforms produced by a speaker to enable speech recognition remains unclear. Here, we used direct neural recordings from implanted electrodes in the auditory cortex of fifteen neurosurgical patients as they listened to thirty minutes of natural speech. We used a multivariate regression framework to predict neural responses from various acoustic and linguistic features of speech and measured the variance explained by each feature. We found an explicit and distinct neural encoding of multiple levels of linguistic processing, including the acoustic, phonetic, phonotactic, lexical-phonemic and lexical-semantic features. Grouping neural sites according to their encoded linguistic features revealed several patterns of joint feature encoding, where the representations of higher-level features were added to the representation of lower-level features. Anatomical and functional localization of linguistic encoding showed a gradual emergence of low- to high-level features from primary to non-primary auditory cortical areas. Furthermore, we observed a temporal order in the appearance of these features, where encoding of higher-level features was correlated with neural response latency and the response time-lag for higher-level features was higher than lower-level features across the population. This joint, anatomically distributed, and temporally ordered appearance of various levels of linguistic features shines a light on what hierarchical processes enable the human auditory cortex to extract meaning from the speech sounds.

Disclosures: M. Keshishian: None. **S. Akkol:** None. **J.L. Herrero:** None. **S. Bickel:** None. **A.D. Mehta:** None. **N. Mesgarani:** None.

Poster

P888. Neural Circuits and Mechanisms III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P888.09

Topic: H.11. Language

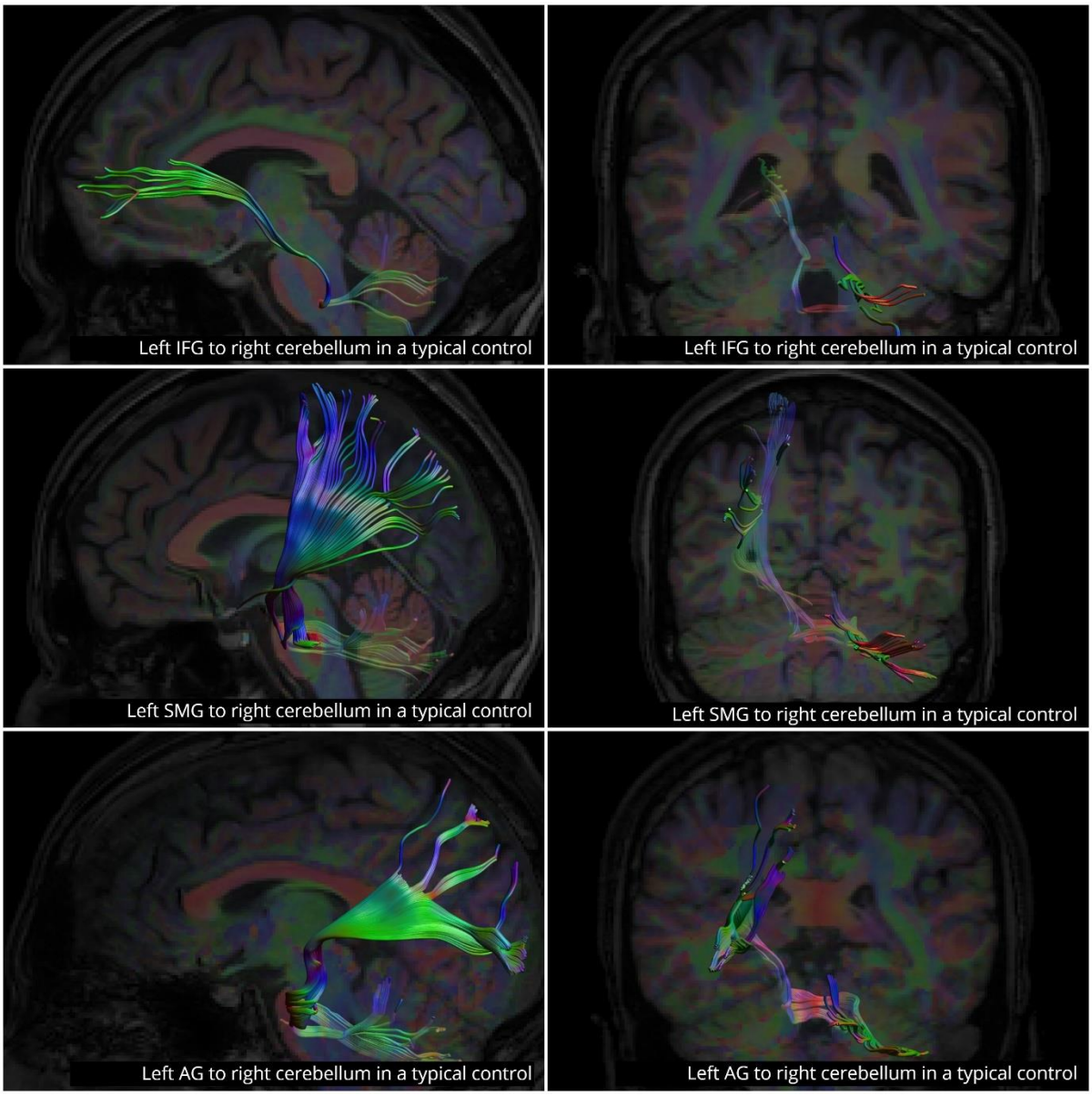
Support: FONDECYT Initiation into Research Study Nº 111150429
Beca ANID doctoral Nº 21201983

Title: Investigating the Cerebellar Connectivity of Language Processing: A DTI Feasibility Study

Authors: *I. THAKKAR[1], L. ARRAÑO-CARRASCO[1], R. ZUNINO-PESCE[1], B. CORTÉS RIVERA[2], F. MERY-MUÑOZ[1], M. RODRIGUEZ-FERNANDEZ[1], A. LEEMANS[3], C. MENDEZ-ORELLANA[1]; [1]Pontificia Univ. Católica de Chile, Santiago, Chile; [2]Univ. Santo Tomás, Santiago, Chile; [3]UMC Utrecht, Utrecht, Netherlands

Abstract: BOLD activations in the cerebellum contralateral to language-dominant cortical regions during a verbal fluency task were first shown in Hubrich-Ungureanu et al., 2002, pointing at the cerebellum's role in language processing. In our previous studies, these activations were observed in both left- and right-handed healthy subjects and brain tumor patients (Mendez Orellana et al., 2014), and during semantic and phonological association tasks (Thakkar et al., 2021). White matter tracts connecting the frontal lobe to the contralateral cerebellum have been observed in tractography studies (Keser et al., 2015;

Oh et al., 2016). Here, we investigate the feasibility to reconstruct white matter tracts directly connecting the contralateral cerebellum specifically with cortical ROIs involved in the dorsal stream of language processing, i.e. the inferior frontal gyrus (IFG), and the supramarginal and angular gyri (SMG, AG).
We use the ExploreDTI Toolbox (Leemans et al., 2009) to demonstrate the presence of these tracts in healthy subjects (n = 14, age-range = 20 - 70 years, mean age = 42.43 years, females = 6, left-handed = 4). With tracking settings used in Keser et al., 2015, we perform whole-brain tractography for all subjects. We identify cortical ROIs in each hemisphere for each subject and analyze tracts from the contralateral cerebellum to the contralateral ROIs separately. In our preliminary analyses, we observe fiber tracts from the contralateral cerebellum in 6 subjects extending to IFG, in 11 extending to SMG, and in 7 extending to AG.
This warrants further investigation in tractography parameters to consistently construct these pathways that may be sustaining the contribution of the cerebellum in language processing in both healthy and brain tumor cohorts. This is crucial due to the occurrence of false positives and crossing fibers in tractography (Jeurissen et al., 2013). We will quantify diffusion properties of these tracts with respect to their functional properties to aid surgical planning in brain tumor patients and shed light on the current model of language processing.



Disclosures: I. Thakkar: None. **L. Arraño-Carrasco:** None. **R. Zunino-Pesce:** None. **B. Cortés Rivera:** None. **F. Mery-Muñoz:** None. **M. Rodriguez-Fernandez:** None. **A. Leemans:** None. **C. Mendez-Orellana:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.01

Topic: A.09. Adolescent Development

Support: CIHR Project Grant (5-year)
CIHR Catalyst Grant
BrainsCAN Postdoctoral Fellowship

Title: Sex-dependent impact of prenatal cannabinoid exposure on neonatal and adolescent neuropsychiatric outcomes

Authors: *M. G. NASHED[1], R. HUDSON[1], M. H. SARIKAHYA[1], K. LEE[2], S. R. VANIN[2], D. B. HARDY[2], S. R. LAVIOLETTE[1];
[1]Anat. & Cell Biol., [2]Obstetrics & Gynecology, Univ. of Western Ontario, London, ON, Canada

Abstract: Objective/Rationale: Recent reports suggest that the prevalence of cannabis use during pregnancy is upwards of 35% in North America, with a rise in use mirrored by increasing legalization and the perception of safety. This project utilizes a rat model of prenatal cannabinoid exposure to assess neonatal and long-term neuropsychiatric liability of in utero exposure. Delta-9-tetrahydrocannabinol (Δ9-THC; the psychoactive component of cannabis) and cannabidiol (CBD; a non-psychoactive component of cannabis) were assessed separately and in combination.
Methods: Pregnant Wistar rat dams were administered daily intraperitoneal (i.p) injections between gestational days (GD) 6 and 20. Dams received vehicle, 3mg/kg Δ9-THC, 30mg/kg CBD, or a combination of 3mg/kg Δ9-THC plus 30mg/kg CBD. In a subset of dams, fetal and placental weights were measured at GD19. Pup body and brain weights were measured at postnatal day (PND) 1 and PND21. Male and female adolescent offspring underwent behavioural testing to assess neuropsychiatric and cognitive domains. The open field test (OFT) and elevated plus maze (EPM) were used to assess anxiety-related behaviours. Cognition was assessed through temporal order novel object recognition (tNOR) and the social memory task.
Results: Δ9-THC and CBD administration did not impact maternal food intake, weight, or litter size. However, Δ9-THC, CBD, and combination treatment all resulted in decreased fetal weight and fetal:placenta ratio at GD19, suggesting placental insufficiency. At PND1, brain and body weight measures were indicative of asymmetrical fetal growth restriction (FGR) for Δ9-THC offspring, and symmetrical FGR for Δ9-THC/CBD combination offspring. At PND21, no differences in brain weights were observed for either male or female offspring in any treatment group, suggesting postnatal catch-up growth. During adolescence, sex-specific neurobehavioural effects emerged. For male offspring, all treatments (Δ9-THC, CBD, and combination) impaired object recall in the tNOR, with no significant effects observed in emotional tasks (EPM and OFT). For female offspring, CBD exposure was associated with anxiety-like behaviour in the EPM, and all treatments (Δ9-THC, CBD, and combination) impaired social recall in the social memory task.
Conclusion: We demonstrated that in utero exposure to Δ9-THC and CBD are associated with impairments in fetal development, as well as sex-specific deficits in adolescent neuropsychiatric and cognitive outcomes. This project will contribute to informing public attitudes and regulatory policies on the use of cannabinoid-based products during pregnancy.

Disclosures: M.G. Nashed: None. **R. Hudson:** None. **M.H. Sarikahya:** None. **K. Lee:** None. **S.R. Vanin:** None. **D.B. Hardy:** None. **S.R. Laviolette:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.02

Topic: A.09. Adolescent Development

Support: University of Buenos Aires (UBA) Grant 20020190100222BA

Title: Effects of ethanol intake and noise exposure on adolescent rat hippocampal reactive oxygen species and glutaredoxins

Authors: S. J. MOLINA[1], A. E. LIETTI[2], C. S. CARREIRA CARO[1], L. D´ALESSIO[3,4], G. E. BUJÁN[3], *L. R. GUELMAN[3,1];
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Abstract: Human adolescents usually consume ethanol (EtOH) for recreational purposes in social gatherings, bars and concerts, places where they are also often exposed to noise of high intensity. According to published animal experimental data, both stimuli presented separately might generate an imbalance in hippocampal (HC) oxidative system that could underlay HC-dependent behavioral alterations. Thus, the aim of this work was to test the effects of EtOH intake followed by noise exposure on the oxidative state of the HC in adolescent rats.Wistar rats of both sexes (28-days-old) were subjected to voluntary 10% EtOH intake using the “two-bottle choice drinking-in-the-dark” paradigm, during 4h/d, for 4 days. After the last session, rats were exposed to noise (95-97 dB, 2h). Finally, HC was dissected to assess the levels of reactive oxygen species (ROS) and catalase activity (CAT) through biochemical techniques as well as the antioxidant enzyme glutaredoxin-1 (Grx-1) through western blot analyses.Results showed an increase in ROS levels after EtOH intake and a decrease in Grx-1 levels after noise exposure in the HC of female rats, when compared with sham animals. In contrast, a decrease in ROS levels after noise exposure was found in males HC. When EtOH intake was followed by noise exposure, a significant decrease in ROS levels was found, both in males and females HC and an increase in Grx-1 was found only in males HC. Finally, non-significant differences were observed in CAT among groups in comparison to sham animals, either in females or males.These findings suggest that EtOH intake and noise exposure might affect HC oxidative state in a sex-dependent way. When both stimuli were presented separately, female rats appear to be more sensitive to EtOH, whereas males showed changes only when exposed to noise. However, when both agents were presented together, both sexes seem to be equally affected, suggesting that the combination of both stimuli might unmask any effects that would not have been observed with each agent individually. Finally, the finding of an increase in Grx-1 levels when ROS levels are decreased, observed only in males, might reveal a relevant role for this enzyme aimed to compensate for an oxidative imbalance triggered by the environmental stressors.

Disclosures: S.J. Molina: None. **A.E. Lietti:** None. **C.S. Carreira Caro:** None. **L. D´Alessio:** None. **G.E. Buján:** None. **L.R. Guelman:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.03

Topic: A.09. Adolescent Development

Title: Developmental exposure to cannabidiol via intraperitoneal injection or passive inhalation is without substantial behavioral consequences on locomotor behavior, anxiety, and spatial learning in mice

Authors: H. STEVENSON[1], T. MCGILLIS[1], J. K. WAGNER[1], K. REED[1], F. MCGUINNESS[1], S. ARVILA[1], M. BROOKS[1], J. JONES[1], B. RISCH[1], R. BUDINICH[1], E. GAMBELL[1], ***J. S. KAPLAN**[2]; [1]WESTERN WASHINGTON UNIVERSITY, BELLINGHAM, WA; [2]WESTERN WASHINGTON UNIVERSITY, Bellingham, WA

Abstract: Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with rapidly escalating popularity for the treatment of numerous off-label conditions including pain, anxiety, depression, hyperactivity, and autism spectrum disorder. Since CBD consumption is generally well-tolerated in adults, the impression of CBD's high safety profile has contributed to an increase in prenatal, early childhood, and adolescent exposure through the placenta, breastmilk, and oral consumption. Yet, the impact of CBD exposure on brain development across different developmental stages is unknown. As the number of CBD-related clinical trials in children and adolescents continues to grow, it has become increasingly important to characterize the long-term consequences of developmental CBD exposure. Here, we tested the effect of CBD exposure during several developmental time periods in male and female C57BL/6J mice on locomotor behavior in the open field, anxiety behavior on the elevated plus maze, and spatial memory on the Barnes Maze using two different exposure methods: intraperitoneal injection (i.p.) and passive CBD vapor inhalation. We first validated the acute anxiety-reducing efficacy of our CBD compounds in adult mice and used these doses to determine our developmental exposure levels. Twice daily 20 mg/kg CBD i.p. injections during the equivalent adolescent period (25-45 days) had no detrimental effects on locomotor behavior or anxiety in adulthood but improved the rate of learning on the Barnes Maze compared to vehicle-treated mice. Two weeks of twice daily passive inhalation sessions of CBD (33.3 mg/ml; 6 3-second hits delivered across 30 minutes) during the perinatal window (7 days prenatal to 7 days postnatal), early postnatal (P7-20), and (P14-27), and adolescent period (P28-41) were without detrimental behavioral effects on these three core assays. We conclude that prolonged adolescent CBD exposure in mice does not have substantive negative impacts on a range of behaviors in adulthood and may even improve the rate of learning when administered under certain stressful experimental conditions. These findings do not detract from the progression of clinical studies investigating CBD’s therapeutic potential in an adolescent population.

Disclosures: H. Stevenson: None. **T. McGillis:** None. **J.K. Wagner:** None. **K. Reed:** None. **F. McGuinness:** None. **S. Arvila:** None. **M. Brooks:** None. **J. Jones:** None. **B. Risch:** None. **R. Budinich:** None. **E. Gambell:** None. **J.S. Kaplan:** None.

Poster

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Program #/Poster #: P899.04

Topic: A.09. Adolescent Development

Support: NIH Grant MH086507
NIH Grant MH105488

Title: Downregulation of parvalbumin expression in the ventral hippocampus during adolescence causes long-lasting impairments in prefrontal cortex function in adults

Authors: *S. DUBE, A. OROZCO, K. Y. TSENG, A. CABALLERO;
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Abstract: The upregulation of the calcium-binding protein parvalbumin (PV) in fast-spiking GABAergic interneurons is necessary for the maturation of GABAergic function and the adjustment of the excitatory-inhibitory (E-I) balance observed in the prefrontal cortex (PFC) during adolescence. Similarly, the developmental increase in the PV expression in the ventral hippocampus (vHC) during adolescence may refine hippocampal activity and output to downstream structures. Notably, a downregulation of PV in both HC and PFC has been observed in post-mortem brains of schizophrenia patients, suggesting that inadequate levels of PV result in a disruption of inhibitory transmission within these structures. Since the vHC is a main afferent to the medial PFC, we hypothesized that downregulation of PV expression within the ventral hippocampus during adolescence would lead to hippocampal overactivity that ultimately disrupts the activity of the PFC in adults. To test this hypothesis, we delivered a PV shRNA vector directly into the ventral hippocampus to reduce PV expression during adolescence and examined its impact on PFC-dependent behaviors during adulthood. The results indicate that animals with reduced PV expression in the vHC had an impaired level of extinction in trace fear conditioning, a behavioral paradigm that relies on intact PFC-vHC connectivity. In addition, PV shRNA-treated animals displayed an impairment in sensory-motor gating as measured by reduced pre-pulse inhibition (PPI) of acoustic startle reflex (ASR). These results indicate the downregulation of PV expression in the vHC during adolescence is sufficient to disrupt prefrontal function, providing a useful translational model to study the effects of ventral hippocampal hyperactivity in neuropsychiatric disorders.

Disclosures: S. Dube: None. **A. Orozco:** None. **K.Y. Tseng:** None. **A. Caballero:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

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Program #/Poster #: P899.05

Topic: A.09. Adolescent Development

Support: NIAAA Grant U01-AA019972-10
NIAAA Grant F31-AA029300-01A1

Title: Social and neuronal alterations in adult male rats following adolescent intermittent ethanol exposure

Authors: *T. T. TOWNER, D. T. APPLEGATE, L. P. SPEAR, E. I. VARLINSKAYA, D. F. WERNER;
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Abstract: Adolescence is a sensitive developmental period during which alcohol use is often initiated. Furthermore, adolescents are also known to consume alcohol in high quantities, often at binge levels or even high-intensity drinking. Our lab has repeatedly found that adolescent intermittent ethanol (AIE) exposure in rats during postnatal days (P) 25-45 results in long-lasting social impairments, specifically in males. The goal of the current study was to further assess these AIE-induced sex-specific social alterations through the measurement of prelimbic (PrL) and infralimbic (IL) neuronal activation associated with exposure to a social stimulus. Based on previous findings and preliminary data, we hypothesized that AIE males would display social anxiety-like alterations accompanied by enhanced PrL neuronal activation in comparison to water-exposed males. Using a Sprague-Dawley cFos-LacZ transgenic rat, we intermittently exposed male adolescents (P25-45) to ethanol (4 g/kg, 25% v/v) or water via intragastric gavage for a total of 11 exposures (n = 13 per group). In adulthood (P70), rats were tested using a modified social interaction paradigm, and brains were collected approximately 60 minutes following the social interaction. Every sixth section of the PrL and IL were then subjected to β-galactosidase (β-gal) enzymatic histology, allowing for the identification of recently activated neurons, with β-gal used as a cFos proxy. We found that AIE exposure induced a social avoidance phenotype, as evidenced by a significantly lower social preference coefficient in AIE-exposed males relative to water-exposed controls. In contrast to our prediction, AIE males tended to have lower neuronal activation in the PrL although this effect of AIE was not statistically significant. No difference in IL activation was evident between water- and AIE-exposed males. Importantly, frequency of social investigation behavior was positively correlated with PrL neuronal activation in water-exposed rats, a relationship not evident in AIE-exposed rats. These data suggest that under normal circumstances the PrL cortex may be involved in the regulation of social behavior, however the involvement of the PrL may be dysregulated by AIE exposure. Further assessment of neuronal activation in other brain regions that modulate social behavior are underway as well as the inclusion of females to confirm whether these are sex-specific changes. Future studies will be focused on the inactivation of the PrL, thus allowing for a better understanding of the functional role of the PrL in AIE-induced social impairments.

Disclosures: T.T. Towner: None. **D.T. Applegate:** None. **L.P. Spear:** None. **E.I. Varlinskaya:** None. **D.F. Werner:** None.

Poster

P899. Aging and Development--Animal Models III

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Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.06

Topic: A.09. Adolescent Development

Support: CIHR PJT-159586

NSERC
Mitacs
BrainsCAN

Title: Adolescent Δ-9 tetrahydrocannabinol exposure induces different long-lasting changes in the dorsal and ventral portions of the hippocampal formation

Authors: *M. DE FELICE, C. CHEN, M. RODRIGUEZ-RUIZ, H. J. SZKUDLAREK, M. LAM, S. SERT, S. N. WHITEHEAD, K. K.-. C. YEUNG, W. J. RUSHLOW, S. R. LAVIOLETTE;
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Abstract: Sustained cannabis consumption during adolescence has been widely associated to cognitive impairments and enhanced risks for anxiety/mood disorders at adulthood. In particular, clinical and preclinical evidence has demonstrated that chronic exposure to the main psychoactive component Δ-9 tetrahydrocannabinol (THC) induces profound hippocampal (Hipp) morphological maladaptations and dysregulations of its glutamatergic signaling. Notably, several studies have reported a functional dissociation in physiological and pathological state between anterior and posterior Hipp subregions, identified as ventral (vHipp) and dorsal (dHipp) in rodents. Hence, in this study we investigated whether adolescent THC exposure induces different long-lasting abnormalities in vHipp and dHipp function. Adolescent male rats were treated from postnatal day (PND) 35 to 45 with increasing doses of THC (PND 35-37 2.5 mg/kg, PND 38-41 5 mg/kg, PND 42-45 10 mg/kg, i.p., twice a day) or vehicle. At adulthood (PND 75), a battery of behavioral tasks was carried out to assess cognitive performances and anxiety. Moreover, a detailed molecular examination in dHipp and vHipp was performed using Matrix-Assisted Laser Desorption/Ionization Imaging Mass Spectrometry (MALDI-IMS) and Western Blots techniques. Lastly, neural activity of glutamatergic cells was investigated in dHipp and vHipp with *in vivo* electrophysiological recordings. We report that adolescent THC exposure induced long-term anxiety and remarkable impairments in memory processing, concomitant with a wide range of molecular modifications. Specifically, IMS relative quantification revealed a significant decrease of dopamine levels in both, dHipp and vHipp, while GABA levels were decreased only in dHipp and no differences were detected in glutamate levels. In addition, protein analyses pointed out an opposite trend for NMDA2B, which was reduced in dHipp and enhanced in vHipp. Consistently, mGlu2/3 was increased in vHipp. Chronic THC exposure did not affect dopamine receptor as well as GAD67 and mTOR expression levels, in both dHipp and vHipp. Finally, chronic THC exposure led to a reduction in spontaneous electrical activity of glutamatergic neurons in dHipp, while no differences were found in vHipp. Overall, our findings provide evidence that THC exposure during adolescence impact differently dHipp and vHipp function, which dysconnectivity may underlie the cognitive and affective pathological outcomes of cannabis consumption.

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Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.07

Topic: A.09. Adolescent Development

Support: R01 DA048150
R01 DA047575

Title: Characterization of resting state networks in awake adolescent and adult squirrel monkeys

Authors: *W. YASSIN[1,4], F. B. DE MOURA[1,4,2], S. L. WITHEY[1,4], L. CAO[1], J. STOVER[1], S. J. KOHUT[1,4,2], B. D. KANGAS[3,4], J. BERGMAN[3,4];
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Abstract: Resting state networks (RSNs) are increasingly used as candidate biomarkers for neuropsychiatric disorders. Such biomarkers could serve as objective measures for novel therapeutic interventions where there is a strong need for translational research using well-controlled animal models. Squirrel monkeys offer advantages over macaques due to their smaller size and ease of handling, and marmosets due to being closer phylogenetically and neurobiologically to humans. This study aimed to characterize the RSNs of awake squirrel monkeys and report the characteristics of those networks from a developmental perspective.Twenty-seven squirrel monkeys (N=12 adolescents [6 male/6 female] approx. 2.5 years and N=15 adults [7 male/8 female] approx. 9.5 years) were gradually acclimated to awake scanning procedures. Whole-brain fMRI images were acquired with a 9.4T scanner. Quality control was evaluated using MRIQC and visual inspection. Modified FSL software pipeline was used for preprocessing and group level independent component (IC) analysis (30 ICs) to detect RSNs that were identified by 3 independent observers. ICs representing noise were excluded, resulting in 16 ICs corresponding to physiologically meaningful networks. In adolescents, the sensory motor network (SMN) was found in 2 ICs; one contained the bilateral supplementary motor areas (SMA), primary motor cortex (M1), anterior parietal cortex (APC), posterior parietal cortex, and parietal ventral area and secondary somatosensory area (PV/S2), the other contained the bilateral M1, APC, and premotor cortex (PMC). In adults, the basal ganglia included the head of the caudate, globus pallidus and putamen. Two single region ICs were identified: one limited to the bilateral cingulate cortex and another limited the thalamus. In the SMN, one IC included the PMC, M1, APC and PV/S2, and the other contained the PMC, M1, APC, and SMA. In adolescents and adults, the visual network was found in 6 of the 16 ICs. Four of the 6 included the bilateral primary visual area (V1), left and/or right V1 IC. The default mode network was found in 2 ICs that contained the anterior precuneus, posterior cingulate cortex and inferior parietal cortices. An inferior temporal cortex activation was also seen bilaterally. The prefrontal cortex (PFC) was found in 3 ICs, all localized to bilateral PFC. A cerebellar component covering the entire structure was also observed.
We report consistent and stable squirrel monkey RSNs previously identified in humans, rodents, and other non-human primate species. This data demonstrates a developmental trajectory of several networks that either varies or remains conserved depending on the RSN of interest.

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Poster

P899. Aging and Development--Animal Models III

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Program #/Poster #: P899.08

Topic: A.09. Adolescent Development

Support: NIH/NICHD grant R01 HD090925
Yerkes National Primate Research Center Base Grant (OD P51OD011132)

Title: The Role of Puberty on Brain and Physical Development: A Longitudinal Study in Adolescent Male Rhesus Macaques

Authors: Z. KOVACS-BALINT[1], J. RAPER[1], R. RICHARDSON[1], R. HONG[1], E. MORIN[1], M. PINCUS[1], L. LI[1], M. A. STYNER[2], E. FECZKO[3], E. EARL[4], D. A. FAIR[3], J. BACHEVALIER[1], ***M. SANCHEZ**[1];
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Abstract: Studies investigating the drastic cognitive, emotional, hormonal and neural changes during adolescence are crucial to understand the vulnerability for psychopathology during this developmental phase. The goal of this study was to investigate the role of pubertal maturation on developmental changes in stress, emotional and cognitive control neurocircuits and physical growth using a translational nonhuman primate model. We collected longitudinal data from 10 male macaques between pre-puberty (23 months) and early adolescence (peri-puberty: 32, 34 and 37 months of age). Testicular volume and physical growth measures (body weight, height) were collected at each timepoint. Structural and resting-state functional MRI scans were acquired at 23 and 34 months using a 3T MRI scanner to examine developmental changes in amygdala (AMY), hippocampus (HIPPO), prefrontal cortex regions (PFC, based on Brodmann Areas -BAs-) and intracranial volumes (ICV), as well as functional connectivity (FC) between these regions of interest (ROIs). We hypothesized that pubertal maturation would be a better predictor than chronological age for developmental changes in physical growth and in brain ROI volumes and FC. Testicular size and physical growth measures showed significant increases from pre- to peri-puberty (RMANOVA, $p<0.1$), but also high individual variability. Structural brain maturation - measured as ICV, AMY, HIPPO and dorsolateral PFC (BA9, 32) volume increases - was also detected, with hemispheric differences in the AMY and HIPPO (RMANOVA, $p<0.5$). Increased FC between left HIPPO and orbitofrontal cortex (BA11), but decreased FC in the right hemisphere (RMANOVA, AGExHEMISPHERE: $F(1,9)=6.897$, $p=0.028$) were detected. Interestingly, pubertal maturation (measured as testicular volume increases) was associated with only a few brain and physical changes: body weight increases (Pearson's r: 0.674, $p<0.05$) and with the whole PFC's volume decrease (Pearson's r: -0.865, $p<0.05$). Despite individual variability in physical growth and structural and functional brain changes, our results suggest that early pubertal maturation may trigger pruning-related remodeling in the PFC. We expect that other neural circuits critical for emotional and stress regulation and cognitive control will show pubertal-dependent maturation during later adolescence stages. Since our subjects are still young and some have not truly reached puberty yet -in male macaques it happens around 3-4 years-, we expect to see more drastic changes associated with pubertal progression (testicular growth, testosterone levels) and stronger associations with brain maturation at later ages.

Disclosures: Z. Kovacs-Balint: None. **J. Raper:** None. **R. Richardson:** None. **R. Hong:** None. **E. Morin:** None. **M. Pincus:** None. **L. Li:** None. **M.A. Styner:** None. **E. Feczko:** None. **E. Earl:** None. **D.A. Fair:** None. **J. Bachevalier:** None. **M. Sanchez:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.09

Topic: A.09. Adolescent Development

Title: Does morphine exacerbate complement dependent synaptic pruning to modify social development?

Authors: *D. NDAMBUKI[1], A. KOPEC[2];
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Abstract: Does morphine exacerbate complement dependent synaptic pruning to modify social development?Introduction: Morphine analgesics are administered annually to approximately 1 million adolescentseach year. Adolescent morphine treatment increases the risk of developing morphine-use disorder laterin life by 30%. Mechanisms to describe this increased vulnerability have primarily focused on the effectsof morphine on opioid receptors. However, little in the literature describes morphine induced-neuroinflammation. Morphine, additionally, is an agonist for the pattern recognition receptor Toll-likereceptor 4 (TLR4). TLR4 is enriched in microglia in the brain. Adolescence is a sensitive period forbehavior development. In pre-clinical models, adolescence is a period for sex-specific social behaviordevelopment via complement dependent synaptic pruning in the nucleus accumbens (NAc); aneuroimmune developmental process. Synaptic pruning is a function of microglia.**Hypothesis:** We hypothesize that adolescent morphine exacerbates complement dependent synapticpruning in a sex-specific manner leading to altered adult social behavior.**Methods:** Rats receive adolescent morphine during sex-specific complement dependent synapticpruning periods of the NAc. Afterwards adolescent synaptic pruning and adult social behavior arequantified.**Results:** Early data suggests that morphine modifies social behavior during the NAc complementdependent synaptic pruning period in a sex-specific manner.**Discussion:** This suggests that the NAc complement dependent synaptic pruning period is a criticalperiod for social behavior development.

Disclosures: D. Ndambuki: None. **A. Kopec:** None.

Poster

P899. Aging and Development--Animal Models III

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P899.10

Topic: A.09. Adolescent Development

Title: Application of electromagnetic field in alleviating aging-induced and diabetes-caused behavioral alterations in the neruonal motor system.

Authors: *J.-W. GAO;
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Abstract: Abstract Naturopathic medication is the newest approach to cure or prevent diseases, including adjusting the daily routine, physical therapy, or natural supplements. The theoretical mechanism is to prevent or slow the disease by reducing the body's free radical, oxidative stress, or inflammatory response. The magnetic field belongs to physical therapy and is usually driven by electric current to produce electromagnetic fields. It is a non-invasive and painless therapy with high patient acceptance. Previous studies have shown that electromagnetic fields stimulate bone cell repair to treat bone fractures, have an anti-inflammatory effect, and are commonly used to treat arthritis or eye inflammation and swelling. Thus, we want to know if low-frequency electromagnetic fields (MF) can improve the effects of disease-induced inflammation or oxidative stress on the nervous motor system. We adopted two disease models that usually cause neuron inflammation or oxidative stress, which are diabetes and aging. The diabetes animal model was achieved by using transgenic mice (KS.Cg-m+/+Leprdb/J (db/db) mice, db/db mice), and the aging animal model was accomplished by subcutaneous application of D-galactose (100 mg/kg) to the Sprague Dawley (SD) rats. The mice were divided into four groups: control (C57BL/6JNarl mice), control with MF, db/db, and db/db with MF; the SD rats were divided into three groups: control, D-gal, and D-gal with MF. The MF groups are exposed to a 1.8 mT magnetic field for 30 minutes per day. The diabetic animal model group was exposed to MF for 22 weeks, and the aging animal model group was treated for 28 weeks while aging is inducing at the same time. Motor neuro-behavior assessments are conducted every four weeks. In the diabetes animal model, we found that the performance of locomotor ability is significantly improved, especially in the lower limb. The tissue staining of muscle slicing also showed significant increases in the area of muscle fibers. Moreover, rising in the number of white blood cells due to diabetes has also improved in MF treated group. In the aging animal model, we found that MF improves the effectiveness of abnormal motor behavior caused by aging. Accordingly, it is assumed that MF can protect the nervous motor system by regulating oxidative pressure and immune response, thus maintaining normal muscle function.

Disclosures: J. Gao: None.

Poster

P976. Software Tools VI

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P976.01

Topic: I.07. Data Analysis and Statistics

Support: Swartz Foundation gift
NIH Grant 5R01NS047293-16

Title: HED-3G tool ecosystem for machine-actionable event annotation

Authors: *D. TRUONG[1], *D. TRUONG[2], *D. TRUONG[1], S. MAKEIG[2], A. DELORME[2], K. A. ROBBINS[3];
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Abstract: Current standards for storing and sharing neuroimaging data such as BIDS (Brain Imaging Data Structure) focus on dataset-level organization and only mandate the inclusion of minimal metadata. However, BIDS allows a much richer specification of machine-actionable experimental event description using Hierarchical Event Descriptors (HED). The HED system has recently undergone a major developmental revision, to HED-3G (K. Robbins, this meeting). HED-3G introduces a more user-friendly way of annotation, greatly increasing the usability of the framework. It also enables the documentation of experiment structure, including tasks, condition variables, and temporal structure as related to experimental events. HED-3G introduces the concept of Library Schemas that allows the expansion of HED to cover all types of time-series data experiments without obfuscating (or bloating) the base schema (S. Makeig, this meeting).
Our working group has been developing a collection of tools to support HED-3G, a key component to making the standard usable and *widely adopted*. Validation tools, which ensure consistency and compliance of dataset annotation, have been updated to support new features of HED-3G and have been integrated into analysis software such as EEGLAB in MATLAB. The graphical user interface tool CTagger guides users through the annotation process, providing hints and shortcuts to expedite event annotation. The EEGLAB *HEDTools* plug-in incorporates CTagger to annotate and perform HED-based analysis on EEGLAB datasets and studies.
HED-3G not only provides a more holistic and detailed way of understanding shared data, but also supports the prospect of automatically aggregating and jointly analyzing data from collections of HED-annotated datasets across laboratories, studies, and data repositories. HED-enabled data discovery requires ongoing development of HED tools for data, tools and compute resources such as the NEMAR portal (*nemar.org*) to OpenNeuro (*openneuro.org*). An important planned component is integration of HED tools with the metadata handling mechanisms of Datalad, the data management software layer underlying current major data portals including OpenNeuro. Future developments also include HED-enabled analysis tools for HED-enabled multiple regression, event-related context analysis, and advanced statistical and machine learning methods suitable for application to large-scale neuroimaging data.

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Poster

P976. Software Tools VI

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Program #/Poster #: P976.02

Topic: I.07. Data Analysis and Statistics

Support: FWF Grant W1233

Title: The use of Hierarchical Event Descriptors with fMRI

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Abstract: Data-sharing is becoming a more common practice in neuroscience. Currently, the majority of shared neuroimaging data consist of fMRI recordings. Many of these datasets include task-based fMRI, where participants engage with controlled sensory stimulation following task instructions. A major flaw is that these datasets are often minimally annotated. While these experiments can include complex events and event combinations, descriptions are often generalized on the level of conditions, at best allowing users to replicate the original analysis but leaving little opportunity to use more of the information about brain dynamics supporting cognition contained in the data to its full extent. The Hierarchical Event Descriptor (HED) system provides detailed and machine-actionable descriptions originally developed to describe neuroimaging experiments recording M/EEG data. HED has been applied successfully to EEG data to facilitate analysis across multiple datasets. Its current release (3G) provides a user-friendly environment for annotation of events using a sparse, human-readable tagging system (K. Robbins, this meeting), and several available tools facilitate annotation (D. Truong, this meeting). Applying HED to fMRI data is straightforward as fMRI and EEG experiments follow a similar structure. Despite the differences in the measured signals, both have similar requirements for analysis. By applying HED annotation to fMRI datasets researchers cannot only improve its reusability, but also benefit from the continuous development of HED-enabled tools that aid in developing and/or automatize parts of the data-analysis. Methods for fMRI analysis are developing rapidly; the use of multivariate rather than standard univariate analysis methods is increasingly common. Such experiments are particularly well suited for reanalysis, since they engage many aspects of cognition that can be linked to brain activity. Detailed information about these experiments, experiment events, and time structure is needed to use these valuable datasets to their full potential, and is also vital for helping researchers find relevant datasets in continuously growing databases. Applying the same HED standard to describe events and structure of fMRI and M/EEG experiments will also allow researchers to better connect results from these datasets on the basis of the underlying brain processes they record. Standardized, machine-actionable descriptors for data are vital to accelerating knowledge accumulation. HED-3G provides a framework for detailed description that is not only useful and necessary for M/EEG datasets, but equally so for fMRI data.

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Poster

P976. Software Tools VI

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Program #/Poster #: P976.03

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R24MH120037-02

Title: Meta- and mega-analysis of electroencephalographic data via the Neuroscience Gateway using the BIDS/HED framework in EEGLAB

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Abstract: EEGLAB is an interactive Matlab toolbox for processing continuous and event-related EEG, MEG, and other electrophysiological data incorporating independent component analysis (ICA), time/frequency analysis, artifact rejection, event-related statistics, and several useful modes of visualization of the averaged and single-trial data. EEGLAB integrates the Brain Imaging Data Structure (BIDS) standards and HED (version 3G) system for event annotation, allowing meta-analysis across a large corpus of datasets. The advantages of using the BIDS standards for analysis use and reuse are several. First, they do not rely on a complex database schema; they simply store data and relevant metadata in text and binary files within an ordinary file folder structure. Second, BIDS text files are both human and machine-readable, making it easier for new users to examine. BIDS data may be imported directly into EEGLAB for processing as an EEGLAB study (a group of related EEG datasets). BIDS allows defining time-marked data events using dedicated text files that can contain detailed event information using the Hierarchical Event Descriptor (HED) system that is currently being upgraded to its third generation (HED-3G). Here we demonstrate an EEGLAB pipeline processing multiple BIDS-formatted, HED-3G-annotated datasets made publicly available on OpenNeuro.org and NEMAR.org. The pipeline imports BIDS datasets, preprocesses the data and extracts data epochs of interests based on HED tags in common across (here) BIDS-formatted datasets from different experiments and laboratories. We then process the data using the Neuroscience Gateway (nsgportal.org) platform using the EEGLAB nsgportal plug-in. The Neuroscience Gateway (NSG) project facilitates neuroscientist access to and use of National Science Foundation (NSF) funded high performance computing (HPC) resources. As a simple demonstration, we compute a 'target' event-related potential containing a P300 positivity, by averaging event-related data epochs collected from more than one experiment. We discuss the planned incorporation of BIDS and HED tools in the NEMAR.org data, tools, and compute resource.

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Title: Brain Imaging Data Structure (BIDS) compatible Hierarchical Event Descriptor (HED) library schema for clinical (i)EEG data annotation

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Abstract: Sharing data in standardized, reproducible formats enables powerful mega-analysis that advances neuroscience and informatics. In particular, in the clinical setting of epilepsy research which must deal with many different data formats acquired and analyzed using various software packages, the standardization of clinical terminology holds great potential. The Brain Imaging Data Structure (BIDS) has moved these standardization efforts forward for neuroimaging data. Within BIDS, there are clearly defined extensions for combining many different data types acquired in neuroimaging studies. The Intracranial Electroencephalography (iEEG) extension standardizes the data and metadata storage and the description of events during an iEEG recording. Additionally, BIDS has accepted the Hierarchical Event Descriptors (HED) system for detailed data and experiment event annotations. The new HED-3G schema library concept gives researchers the option to extend the base HED schema vocabulary by supporting the use of specialized vocabularies to describe events of specific interest to their field adequately. In this study, we developed a HED schema library for the Standardized Computer-based Organized Reporting of EEG (SCORE). SCORE is a textual description now implemented in commercial software for annotating EEG and ictal clinical events using standardized terms to create a standardized report. Our SCORE implementation in HED tackles these textual reports' lack of machine readability and makes SCORE available for and machine-readable by open-source software. To further make epilepsy terms available within BIDS, we use the HED convention to enrich BIDS datasets with epilepsy classification and seizure onset zone terms. These efforts, including a HED schema library for the SCORE standard to annotate events and features, including epilepsy classification and seizure onset zone, support the machine-readability of clinical annotation. These tools can be used by many researchers worldwide alongside other standard machine-readable formats for data sharing using standard definitions, to reduce errors in clinical evaluations, and to perform advanced mega-analyses, ultimately advancing the understanding of the human brain.

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Topic: I.07. Data Analysis and Statistics

Support: The Swartz Foundation

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Title: Extending HED-3G event annotation using Library schemas

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Abstract: A major current gap in standards for storing and sharing any neuroimaging time series data is a system for detailed description of experiment events. The Hierarchical Event Descriptor (HED) system, first proposed a decade ago by Nima Bigdely-Shamlo (2012), has recently undergone a major developmental revision to HED-3G (K. Robbins, this meeting), whose architecture and syntax is now based on a root schema (set of supported terms) and syntax, plus a provision for extending the annotation vocabulary established by the root schema using specialized HED Library Schemas. HED Library schemas are designed to eliminate the need for the root HED schema to grow unwieldy, and to promote incorporation of maximally efficient and accepted sets of terms for use by the relevant research communities who build and maintain them. Thereby, HED-3G can be made suitable for annotating all types of time-series data and experiments. For example, annotations of neuroimaging datasets recording brain activity during performance of language tasks will require terms such as noun, verb, dependent-clause, etc., defined in a Language library schema. One HED library schema under development incorporates terms from the international standard SCORE vocabulary for clinical reporting of human scalp EEG data features (T. Pal Attia, this meeting), including terms such as ‘sleep spindle’, ‘interictal spike’, ‘alpha burst’, etc. Four more HED library development projects are now planned or underway: one for experiments involving viewing Moving-Pictures, a second for annotating events in Story-Narratives (presented in either text, audio, or audiovisual formats), a third for annotating Spatial-Relationships, and a fourth for describing Task-Design. Other research community areas needing development include: Human-Anatomy, Health-Disease, Human-Kinematics, Rodent-Kinetics, Sport, Virtual-reality, Music, Driving, etc. HED-3G is designed to work efficiently with data stored per the BIDS (Brain Imaging Data Structure) or other archiving frameworks. As the amount of shared, well-annotated neuroimaging data accumulates, the foreseen rewards of identifying new information by applying machine learning and related methods to large, inhomogeneous neuroimaging data collections can be realized. Leveraging this technology to apply statistical machine learning methods to large collections of well-annotated neuroimaging data, cognitive neuroscience researchers should be able to identify yet unknown patterns of behavior-related brain dynamics and apply the results in healthcare and other application areas.

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Topic: I.07. Data Analysis and Statistics

Title: Rapid spatiotemporal analysis of astrocytic calcium dynamics using deep learning

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Abstract: Astrocytic intracellular calcium dynamics convey key information about both local synaptic function and distributed activity of neuronal networks. However, available methods to analyze astrocytic calcium data are slow and they extensively rely on user-defined parameters, limiting reproducibility and scalability of the workflow and preventing closed loop experimental approaches. Moreover, automated segmentation methods for the analysis of neuronal calcium signals cannot be readily applied to the segmentation of astrocytic calcium dynamics, because of the intrinsic anatomical and functional differences between neurons and astrocytes. Therefore, the development of a fast, precise, and fully automated image segmentation method to analyze astrocytes calcium dynamics is of utmost importance. Here, we present Rapid Astrocytic Spatio-Temporal Analysis (RASTA), a novel software for spatiotemporal semantic segmentation of astrocytes. RASTA combined deep learning algorithms with feature engineering of calcium data and operated without human intervention. In two-photon calcium imaging movies from *in vivo* recordings, RASTA achieved fast and precise identification of astrocytic cell somata, processes, and cellular domains showing correlated calcium dynamic. We validated RASTA on multiple two-photon imaging datasets against human manual annotation, obtaining near-human performance in astrocyte detection and segmentation. Moreover, when detecting and segmenting astrocytic regions of interests RASTA performed better compared to state-of-the-art algorithms for the analysis of astrocytic and neuronal calcium imaging data. Overall, RASTA is an end-to-end analytical tool providing fast, automated, and accurate semantic segmentation of astrocytes two-photon imaging data, which will facilitate the analysis of astrocytic calcium signals *in vivo* and will enable new experimental approaches.

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Title: Comparison of manual, semi-automatic and fully automatic counts of immunostained neurons in mouse brains

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Abstract: Enhanced morphometric methods allow for accelerating hypothesis testing and preclinical drug studies focused on neurological disorders and mental illnesses. In this study, we assessed the performance of fully manual, semi-automatic and fully automatic methods for quantifying total number of neurons in digital images from an anatomically well-defined region of the mouse brain. Stacks of digital images 1-um apart (disector stacks) were automatically collected at systematic-random locations in the neocortex (NCTX) of NeuN-immunostained sections from the Tg4510 transgenic mouse model of tauopathy (n=3) and age- and sex-matched littermate controls (n=3). Manual stereology-based estimates of total neuron number in NCTX were done by trained technicians counting (clicking on) neurons while scanning through the digital planes of each disector stack [i.e., manual optical disector (MOD)]. These MOD counts provided the gold standard for assessing the performance of 5 methods applied to extended depth of field (EDF) images created from the same disector stacks, including two automatic methods [deep learning (DL) and adaptive segmentation algorithm (ASA)]; two semi-automatic methods (DL, ASA) each followed by manual correction for over-counts (false positives) and under-counts (false negatives); and one Active DL approach in which images from automatic DL counts were user-corrected and the corrected images used for further training of the DL model. Manual counts on disector videos created from disector stacks were compared for accuracy, inter-rater agreement and throughput efficiency to neuron counts using MOD on the same disector stacks. Overall, there was a significant 61% difference in mean total number of NeuN-immunostained neurons in NCTX of Tg4510 mice compared to non-Tg controls ($p < 0.02$). The DL-based semi-automatic and fully automatic methods showed comparable results, but with >5x and >10x enhanced efficiency, respectively, as compared to neurons counts using the MOD. At an optimal speed of 1 frame per second, disector videos allowed for neuron counts with 100% agreement to the MOD method in less than half the time. We conclude that DL-based stereology counts of immunostained neurons on digital images can achieve comparable results to manual stereology on digital images with substantially higher efficiency and without the need for labor-intensive, subjective manual counting by well-trained technicians. An added benefit of digital images for stereology studies is that a record of cells counts is created for validation, training, and archival purposes.

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Poster

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Title: Global Estimates of Microglial Cell Numbers using Deep Learning

Authors: *H. MORERA[1], P. DAVE[1], D. GOLDGOF[1], L. O. HALL[1], Y. KOLINKO[2], K. ALLEN[1], S. ALAHMARI[3], R. ALBAY, III[4], A. BECKER[4], W. C. MOBLEY[4], P. R. MOUTON[5];
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Abstract: There is a large and growing need for computer-assisted methods to accelerate the testing of hypotheses associated with neuroinflammation in normal aging, neurological disease, neurotoxicology, and other conditions. The combination of artificial intelligence-based deep learning (DL) and unbiased stereology provide an innovative strategy for accurate, reproducible, and high-throughput quantification of stained biological structures in tissue sections. Previous work emphasized the automatic optical fractionator: automatic detection (cell-level segmentation) with fractionator-based estimation of total cell number at high magnification (100x). Here we use DL to automatically classify global changes in total number of Iba-1 immunostained microglial cells based on training with cell densities at low magnification (20x). Specifically, we tested if a DL model could predict high verses low total number of microglial cells in the neocortex (NCTX) of the Dp16 mouse model of Down syndrome (i.e., trisomy Hsa21) in which the APP gene is overexpressed versus sex- and age-matched littermate controls. A computerized stereology system (Stereologer, SRC Biosciences, Tampa, FL, USA) was used to quantify relatively high (n=7) or low (n=7) total number of microglia cells using the ordinary (manual) optical fractionator at 100x magnification. Second, we imaged a minimum of 380 low magnification fields of microglia cells at systematic-random locations in a minimum of 15 sections through NCTX of each brain (2660+ total images with low and high mean cell densities). After center cropping to remove lens distortion and regions outside the NCTX, the images were used to train a DL model evaluated by cross validation using n=6 cases of each group for training with 1 case from each group for validation. All training images were labeled according to the total microglial estimate in NCTX (i.e., global label). For automatic classification, if the DL model predicted over half the images from a brain belonged to one class (high or low density), the brain was assigned to that class. The findings showed the DL model correctly predicted the global class (high vs. low number) of microglial cells in 80% of the cases (i.e., 11 of 14 correct, 78.6%) based on microglial cell densities in low magnification images. Thus, a DL model trained with low magnification images of microglia cells can automatically predict two extremes (low vs. high) for the total microglial cell number in NCTX without cell-level segmentation or manual stereology at high magnification. Further accuracy and a more robust model are expected after training with more low-, middle-, and high-density images from additional animals.

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Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1926990. **D. Goldgof:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1926990. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent # 11,404,199. **L.O. Hall:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1926990. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent # 11,404,199. **Y. Kolinko:** None. **K. Allen:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1926990. **S. Alahmari:** None. **R. Albay:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH RO1AG055523-01A1. **A. Becker:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH RO1AG055523-01A1. **W.C. Mobley:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH RO1AG055523-01A1. **P.R. Mouton:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSF 1926990. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent # 11,404,199.

Poster

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Title: A Novel Automatic Approach for Total Neuron Counts using the Unbiased Disector Method

Authors: *P. DAVE[1], D. GOLDGOF[1], L. O. HALL[1], Y. KOLINKO[2], K. ALLEN[1], S. ALAHMARI[3], H. MORERA[1], G. DENHAM[1], S. GALVEZ[1], A. BECKER[4], R. ALBAY[4], W. C. MOBLEY[4], P. R.

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Abstract: Disector-based stereology methods provide an unbiased approach for quantifying the number of well-stained biological objects in tissue sections. Artificial intelligence (AI) may be used to automate these approaches for improved efficiency, repeatability, and reduced error and subjectivity due to human factors. Current state-of-the-art methods for AI-based cell quantification rely on Extended Depth of Field (EDF) images created by converting a disector volume containing a z-axis stack of digital images (disector stack) into a synthetic 2D image showing all stained objects (neurons) at their maximal plane of focus. A limitation of all cell counting methods (AI or non-AI) on EDF images is the possibility of under-counts due to masking, i.e., overlapping cells or smaller cells occluded by larger cells in the z-plane. Here we propose an automatic disector-based approach using a multichannel input and multichannel output (MIMO) U-Net deep learning (DL) model. The MIMO model avoids masking errors by automatic z-axis scanning through the individual planes of each disector stack combined with cell counts obtained using the optical disector principle and unbiased counting rules. Each focal plane (image) in a disector stack serves as an input channel to the DL model and each segmented cell is counted only once (in its best focus plane) as output. Like the manual optical disector, the MIMO approach automatically counts each cell through a known tissue volume without bias due to the cell's size, shape, or orientation. We applied the MIMO model to counting neurons in tissue sections through the neocortex (NCTX) of the Dp16 mouse model of Down syndrome (i.e., trisomy Hsa21) in which the APP gene is overexpressed versus sex- and age-matched littermate controls. The results show similar counts to manual disector counts of the same disector stacks by multiple experts, with higher repeatability and improved throughput efficiency than manual counts. Furthermore, the proposed approach is highly efficient in terms of computational cost and training data requirements. Moreover, it requires no additional expert time for Ground Truth preparation as compared to the state-of-the-art AI-based cell counting. We present results for the total number of NeuN-immunostained neurons in the mouse NCTX together with results for tuning the same model for automatic counts of another population of immunostained neurons (ChAT-immunostained neurons in the basal forebrain). Thus, automatic quantification of immunostained neurons using a combination of DL and unbiased stereology can be achieved with comparable or enhanced accuracy compared to manual counts using disector-based methods.

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Poster

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Title: Enhancements to the NWB Data Standard and Software Ecosystem for Neurophysiology

Authors: *R. LY[1], P. M. BAKER[2], B. DICHTER[3], A. TRITT[1], M. AVAYLON[1], S. GHOSH[4], L. NG[2], O. RUEBEL[1];
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Abstract: Neurodata Without Borders (NWB) is a community-driven data standard that provides neuroscientists with a common format to share, archive, use, and analyze neurophysiology data. NWB supports a wide range of neurophysiology data and metadata, including from intracellular and extracellular electrophysiology and optical physiology experiments. After the initial release of NWB 2.0 in 2019, we have made significant enhancements to the standard and software ecosystem. First, to enhance FAIR data sharing, we have extended NWB to support the integration of ontologies and

controlled vocabularies. Users can now associate metadata/data in an NWB file, such as the subject's species and genotype, with persistent identifiers in external ontologies, such as the NCBI Taxonomy database and the Mouse Genome Informatics database. Second, we have extended NWB to formalize the description of the hierarchical organization of intracellular electrophysiology experiments. Users can now store metadata about simultaneous and sequential recordings, repetitions, and experimental conditions in a structured tabular way in NWB. Third, because neurophysiology data is often large, downloading complete NWB files from online archives can be expensive and ultimately hinder reuse of valuable data. To address this challenge, we have developed new methods for streaming select data and metadata from NWB files stored in the cloud. Users can now open NWB files from S3 data stores (e.g., the DANDI data archive) remotely using standard NWB APIs, and then load selected slices of large NWB data arrays from the DANDI S3 bucket for interactive exploration, visualization, and analysis in the cloud, without having to download the entire file. Finally, we present our progress toward dissemination and integration of NWB across the neurophysiology community, and our vision for NWB over the next five years.

Disclosures: R. Ly: None. **P.M. Baker:** None. **B. Dichter:** None. **A. Tritt:** None. **M. Avaylon:** None. **S. Ghosh:** None. **L. Ng:** None. **O. Ruebel:** None.

Poster

P976. Software Tools VI

Location: Virtual Only

Time: Thursday, November 11, 2021, 9:45 AM - 10:45 AM

Program #/Poster #: P976.11

Topic: I.07. Data Analysis and Statistics

Support: NIMH/NIH Grant R24MH116922

Title: Modeling Patch-seq experiment data using ontologies in NWB

Authors: *P. M. BAKER[1], R. LY[2], M. AVAYLON[2], A. TRITT[2], P. RAY[1], T. GILLESPIE[3], O. RUEBEL[2], L. NG[1];
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Abstract: The term 'Patch-seq' refers to the combined application of whole-cell patch clamp recording and single-cell RNA-sequencing (scRNA-seq) to individual cells which can additionally include high resolution morphological imaging and reconstruction. Patch-seq links cell structure and function; correlates cell phenotype with gene expression profiles; and automation of the technique has facilitated large-scale collection of data for cell census and atlasing efforts such as the BRAIN Initiative Cell Census Network (BICCN: https://biccn.org). Patch-seq datasets shared online, including those at the BICCN and through the Allen Institute online portal (https://portal.brain-map.org), are of great value to the broader community. To enable reuse, it is essential to conform with FAIR principles through the use of common controlled vocabularies, integration of consensus knowledge in the form of ontologies, and robust links to definitions, reagents, protocols, and associated datasets through persistent identifiers (PIDs). Neurodata Without Borders (NWB: https://nwb.org) is a unified data format that provides a comprehensive standard for storing electrophysiological data including the intracellular recordings generated by Patch-seq. As a

community standard for data and metadata storage, NWB is committed to adhere to the FAIR principles for data sharing. Rigorous descriptions of experimental methods and other metadata are critical for facilitating the uses of publicly shared data, including replicating protocols, applying novel analysis techniques, and enabling dataset comparison and search. In this work we extend the NWB standard to include links to the external resources and PIDs that are a critical component of FAIR data sharing, with the goal of facilitating the reuse of large datasets such as the Patch-seq data stored at the DANDI archive (https://dandiarchive.org). We implemented schema extensions to NWB to support integration of external resources and PIDs and will demonstrate their use with examples from Patch-seq datasets hosted at DANDI. The new schemas include data structures for storing genotype metadata including animal strains, gene loci, and alleles that are essential for describing experimental subjects. We also extended NWB to use a recently developed stimulation ontology to support rigorous description of the stimulus waveforms used in these experiments. Finally, we show how spatial location metadata (coordinates, structural annotations, and anatomical terms) from reference atlases can be stored in NWB.

Disclosures: P.M. Baker: None. **R. Ly:** None. **M. Avaylon:** None. **A. Tritt:** None. **P. Ray:** None. **T. Gillespie:** None. **O. Ruebel:** None. **L. Ng:** None.

Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.01

Topic: A.03. Stem Cells and Reprogramming

Support: NIH NIEHS SBIR grants 1R43ES029898-01A1, 1R43ES029897-01 and 1R43ES029897-01S1

Title: Induced pluripotent stem cell-derived neural organoids generated on synthetic hydrogels for assessment of neural inflammation and toxicity

Authors: *J. ZIMMERMANN, W. RICHARDS, S. VISURI, C. LEBAKKEN;
Stem Pharm Inc, Madison, WI

Abstract: While animal models have value in drug discovery and toxicology applications, they also have many limitations including translation, cost, and ethical concerns. There is a critical need to develop advanced neural microphysiological systems (MPS) that complement or reduce the use of animal models. Most current *in vitro* models, however, do not adequately reflect the complexity of non-neural cell types and cell-cell interactions found within neural tissue. To address these limitations, Stem Pharm has developed synthetic hydrogels that enable the formation of complex, reproducible iPSC-derived neural organoids containing microglia and vascular cells. Organoids are generated in 96-well plates and ready for screening within one month and high intraclass correlation and low coefficients of variation are observed between biological replicates through RNA-seq analysis. The organoids are cell-type diverse; single-cell RNAseq analysis demonstrates organoids are comprised of multiple neuron types, astrocytes, microglia, and endothelial cells. Microglia express over 95% of core signature gene sets of primary human microglia and microglial activation within organoids was validated through stimulation with

lipopolysaccharides, interferon gamma, TGFβ & IL-10, or IL-4 & IL-13 to activate inflammatory or alternatively activated phenotypes. To demonstrate application for toxicology screening, organoids were subjected to a screen of known neurotoxins: chlorpyrifos, an organophosphate insecticide; lead acetate, known to cause developmental defects; valproic acid (VPA), an anti-convulsant; and PLX-3397 a CSF-R inhibitor. Transcriptional data and differential expression (DE) analysis between treatment groups was utilized to identify gene ontology (GO) sets affected by compound treatment. We detected perturbations in expected pathways including neural development, axon guidance, and mitochondria upon exposure to chlorpyrifos, depletion of microglia with PLX-3397 treatment, and response to metal ion and toxin and metallothionine production to lead treatment. Lead and VPA treatment also resulted in downregulation of GO sets involved in inflammatory and innate immune responses and microglial-specific genes, demonstrating the importance of using multicellular systems to assess toxicities. These preliminary data demonstrate the promising application of Stem Pharm's neural organoids for toxicology screening in complex multicellular systems and broader potential for facilitating translation between pre-clinical and clinical discovery and development.

Disclosures: J. Zimmermann: A. Employment/Salary (full or part-time):; Stem Pharm. **W. Richards:** A. Employment/Salary (full or part-time):; Stem Pharm Inc. **S. Visuri:** A. Employment/Salary (full or part-time):; Stem Pharm Inc. **C. Lebakken:** A. Employment/Salary (full or part-time):; Stem Pharm Inc.

Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.02

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant RF1 MH 123978-01
Kavli Institute for Neuroscience at Yale Engineering of organoid-based brain circuits

Title: Human iPSC-derived brain organoids regional specification in a mesofluidic device

Authors: *S. SCUDERI[1], T.-Y. KANG[2], A. JOURDON[1], L. YANG[2], A. LEVCHENKO[2], F. M. VACCARINO[1,3];
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Abstract: Morphogen gradients play a critical role in directing cell fate specification during development but are not yet implemented by current *in vitro* human organoid models. Among these, the WNT and SHH are crucial for the development of posterior and ventral regions in the brain. Human brain organoids recapitulate early cellular and molecular mechanisms of brain development as well as histological features (e.g. ventricle-like structures), but they lack spatial topographical organization. Here we introduce a new method to model early neural tube patterning by using human induced pluripotent stem cells (iPSC)-derived organoids exposed to continuous and spatially defined gradients inside a mesofluidic chamber (5c-orthoDev). We hypothesized that the introduction of oriented signaling centers over a culture system of brain organoids would allow the organized specification of their identity in a distance-dependent manner. Our gradient patterning device has the advantage of not relying on externally driven

flow, but only on short-range diffusion, simplifying the approach and offering a wide range of applications. We also developed a compatible hydrogel matrix which ensures both the spatial stability of the organoids exposed to orthogonal gradients and allows their transfer in standard open cultures after the regionalization. We demonstrate that this brain-on-a-chip platform serves to spatially control cellular fate decisions. We used a potent activator of Wnt signaling, CHIR99021, and, on a perpendicular axis, the canonical ventral morphogen SHH in our 5c-orthoDev device to generate brain organoids spatially defined not only along the antero-posterior axis, as demonstrated by gene networks specific for forebrain (FOXG1, LHX2, SIX3), midbrain (WNT1, EN1) and hindbrain (GBX2, IRX3), but also along the dorsal-ventral axis as demonstrated by dorsal (GLI3, PAX6) and ventral markers (DLX1, NKX2.1 and NKX6.1). This practical and versatile device will facilitate research on factors and molecular cascades that mediate primary brain and neural tube patterning, as well as secondary organizing centers formation, like the isthmic organizer. Finally, the ability to separatly obtain multiple brain regions, at once, in a simple protocol will further facilitate the generation of assembloids and the investigation of the connectome in normal and diseased iPSC lines.

Disclosures: S. Scuderi: None. **T. Kang:** None. **A. Jourdon:** None. **L. Yang:** None. **A. Levchenko:** None. **F.M. Vaccarino:** None.

Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.03

Topic: A.03. Stem Cells and Reprogramming

Support: DGAPA/PAPIIT/UNAM IA210620
CONACYT PhD Student Fellowship
CONACYT Postdoctoral Fellowship

Title: Generation of cerebral organoids from dental pulp stem cells to model neurodegeneration

Authors: A. GUTIERREZ-MALACARA, M. SILVA-LUCERO, G. LOPEZ-TOLEDO, *M. CARDENAS-AGUAYO;
Physiology, Sch. of Med., Natl. Autonomous Univ. Mexico, Ciudad de Mexico, Mexico

Abstract: Introduction: Cerebral Organoids (CO) are a recently described 3D-cell cultures that shows more complex process in an *in vitro* environment as compared to monolayers. CO mimic molecular changes seen in diseases such as Alzheimer´s disease. Most of the CO are generated from Induced Pluripotent Stem Cells (iPSC) or human Embryonic Stem Cells (hESC). However, Dental pulp Stem Cells (DPSCs) could be a suitable source to generate CO, with the advantage, to model neurodegeneration when obtained from affected patients. DPSCs have proved to be capable of differentiating into several phenotypes, including neuronal. The aim of this study was to differentiate DPSCs obtained from a healthy donor into an organoid-like structure with a neuronal phenotype. **Methods:** The DPSCs were obtained by dissociation of the dental pulp of a healthy 46 years old female, with a colagenase-dispase mix at 37ºC, isolated and cultured. The cells phenotype was characterized by Western-Blot, RT-PCR and

immunofluorescence staining. We placed the DPSC into low-adherence wells for 6 days in a DMEM/F12 + thiazovivin 50 mM, bFGF 4ng/mL, FBS 20%, Glutamax 200x, MEM-NEAA 1:100, 2-mercaptoethanol 100 µm and murine LIF 10 µg/mL until cell aggregation into embryoid-like structures. Thereafter, neural induction was carried out in DMEM/F12 + N2 1%, Glutamax, MEM-NEAA and heparin 1 µg/mL for 48 hours, and then transferred into a Geltrex matrix to form droplets which were placed into a cerebral organoid differentiation medium composed by DMEM/F12, Neurobasal medium 50%, N2 1%, ITS 0.01%, Glutamax 1x, MEM-NEAA 1%, penicillin-streptomycin 1x, 2-mercaptoethanol and B27 without retinoic acid 1x. Finally, the obtained cerebral organoid-like structures were immunostained against MAP2, NeuN, β-III Tubulin and Tau. **Results:** We characterized the DPSC phenotype by detecting pluripotential markers: OCT4, Actin, Nanog, mesenchymal markers: CD105, CD73 and the neuronal marker: β-III Tubulin which is always present in the DPSCs lineage, as well as the lack of hematopoietic markers: CD14, CD34 and CD45. We obtained CO-like structures from de DPSCs after 35 days of the differentiation protocol and detected NeuN, Map2, β-III Tubulin and Tau. **Conclusion:** Our results suggest a potential use of DPSCs CO to model neurodegenerative disease, instead of iPSC or hESC with the benefits of a simple and less expensive protocol, thus DPSCs could reflex the molecular changes associated to aging, such as DNA damage, free radicals, shortening of telomeres an micro RNA's regulation mechanisms that cannot be studied using hESC. Further studies need to be done to fully characterize this model and its potential clinical applications.

Disclosures: A. Gutierrez-Malacara: None. **M. Silva-Lucero:** None. **G. Lopez-Toledo:** None. **M. Cardenas-Aguayo:** None.

Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.04

Topic: A.03. Stem Cells and Reprogramming

Support: Dutch ZonMw Create2Solve initiative

Title: Myelination and inflammation cortical network platform for high content screening: 3D MICro-brains

Authors: M. VAN DER KROEG[1], S. BANSAL[1], V. WONG[2], D. A. EGAN[2], S. A. KUSHNER[1], *F. M. S. DE VRIJ[1];
[1]Psychiatry, Erasmus MC, Rotterdam, Netherlands; [2]Core Life Analytics, 's-Hertogenbosch, Netherlands

Abstract: Recent developments in induced pluripotent stem cell (iPSC) technology make it possible to implement cell-type-specific human cell culture models for research and drug development. Here, we present a 3D model with human neural networks that recapitulate the complex structure of the frontal brain in early development. These micro-brains (3D MICro-brains) reduce the modelling of the frontal cortex to a millionth of the normal brain volume. The platform contains all major brain cell types: functional neurons and glia in layered radial structures, along with astrocytes, myelin-producing oligodendrocytes and microglia. The 3D MICro-brain differentiation protocol is based on our recently

published widely recognized protocol to derive functionally mature synaptic networks of human iPSC neurons. Briefly, iPSCs are differentiated to form neural progenitor cells (NPCs) using an embryoid-based method creating NPCs with a frontal cortical identity. Importantly, this protocol was specifically designed to create both neuronal and glial cell types from a common iPSC-derived forebrain neural progenitor, without the need for rodent astrocyte co-culture. The result is a neural network that is fully derived from a single individual. We have now expanded this protocol to develop functional adherent cortical organoids in standard 384-well plates. These cortical organoid cultures develop spontaneously from NPCs and show radial outgrowth, including neurodevelopmentally timed formation of segregated cortical layer markers, highly reminiscent of early human neurodevelopment of the cerebral cortex. We have now further enhanced this model by implementing human iPSC-derived myelinating oligodendrocytes and functional microglia that fully integrate into the structures, creating the 3D MICro-Brain platform that is suitable for the study of myelination and inflammation in human adherent cortical brain organoids. Due to its scale and reproducibility, the 3D MICro-brain platform is ideally suited for automated high-content (HC) imaging. Together with Core Life Analytics, we have developed a robust and practical HC workflow that combines automated microscopic imaging, image analysis and advanced data analytics for phenotypic studies. This platform will be useful for toxicological and nutritional screening, as well as therapeutic target and drug development.

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Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

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Program #/Poster #: P017.05

Topic: A.03. Stem Cells and Reprogramming

Support: FETPROACT-2018-2020 HEREMES [grant number 824164]
Fondazione Telethon–Italy (Grant Number GSP20004_PAsMCT8006)

Title: Development of robust and reproducible murine brain organoids endowed with networks of functional neurons and specific brain-region signature

Authors: F. CIARPELLA[1], R. G. ZAMFIR[1], A. CAMPANELLI[1], E. REN[2], G. PEDROTTI[1], E. BOTTANI[1], A. BORIOLI[1], D. CARON[3], M. DI CHIO[1], *S. DOLCI[1], A. AHTIAINEN[4], G. MALPELI[1], G. MALERBA[1], R. BARDONI[2], *G. FUMAGALLI[1], J. HYTTINEN[4], F. BIFARI[5], G. PALAZZOLO[3], G. PANUCCIO[3], G. CURIA[2], I. DECIMO[1];
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Abstract: Brain organoids are in vitro three-dimensional (3D) self-organized neural structures, which have been used for several applications, including the study and mimicking of brain development, the modeling of neuronal disorders and their employment in preclinical drug screening tests. A fine in vitro modulation of specific molecular cues enabled the generation of a broad range of cerebral organoids,

either resembling macro brain identities (e.g. whole-brain organoids) or specific brain regions (e.g. cortical organoids). So far, organoids were obtained from human induced pluripotent stem cells (hiPSCs) but the high batch-to-batch variability, long differentiation time (10-20 weeks), and high cost required for production limit their use for standardized large-scale studies. We developed, for the first time, a highly standardized, reproducible and fast (5 weeks) murine brain organoid model starting from multipotent neural stem cells (NSCs) isolated from embryonic subgranular zone (SGZ). Global transcriptome, protein expression, and cell metabolism data showed that murine brain organoids progressively differentiate trough defined early, intermediate, and mature stages. During differentiation, brain organoids acquire a self-organized neural structure with a compact and interconnected neuronal layer at its edge. Functional neuronal properties measured by electrophysiological techniques (patch-clamp and MEA recordings), transsynaptic tracing and calcium imaging analysis revealed that organoids own functional neurons organized in 3D networks with synaptic connections. Furthermore, we validated the potential of murine brain organoids to acquire a specific brain-region signature; by adding the morphogen WNT3a, we were able to generate brain organoids enriched in neurons with CA3 hippocampal region signature. Overall, our results showed the establishment of a novel fast, robust and reproducible murine 3D in vitro brain model that may represent a useful tool for high-throughput drug screening and disease modelling. The possibility to obtain functional mouse hippocampal organoids could be further exploited as an innovative cell source for transplantation procedures and regenerative purposes in pathological conditions, such as epilepsy.

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Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.06

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R21EY030727

Title: Neurophotonics and transparent graphene microelectrode arrays for multimodal monitoring of human cortical organoid xenografts

Authors: *M. THUNEMANN[1], M. N. WILSON[3], X. LIU[3], Y. LU[3], F. PUPPO[4], J. ADAMS[4], J.-H. KIM[3], H. D. RICKNER[2], E. P. BORTZ[1], D. P. PIZZO[5], S. DJUROVIC[6], O. A. ANDREASSEN[7], A. A. MANSOUR[8,9], B. L. WOLOZIN[2], X. HAN[1], F. H. GAGE[8], A. R. MUOTRI[4], A. DEVOR[1,10], D. KUZUM[3];
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Inst., La Jolla, CA; [9]Dept. of Med. Neurobio., The Hebrew Univ. of Jerusalem, Ein Kerem-Jerusalem, Israel; [10]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Cortical organoids, three-dimensional neuronal cell cultures derived from human induced pluripotent stem cells, have recently emerged as promising models of human brain development and dysfunction. However, lack of oxygen and nutrients often renders the organoid core necrotic, interfering with further maturation. Therefore, organoids have been implanted into mouse brain, where they were vascularized, which enabled further growth and development, including generation of functional synapses between xenograft and host neurons (Mansour, et al., 2018, Nat Biotech 36: 432-41). This approach enables longitudinal studies, for which effective multimodal recording technologies are crucial. Here, we demonstrate multimodal monitoring of human cortical organoids transplanted into mouse cortex using transparent graphene microelectrode arrays and two-photon imaging. We implanted single organoids into the retrosplenial cortex of adult NOD/SCID mice, placed a graphene array bonded to coverglass on top of implant and surrounding host cortex, and monitored the implant using electrophysiology and two-photon imaging over 11 weeks. We performed recordings of both local field potentials and multi-unit activity during spontaneous activity and in response to sensory stimulation. As the implantation site is close to visual cortex, we were able to record electrical activity in host cortex and organoid implant in response to photic stimulation of the contralateral eye. Low-pass filtered signals followed the stimulation frequency, but we also observed a stimulus-locked frequency component at ~80 Hz. In high-pass filtered data, we observed spontaneous activity in host and implant and responses to individual light pulses, likely reflecting multi-unit activity. Isoflurane anesthesia of the host led to stronger suppression of ongoing gamma activity in the organoid implant than in surrounding host cortex. In two-photon imaging with intravascular Alexa 680-Dextran, we observed vessel regrowth within the implantation site. Imaging of organoid implants transduced with fluorescent protein-encoding adeno-associated virus before implantation showed sustained transgene expression over 11 weeks. We performed immunohistochemistry at the end of the study; staining of human cell nuclei revealed some variability in xenograft size across animals while staining of endothelial cells confirms vascularization of the implant. This novel combination of stem cell and neurorecording technologies provides a unique opportunity for comprehensive evaluation of the development, maturation, and functional integration of human neuronal networks within the mouse brain.

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Poster

P017. Advances in Neural Stem Cell and Organoid Techniques

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P017.07

Topic: A.03. Stem Cells and Reprogramming

Title: Generating Neural Organoids with Anatomically Distinct Identities

Authors: *R. MOTAHER, J. TANCREDI, M. DERR, A. IBRAHIMI, B. SCOTT, R. E. JOSEPHSON, S. SHIN;
Res. and Develop., Thermo Fisher Scientific, Frederick, MD

Abstract: While organoid development is not new technology, generating neural organoids with specific developmental identities in an efficient manner remains a challenge. Previously we reported a protocol to generate organoids with hindbrain and midbrain specific identities using our established kit. Here we report a protocol to generate organoids with forebrain specific identity. While most protocols in circulation require over 40 days to generate neural organoids, we established a novel protocol to obtain cortical organoids with forebrain specific identity, within 28 days. Large scale PSC culture either in defined medium (Essential 8, Essential 8 Flex), or in enriched medium (StemFlex, StemScale) can be differentiated into a forebrain phenotype and maintained either in 2D or 3D configuration using this protocol. Our protocol is specifically designed to overcome the hurdle of excessive cell death during differentiation, especially for PSC cultured in defined media. In addition, this protocol utilizes fewer steps to obtain mature organoids, with fully optimized conditions designed to promote healthy and observable growth at each stage. First, PSCs are induced to form spheroids in PSC medium to reach 300-400 microns. Next, spheroids are specified to develop a forebrain identity in a two-step induction media. Finally, forebrain spheroids are differentiated to form mature cortical organoids with forebrain specific identity in Neuronal Maturation Medium. To confirm the phenotype, we designed a gene expression panel to verify forebrain, midbrain and hindbrain regions. After generating region specific organoids with respective phenotypes, their relative gene expression profiles were compared using this custom designed Taqman qPCR panels. In addition, to verify electrophysiological integrity of the neural organoids, we examined the ability of the differentiated forebrain organoids to fire action potentials. Our protocols demonstrate rapid, healthy growth of organoids grown from PSC cultured in multiple media systems, with mature organoids forming in as little as 21 days using a simplified protocol. This protocol completes a series generating organoids with specific developmental identities: forebrain, midbrain and hindbrain, verified by immunohistochemistry, qPCR panel testing and electrophysiology.

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Poster

P115. Homeostatic Plasticity: Modulation and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P115.01

Topic: B.07. Synaptic Plasticity

Title: Chronic optical stimulation of sparsely transfected cortical circuits induces homeostatic plasticity and neural clustering.

Authors: *B. LIU, M. J. SEAY, D. V. BUONOMANO;
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Abstract: Cortical computations emerge from the dynamics of neurons embedded in complex cortical circuits. Up-states are one of the best studied examples of emergent neural dynamics at both the experimental and computational levels. Typically, Up-states are defined as transient global dynamic regimes in which all neurons in a circuit are co-active and fire at a constant firing rate. This self-sustained firing is maintained by recurrently connected excitatory neurons, which, critically, is held in check through strong inhibition. Relatively little is known, however, about how Up-states can arise in a self-organizing manner, nor is it known if different subnetworks, or clusters can exist and differentially contribute to Up-states. Here we first show that chronic optical stimulation (24 - 48 hrs) of cortical organotypic networks in which most excitatory neurons express Channelrhodopsin2 (ChR2) produces a homeostatic downregulation of Up-state frequency. In chronically stimulated but sparsely transfected slices, paired recordings revealed differential activity patterns during Up-states in $ChR2^+$ and $ChR2^-$ neurons (3.2 ± 3.0 and 0.3 ± 0.5 Hz, respectively). These cell-specific changes in Up-state firing were associated with decreases in intrinsic excitability of the $ChR2^+$ neurons, and an apparent decrease in connectivity between $ChR2^+ \leftrightarrow ChR2^-$ pyramidal neurons. Furthermore, there was a decrease in the correlation of activity between $ChR2^+$ and $ChR2^-$ neurons, compared to controls. These results indicate that while Up-states are a global network-wide phenomenon, different populations of pyramidal neurons can exhibit different levels of activity during Up-states depending on their stimulation history. Computational models suggest that Up-states reflect bistable regimes, in which during the Up-state component, all neurons exhibit a steady-state firing rate (representing a fixed-point attractor). By incorporating the observed changes in intrinsic excitability into a two-population model we observed that changes in the gain and threshold of intrinsic excitability were sufficient to account for the decrease in Up-state frequency. Ongoing simulations with multi-unit models suggest that intrinsic changes in a subpopulation of neurons are sufficient to account for the observed decrease in firing rate of the $ChR2^+$ cluster. Together our results suggest that imposing differential correlations through chronic optical stimulation can generate partial decoupling of cortical subnetworks, potentially leading to neural clustering.

Disclosures: B. Liu: None. **D.V. Buonomano:** None.

Poster

P115. Homeostatic Plasticity: Modulation and Disease

Location: Virtual Only

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Program #/Poster #: P115.02

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1R56AG068063-01
NIH Grant R01 AG068063-01A1

Title: Endocannabinoid Adaptation During Homeostatic Scaling Down

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Abstract: Homeostatic regulation of neuronal activity in response to hyperexcitation is critical to maintaining network stability and functional signaling. Endocannabinoids (eCBs) are bioactive lipids synthesized in the post-synaptic compartments in response to neuronal activities to activate pre-synaptic cannabinoid receptor CB1. Therefore, the eCB system is well suited to coordinate pre- and post-synaptic activity. However, the role of the eCB system remains elusive in homeostatic adaptation to neuronal hyperexcitation. We induced hyperexcitation in cultured rat cortical neurons with chronic bicuculline treatment (BCC), known to induce homeostatic scaling down. We combined western blotting with targeted lipidomics to investigate biochemical changes during neuronal adaptation to hyperexcitation over 48 hours. Neurons adapt to hyperexcitation by downregulating total fatty acid amide hydrolase (FAAH), upregulating N-acylethanolamines (NAEs) and surface CB1. We used multi-electrode array and live-cell imaging (iGluSnFR) to investigate spontaneous synchronous network activities. CB1 antagonism suppresses spontaneous glutamatergic network events. Our data shows that coordinated adaptation of the eCB system supports homeostatic plasticity.

Disclosures: M. Ye: None. **S. Monroe:** None. **S.M. Gay:** None. **M.L. Armstrong:** None. **D. Youngstrom:** None. **F. Urbina:** None. **S.L. Gupton:** None. **N. Reisdorph:** None. **G.H. Diering:** None.

Poster

P115. Homeostatic Plasticity: Modulation and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P115.03

Topic: B.07. Synaptic Plasticity

Support: Ellison Medical Foundation
Overland Foundation

Title: Role of transmitter plasticity in fear generalization

Authors: *H. LI[1], W. JIANG[1], C. CHEN[2], D. W. CLEVELAND[2], N. C. SPITZER[1];
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Abstract: Fear is an essential emotion for survival. Acquired fear responses can be specific to the cue or context associated with an aversive stimulus (conditioned fear) and/or spread to other environmental cues or contexts (generalized fear). Fear generalization can be harmful when fear responses are exaggerated and inappropriate to the threat of a novel environment. However, little is known about the cellular and circuit mechanisms by which fear is generalized. We have studied the transmitter plasticity underlying fear generalization in the adult mouse brain. Two weeks after intense footshock stress, a subset of serotonergic (5-HT) neurons in the lateral wings of the dorsal raphe (lwDR) of shocked mice were found to have switched their co-transmitter from glutamate/VGLUT3 (vesicular glutamate transporter type 3) to GABA/GAD67 (glutamic acid decarboxylase 67). Strikingly, by examining post-mortem human brain tissue, we found a similar switch from VGLUT3 to GABA in the 5-HT^{lwDR} neurons of PTSD subjects

compared to age-matched controls. To investigate whether the loss of VGLUT3/glutamate and gain of GAD1/GABA occur in the same neurons, we used a VGLUT3-Cre transgenic mouse line crossed with a Rosa-mCherry reporter line to permanently label VGLUT3+ neurons. We found more mCherry+GAD67+VGLUT3- neurons in shocked mice compared to controls, demonstrating the occurrence of the transmitter switch in single neurons. To study the causal relationship between the transmitter switch and generalized fear, we used Cre-dependent adeno-associated viruses (AAVs) to express exogenous VGLUT3 and/or suppress expression of GAD1 in 5-HT^{lwDR} neurons and tested their impacts on the stress-induced fear responses. Our data show that expression of exogenous VGLUT3 partially reduced generalized fear and expression of GAD1 entirely erased it. We then investigated whether fluoxetine, a selective serotonin reuptake inhibitor (SSRI) that is a first-line pharmaceutical treatment for fear disorders, affects transmitter switching and fear. Our results show that prompt delivery of fluoxetine right after the shock blocks both the glutamate-to-GABA switch in the lwDR and generalized fear responses. When the delivery of fluoxetine was delayed, e.g. starting two weeks after the shock, no effect was seen. We are now using AAVs to create a similar switch in the 5-HT^{lwDR} neurons to determine whether this will suppress the effect of fluoxetine in blocking the switch and fear generalization. This study is expected to identify brain plasticity underlying fear generalization and provide mechanistic understanding of the action of a pharmacological treatment for fear disorders.

Disclosures: H. Li: None. **W. Jiang:** None. **C. Chen:** None. **D.W. Cleveland:** None. **N.C. Spitzer:** None.

Poster

P115. Homeostatic Plasticity: Modulation and Disease

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Program #/Poster #: P115.04

Topic: B.07. Synaptic Plasticity

Support: CIHR Grant 142420
HSF GIA G-15-0009399

Title: Homeostatic-like potentiation of the aversive habenulo-raphe pathway in an animal model of post-stroke depression

Authors: *S. MAILLÉ[1], S. D. GEDDES[1], D. LEMELIN[2], S. ASSADZADA[2], J.-C. BEIQUE[2];
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Abstract: Stroke is one of the leading causes of death and adult long-term disability across the world. Despite increasingly efficient rehabilitation programs, stroke survivors experience an unusually high incidence of depressive symptoms which, beyond the emotional suffering, also undermine recovery outcomes by reducing patient motivation levels. Human and animal studies have linked the incidence of post-stroke depression to the extent of prefrontal cortex (PFC) damage. We hypothesized that PFC stroke promotes the development of depressive phenotypes by triggering maladaptive network remodelling in mood-related networks. The PFC and the epithalamic lateral habenula (LHb) are limbic structures that send powerful, top-down axonal projections to the serotonergic dorsal raphe nucleus (DRN), a key

neuronal hub for mood regulation. We used viral, optogenetic and electrophysiological strategies to outline the functional architecture of the PFC and LHb projections to DRN. We found that an endothelin-1-mediated stroke in PFC triggers a time-dependent remodeling of the glutamatergic input from the LHb to DRN 5-HT neurons. This remodeling resulted in an increased AMPAR/NMDAR ratio, insertion of GluA2-lacking AMPARs and an increased quantal size and faster decay kinetics of quantal excitatory postsynaptic currents. Because the LHb-DRN pathway is believed to encode emotional features such as aversion and anticipation of threat, a maladaptive, homeostatic-like upregulation of this pathway may contribute to the depressive symptomology following stroke.

Disclosures: S. Maillé: None. **S.D. Geddes:** None. **D. Lemelin:** None. **S. Assadzada:** None. **J. Beique:** None.

Poster

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Program #/Poster #: P115.05

Topic: B.07. Synaptic Plasticity

Support: Start up funding-UIC

Title: Disruption of developmental synaptic plasticity contributes to hypersynchrony of the visual circuit in a mouse model of infantile neuronal ceroid lipofuscinosis

Authors: *K. KOSTER[1], E. FLORES-BARRERA[1], T. NGUYEN[1], A. NIQULA[1], L. NORIEGA-GONZALEZ[1], S. COLOGNA[1], K.-Y. TSENG[2], A. YOSHII[3];
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Abstract: Developmental synaptic plasticity is the basis for long-term brain function and hinges on the function of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Protein palmitoylation is an understudied reversible lipid posttranslational modification that regulates the trafficking of many synaptic proteins, including all AMPAR subunits (GluA1-4) and the postsynaptic scaffold A kinase anchor protein 5 (Akap5). While understanding of palmitoylation has recently improved, less is known about protein depalmitoylation. Importantly, mutation of the depalmitoylation enzyme palmitoyl-protein thioesterase 1 (PPT1) causes Infantile neuronal ceroid lipofuscinosis (CLN1), a devastating pediatric neurodegenerative disorder characterized by seizure and death by age 5. However, how synaptic protein depalmitoylation by PPT1 regulates developmental plasticity and how its loss causes neurodegeneration in CLN1 is not understood. Here, we studied visual cortex plasticity in the *Ppt1*$^{-/-}$ mouse model to decipher how lack of protein depalmitoylation drives neuronal dysfunction in CLN1, with a particular focus on synaptic scaling, a form of homeostatic plasticity important for regulating neuronal population excitability. *Ppt1*$^{-/-}$ cultured neurons fail to downscale synapses and respond excessively to induction of synaptic upscaling, incorporating an increased number of calcium-permeable (CP)-AMPARs at synapses compared to wild-type (WT) cells. Amplified recruitment of CP-AMPARs was correlated with increased GluA1 palmitoylation solely in *Ppt1*$^{-/-}$ upscaled neurons. Further,

inducing synaptic upscaling in the visual cortex by dark rearing *Ppt1*$^{-/-}$ animals exacerbated CLN1 progression. Performing a palmitoyl-proteomic screen revealed excessive palmitoylation of Akap5, protein kinase A, and calcineurin, which regulate synaptic scaling of CP-AMPARs, in *Ppt1*$^{-/-}$ visual cortical synaptosomes. Akap5-calcineurin signaling is also linked to a neuroinflammatory response via nuclear factor activated in T-cells (NFATc3). Not only was this pathway sensitized in *Ppt1*$^{-/-}$ cultured neurons, but neuroinflammatory activation of microglia was accelerated in dark reared (upscaled) *Ppt1*$^{-/-}$ visual cortices. To evaluate the contribution of disrupted synaptic scaling to the visual circuit, we performed *in vivo* two-photon calcium imaging in awake mice. Intriguingly, layer 2/3 excitatory cortical neurons were hypersynchronous in *Ppt1*$^{-/-}$ animals. Together, these data point to a crucial role for protein depalmitoylation in developmental plasticity mechanisms whose disruption leads to circuit level dysregulation in CLN1.

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Poster

P115. Homeostatic Plasticity: Modulation and Disease

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Program #/Poster #: P115.06

Topic: B.07. Synaptic Plasticity

Support: NIMH grant MH065635
Foundation for Angelman Syndrome Therapeutics (FAST)

Title: Dysregulation of protein metabolism in Angelman Syndrome

Authors: *F. ARIA, K. PANDEY, C. M. ALBERINI;
New York Univ., New York City, NY

Abstract: Angelman syndrome (AS) is a neurodevelopmental genetic disorder characterized by intellectual disability, speech and motor defects, sleep problems, and seizures. The mechanisms by which the genetic defects result in AS symptoms are still poorly understood, despite, in most cases, they appear to be linked to the loss of function of the maternal copy of ubiquitin-protein ligase E3A (UBE3A) which is located on the maternal chromosome region 15q11-13. By focusing on the hippocampus, a region critical for memory consolidation, here we show that maternal deletion of Ube3a (Ube3a m-/p+) in mice, which in fact reproduce most core symptom of AS, is accompanied by significant alteration of a hallmark mechanism of synaptic plasticity: the stimulus-dependent increase of *de novo* protein synthesis coupled to autophagic flux. We found that compared to wild type control mice (WT), AS mice have: i) a significant increase in hippocampal de novo protein synthesis, measured by *in vivo* Surface Sensing of Translation (SUnSET), ii) an accumulation of proteins involved in autophagy including LC3B, p62 and LAMP1, and iii) a blunted autophagic flux, in both basal conditions and following contextual fear conditioning (CFC) learning. Furthermore, while, as expected, CFC learning led to an increase in the levels of the immediate early gene (IEGs) ARC, c-FOS and EGR-1 proteins in the hippocampus of WT mice, it failed to do so in AS mice, which also had an accumulation of IEG proteins in basal condition. Take together these data

lead us to conclude that AS is characterized by a significant accumulation of proteins and a stalled autophagic flux with consequent defect of protein metabolism homeostasis, also known as proteostasis. We suggest that this proteostasis alteration is a major neurological problem that leads to AS symptoms.

Disclosures: F. Aria: None. **K. Pandey:** None. **C.M. Alberini:** None.

Poster

P115. Homeostatic Plasticity: Modulation and Disease

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P115.07

Topic: B.07. Synaptic Plasticity

Support: NIMH grant MH065635

Title: Activity-dependent cytoskeleton associated protein is regulated by the autophagy pathway

Authors: *K. PANDEY, F. ARIA, C. M. ALBERINI;
New York Univ. Ctr. For Neural Sci., NEW YORK, NY

Abstract: Learning increases autophagy and this increase requires *de novo* translation. Autophagy is an evolutionarily conserved protein degradation mechanism that, through lysosomes, removes damaged organelles or proteins but is also important for recycling cytosolic components. Recent studies have shown that autophagy is critical for long-term memory formation. Previously, we found that learning-induced autophagy is coupled to the *de novo* protein synthesis evoked by learning (Pandey, K., Yu, X. W., Steinmetz, A., and Alberini, C. M., Autophagy, 1-22, 2020. doi: 10.1080/15548627.2020.1775393). The target molecules of this learning-induced autophagy remain to be identified. Using episodic learning paradigm in rats, here we show that learning-induced increase of the immediate early gene activity-dependent cytoskeleton associated protein (ARC/ARG3.1 thereafter ARC) in the dorsal hippocampus colocalizes with microtubule-associated protein 1 light chain 3 beta (LC3B), a protein that is recruited to the autophagosomal membrane and considered a typical marker of autophagic vesicles. Pharmacological inhibition of autophagy and lysosomal pathways or targeted molecular disruption of critical regulators of autophagy, which are known to impair long-term memories, led to a significant accumulation of ARC protein without changing its mRNA level. In addition, a reporter system generally employed to measure autophagic flux, which was engineered to express ARC, revealed that learning leads to ARC transport along an intracellular compartment that traffics from basic to acidic compartments, suggesting that ARC undergoes autophagic flux. Collectively, these data suggest that the autophagy pathway, which is activated in response to learning, regulates ARC protein degradation.

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Poster

P124. Translation in Plasticity

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Program #/Poster #: P124.01

Topic: B.07. Synaptic Plasticity

Support: NIH R21 MH120496
NIH R01 NS083085

Title: Fmrp phosphorylation leads to enhanced granule assembly and clustering

Authors: *Y. J. YOON[1], L. NUNEZ[1], D.-W. HWANG[1], S. KHAROD[1], R. H. SINGER[2];
[2]Anat. & Structural Biol., [1]Albert Einstein Col. of Med., Bronx, NY

Abstract: Fragile X syndrome is the leading single-gene cause of autism and the most common form of inherited intellectual disability. While we understand the genetic mechanism of fragile X mental retardation (*FMR1*) gene silencing and the resulting loss of fragile X mental retardation protein (FMRP) expression, what is not clearly defined is how FMRP function is regulated. Previous biochemical and genetic evidence suggested that phosphorylation of serine residue 499 (S499) was key to FMRP function in repressing protein synthesis. However, what was less clear was how phosphorylation of S499 could impart FMRP function in the context of the intracellular milieu. To address this question, we have generated FMRP fluorescent reporters (GFP-FMRP and Halo-FMRP), along with the phospho-deficient and phospho-mimic mutants, S499A and S499D, respectively, to visualize the intracellular dynamics of FMRP. Analysis of our imaging results show that the S499A mutant exhibits smaller and more motile granules when compared to the wildtype GFP-FMRP or the S499D mutant reporter. Also, the S499A mutant showed reduced clustering relative to the wildtype and S499D counterparts, suggesting that the phosphorylation of S499 is necessary for FMRP granule formation and persistence at dendritic spines. Our high resolution approach can detect measurable differences in the dynamics of FMRP granules between the wildtype and mutant FMRP reporters and can advance our understanding of FMRP granule dynamics in live neurons.

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Poster

P124. Translation in Plasticity

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Topic: B.07. Synaptic Plasticity

Support: R01EY011261
R01EY027437 to HTC
P41GM103533
R01MH067880 to JRY

Title: Activity-induced proteomics dynamics in different cell types following PTZ-induced seizure and visual experience in mouse

Authors: *Y. XIE, L. SCHIAPPARELLI, Y. MA, P. SHARMA, J. CHANG-WEINBERG, A. MAXIMOV, J. YATES III, H. CLINE;
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Abstract: Proteome dynamics induced by sensory stimulation differ among neuronal cell types. Being able to temporally dissect the changes of cell-type specific proteomics in a given brain region allows the discovery of novel protein candidates associated with developmental plasticity and disease progress. To analyze acute proteomics dynamics in genetically defined neuronal cell types, we applied metabolic labeling with the non-canonical amino acid Azidonorleucine (ANL) in a transgenic mouse line (JAX#028071; Alvarez-Castelao B, 2017), where a mutant methionine tRNA synthetase ($MetRS^{L274G}$) is knocked-in in a cre-dependent manner. We used the Direct Detection of Biotin-containing Tag (DiDBiT, Schiapparelli L, 2014) method in the sample preparation and mass spectrometry pipeline, which ensured high fidelity in filtering out background signal. With this system, we performed a 'proof of principle' proteomics analysis in $MetRS^{L274G}EMX^{Cre}$ mice, following brain-wide neuronal activation by pentylenetetrazol (PTZ). EMX^{Cre} is expressed predominantly is excitatory neurons. First, we demonstrated that constitutive expression of $MetRS^{L274G}$ from embryonic stage didn't elicit any major pathological changes in cortical lamination, cell population or mouse behavior. Second, we showed that intraperitoneal injection of ANL acutely before PTZ-induced neuronal activation successfully identified >1500 biotin-labeled newly synthesized proteins with our pipeline, the majority of which are annotated to excitatory neurons, as expected. Among these, the synthesis of ~100 proteins was significantly regulated by activity. Bioinformatic analysis showed that the significantly regulated dataset was enriched in components pertaining to synaptogenesis as well as chromatin and cytoskeleton remodeling. Building on this 'proof-of-principle' experiment, we are testing for acute proteomic dynamics in the visual cortex induced by visual input at P28 and P56. We identified >2000 proteins in the excitatory proteomics 12-hour post visual experience in both sexes. >200 protein was significantly regulated by visual experience. The hits in P28 and P56 only share ~25% overlap, which suggests different regulatory program in the visual critical period and in adult. We are also exploring the inhibitory proteomics induced by visual experiences at different ages. By comparing activity-dependent proteomics in these neuronal cell types, we will be able to gain more insight into the molecular regulations of critical period and adult visual plasticity.

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Poster

P124. Translation in Plasticity

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Program #/Poster #: P124.03

Topic: B.07. Synaptic Plasticity

Support: NIMH R00MH109626

Title: Differential location of Golgi apparatus proteins in adult hippocampal dendrites

Authors: *D. LAL[1], K. E. PANNONI[2], L. CAMPBELL[2], S. FARRIS[3];
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Abstract: Local protein translation affords neurons the ability to differentially regulate cellular functions in distinct compartments by controlling when and where mRNA translation occurs. The endoplasmic reticulum (ER) and Golgi apparatus (GA) are responsible for synthesizing and "tagging" secretory and transmembrane proteins (i.e., glycosylation) for their final destinations, respectively. An unresolved issue in local translation is whether the GA or a separate processing pathway is present in dendrites to process transmembrane proteins. Mutations in GA proteins have been implicated in autism spectrum disorders (ASD) where dysregulation of protein synthesis at synapses can lead to disease (Giannandrea et al, 2010). Early studies identified polyribosomes and ER in adult dendrites in vivo using electron microscopy (Steward & Levy, 1982 & Pierce et al, 2000). GA and trans Golgi network were similarly identified in adult dendrites using electron microscopy with immunogold staining for organelle markers (Pierce et al, 2001). In contrast, more recent studies using developing neurons in culture found no evidence of the GA in dendrites using confocal microscopy, and instead identified a separate processing pathway through which proteins are trafficked from dendritic ER to the membrane by recycling endosomes (Bowen et al, 2017). Thus, it remains unclear whether the GA is present in distal dendrites to locally process proteins for destined for the membrane.
To address whether GA proteins are localized in dendrites, we used transgenic reporter mice to label a subset of hippocampal neurons and immunostained sections for three GA markers (GOLGA5, ST3GAL, and ERGIC), which label canonical GA, Golgi outposts (GO), and ER to Golgi intermediate complex, respectively. Confocal imaging was used to quantify the fluorescence intensity of each marker in cell bodies and dendrites. Additional high-resolution images were acquired to determine the relative fluorescence between dendrites and spines. We found that canonical GA marker GOLGA5 is confined to the cell body and very proximal dendrites, while both GO and ER to Golgi intermediate markers are found throughout the cell body and dendrites, with evidence for localization in distal dendrites and dendritic spines. Our data are consistent with evidence that canonical GA markers are not found in distal dendrites, and provide support for a noncanonical trafficking pathway utilizing GO to process transmembrane proteins in distal dendrites. Identifying the mechanisms regulating local translation at synapses is critical for understanding the processes underlying learning and memory and for developing effective therapies for ASD.

Disclosures: D. Lal: None. **K.E. Pannoni:** None. **L. Campbell:** None. **S. Farris:** None.

Poster

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Title: Neuronal membrane-specific proteasomes homeostatically regulate neural circuit activity and are required for learning-induced behavioral plasticity in vivo

Authors: *H. HE[1], K. RAMACHANDRAN[2], N. MCLAIN[3], R. L. FAULKNER[3], A. AHSAN[1], R. BERA[1], S. S. MARGOLIS[4], H. T. CLINE[3];
[1]Gorgetown Univ., Washington, DC; [2]Columbia University,, New York City, NY; [3]The Scripps Res. Inst., La Jolla, CA; [4]Johns Hopkins Univ., Baltimore, MD

Abstract: Recent studies in neuronal cultures found that uncapped 20S core subunits of proteasomes specifically bind to the neuronal plasma membrane and may be involved in the regulation of neuronal activity, possibly through degradation of nascent proteins. The *in vivo* function of these neuronal membrane-specific proteasomes (NMPs) is unknown. Here, we examined the expression and function of NMPs in Xenopus laevis tadpole brains. A significant proportion of 20S core subunits was detected in the membrane fractionation of brain homogenate and were found to colocalize with the neuronal membrane in electron micrographs, demonstrating the presence of NMPs in tadpole brain. To probe the proteolytic function of NMPs *in vivo*, we employed a bio-orthogonal metabolic labeling method to tag nascent proteins with azidohomoalanine (AHA) in the brain of live tadpoles, which allows specific detection and purification with subsequent biotinylation of tagged proteins. Application of bicuculline methiodide (BMI), a $GABA_AR$ antagonist, significantly increased the amount of nascent protein, consistent with activity-dependent increase in protein synthesis. Acute NMP inhibition resulted in a further increase in the total amount of nascent protein, suggesting that NMPs actively degrade nascent proteins in response to elevated neuronal activity. Further examination of specific protein candidates in purified nascent protein samples suggest that not all nascent proteins are degraded by NMPs. *In vivo* Ca^{2+} imaging in the optic tectum showed that NMP inhibition in BMI-treated tadpole brain rapidly increased spontaneous neuronal activity on top of the BMI-induce activity increase and significantly increased the synchronization among the neuronal population. Such an elevation of the network activity is predicted to reduce the signal to noise ratio of the signal processing and impair circuit function. Indeed, NMP inhibition during visual training abolished learning-induced behavioral plasticity and resulted in a deterioration of baseline visual avoidance behavior in tadpoles. Intriguingly, without the visual training, NMP inhibition did not interfere with the behavior, suggesting a specific protective role of NMPs in experience-dependent circuit plasticity. Activity-induced protein synthesis is a signature of synaptic plasticity. Timely degradation of nascent proteins may hold activity-induced synaptic changes in check, preventing them from plunging into a destabilizing positive-feedback loop. Together our data suggest that NMP-mediated degradation of nascent proteins may serve as a novel homeostatic mechanism in neurons for the regulation of circuit plasticity.

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Poster

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U54 HD090260 to PEC
F31-MH114431 to HRM
R01-NS083085 to RHS
R21-MH120496 to YJY

Title: Presynaptic FMRP and local protein synthesis support structural and functional plasticity of glutamatergic axon terminals

Authors: *S. C. KHAROD[1], H. R. MONDAY[1], Y. J. YOON[2], R. H. SINGER[2], P. E. CASTILLO[3]; [1]Neurosci., [2]Anat. and Structural Biol., [3]Neurosci.; Psychiatry and Behavioral Sci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The molecular mechanisms that govern long-term forms of presynaptic plasticity are largely unknown. The hippocampal mossy fiber (MF)-CA3 synapse, which expresses robust presynaptic plasticity and has notably large and complex boutons (MFBs), contains surprisingly high levels of Fragile X mental retardation protein (FMRP), an RNA-binding protein known to repress translation, but whose function at the presynapse and in long-term plasticity is unclear. FMRP interacts with polyribosomes and mRNAs to form granules, which can be trafficked in an activity-dependent manner, and dephosphorylation of FMRP triggers granule disassembly and loss of translational repression. Here, using mouse acute hippocampal slices, we found that MF-LTP and associated structural plasticity requires protein synthesis. Moreover, selective deletion of FMRP from presynaptic neurons impaired both structural and functional MF-LTP and resulted in an increase in protein synthesis in the MF tract. Taking advantage of a novel viral vector expressing an FMRP-Halotag fusion protein, we not only confirmed that FMRP granules are localized to MFBs, but also found that MF-LTP induction disassembled FMRP granules in the MF tract. Remarkably, enriched environment exposure also increased protein synthesis in the MF tract and this increase was exacerbated by presynaptic deletion of FMRP. Finally, using high-resolution microscopy, we identified endogenous ribosomes in presynaptic MFBs, suggesting that these boutons are capable of synthesizing protein locally, likely under the regulation of FMRP. Together, these results indicate that presynaptic FMRP dynamically regulates protein synthesis and plastic changes at an excitatory synapse in the mature mammalian brain, which may have important implications in memory formation.

Disclosures: S.C. Kharod: None. **H.R. Monday:** None. **Y.J. Yoon:** None. **R.H. Singer:** None. **P.E. Castillo:** None.

Poster

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1K08NS114039

Title: Autophagy regulates local synaptic RNA metabolism

Authors: *Y. JOO, D. R. BENAVIDES;
Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: RNA transport and local translation are crucial for neuronal signal transmission and synaptic plasticity. Dysfunction of RNA metabolism has been implicated in numerous neuronal disorders. However, the RNA metabolism for local translation in the postsynaptic density (PSD) remains to be fully elucidated. We used dissociated primary neuron culture, proteomics, pharmacology, and RNA imaging to investigate the translational mechanisms of local RNA and translational regulation in the PSD. We discovered that activity-dependent regulation of local RNA content is induced in the PSD. In addition, pharmacological inhibition of autophagy, using Bafilomycin A1, results in local synaptic RNA regulation. mRNAs encoding synaptic proteins such as NMDA receptor subunits, AMPA receptor subunits, and adhesion molecules as well as immediate early genes displayed differential regulation. Thus, autophagy may contribute to synaptic plasticity via regulation of local RNA metabolism. This study may contribute to understanding of the underlying pathophysiology of neurological disorders and pathways for novel therapeutics.

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Poster

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Program #/Poster #: P124.07

Topic: B.07. Synaptic Plasticity

Support: NCN OPUS 2018/31/B/NZ4/01603

Title: Ubiquitination of Arc regulates alcohol-induced synaptic plasticity in central nucleus of amygdala and alcohol seeking

Authors: *A. SALAMIAN, P. TAHERI, E. SKONIECZNA, K. RADWANSKA;
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Abstract: The activity-regulated protein Arc/Arg3.1 (Arc) is one of key molecules that regulate synaptic plasticity and memory processes. The role of Arc in psychiatric disorders, including alcohol use disorder (AUD), remains less understood. However, our data show that Arc mRNA and protein is upregulated in the amygdala during alcohol withdrawal, suggesting its function in alcohol-induced plasticity and

behaviours. The expression of Arc protein at synapses is tightly controlled: it rapidly increases following enhanced network activity and quickly declines due to protein ubiquitination. We found that alcohol withdrawal along with Arc mRNA upregulates mRNA of Arc E3 ubiquitin-protein ligase, RNF216. To investigate the role of Arc ubiquitination in AUD-related behaviours, we used Arc ubiquitination-deficient mutant mice (ArcKR) (Mark et al. 2018) with disrupted temporal control of Arc degradation. Arc KR and wild-type littermates (WT) underwent alcohol self-administration training in the IntelliCages: free access to 8% ethylalcohol (30 days) followed by 7-day withdrawal (7DW) and presentation of alcohol-predicting cue light (cue relapse) in the reward corner. Next, we analyzed synaptic transmission and plasticity in the central nucleus of the amygdala (CeA) following 7DW: evoked local potentials were recorded in medial part of CeA after electrical stimulation of basolateral amygdala (BLA). There was decreased synaptic strength, measured as input/output, and decreased GluN1, but increased GluN2B, NMDAR subunits levels in Arc WT following 7DW compared to water, yet, no difference in Arc KR mice. Furthermore, theta burst stimulation-induced LTP was significantly boosted in Arc WT mice following 7DW compared to water group. We did not observed, however, such plasticity in Arc KR littermates. Finally, we found less alcohol seeking by Arc KR mice during alcohol withdrawal and cue relapse compared to Arc WT littermates. Together, our data suggest that temporal control of Arc degradation plays a crucial role in alcohol-induced synaptic plasticity in CeA and alcohol seeking during withdrawal.

Disclosures: A. Salamian: None. **P. Taheri:** None. **E. Skonieczna:** None. **K. Radwanska:** None.

Poster

P124. Translation in Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P124.08

Topic: B.07. Synaptic Plasticity

Support: RO1 DA035430
RO1 DA044760
RO1 DA043361
R01 GM104010
T32 GM007183
Peter F. McManus Foundation

Title: Alteration of neuronal surface glycoproteome by Nicotine and Activity-dependent Golgi satellite formation.

Authors: *A. P. GOVIND[1], O. JEYIFOUS[1], T. A. RUSSEL[1], Z. YI[1], A. V. WEIGEL[2], A. RAMAPRASAD[1], L. NEWELL[1], W. RAMOS[1], F. M. VALBUENA[3], J. C. CASLER[3], J.-Z. YAN[4], B. S. GLICK[3], G. T. SWANSON[4], J. LIPPINCOTT-SCHWARTZ[2], W. N. GREEN[1];
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Abstract: Activity-driven changes in the neuronal surface glycoproteome are known to occur with synapse formation, plasticity and related diseases but their mechanistic basis and significance are unclear. *N*-glycans on surface glycoproteins of dendrites shift from immature to mature forms containing sialic acid in response to increased neuronal excitation. In exploring the basis of these *N*-glycosylation alterations, we discovered they results from the growth and proliferation of Golgi satellites scattered throughout the dendrite. Golgi satellites that formed with neuronal excitation were in close association with ER exit sites and early endosomes and contained glycosylation machinery without the Golgi structural protein, GM130. They functioned as distal glycosylation stations in dendrites, terminally modifying sugars either on newly synthesized glycoproteins passing through the secretory pathway, or on surface glycoproteins taken up from the endocytic pathway. These activities led to major changes in the dendritic surface of excited neurons, impacting binding and uptake of lectins, as well as causing functional changes in neurotransmitter receptors, such as the nicotinic acetylcholine receptor. Neural activity thus boosts the activity of the dendrite's satellite micro-secretory system by redistributing Golgi enzymes involved in glycan modifications into peripheral Golgi satellites. This remodeling of the neuronal surface has potential significance for synaptic plasticity, addiction and disease.

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Poster

P124. Translation in Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P124.09

Topic: B.07. Synaptic Plasticity

Title: Translation regulation in development of hyperalgesia

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Abstract: Despite widespread abuse of opioids, we know little about the long-term consequences of chronic use. Several studies demonstrated that chronic opioid exposure alters gene expression profiles underlying the acute and chronic neuronal plasticity. These changes in gene expression contribute to the opioid-induced analgesic effect, as well as the development of addiction, tolerance, dependence, and hyperalgesia. Eukaryotic elongation translation factor 2 kinase, eEF2K, is a non-conventional calmodulin-dependent protein kinase (CaMK III) belonging to the alpha kinase family. It is activated downstream of AMPK and PKA signaling as well as by Ca^{2+}-dependent calmodulin binding. The eEF2K phosphorylates eEF2 on Thr56, leading to inhibition of elongation step of protein synthesis and, thus, a suppression of general protein synthesis. However, translation of several specific mRNAs is upregulated by phosphorylated eEF2. Among them, mRNAs involved in the control of synaptic plasticity: CamK II ,

activity-regulated cytoskeleton associated protein Arc/Arg3.1, brain-derived neurotrophic factor BDNF, and microtubule-associated proteins. Both eEF2K and eEF2 are ubiquitous in all eukaryotes and are present in various tissues including brain. It was shown that prolong opioid administration is associated with development of hyperalgesia or increased pain sensitivity. In our experiments, we observed increased phosphorylation of eEF2 in various brain areas in rats and mice chronically treated with opioids. Moreover, it coincided with translational upregulation of BDNF, factor implicated in nociceptive response. To investigate the eEF2K role in development of hyperalgesia, WT and eEF2K KO mice were chronically treated with morphine for 12 days. WT mice demonstrated signs of hyperalgesia by 4th day of morphine treatment, while KO mice demonstrated lack of increased sensitivity to pain during 12 days. It was shown that microglia-released BDNF promotes development of morphine-induced hyperalgesia in mice. In our experiments, we observed increase in BDNF level in brain stem samples of WT but not in KO mice treated with morphine. Lower level or delayed increase in morphine-induced BDNF expression in brain may explain lack of hyperalgesia after chronic morphine administration in KO mice.

Disclosures: N. Korneeva: None. **R. Fan:** None. **A. Ryazanov:** None. **T. Arnold:** None.

Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.01

Topic: B.10. Epilepsy

Title: Longitudinal characterization of hippocampal pathology in the intrahippocampal kainate mouse model of temporal lobe epilepsy

Authors: D. TRAVER, M. B. PAREKH, E. T. SEVILLA, W. BLANKENBERGER, H. KIM, P. HAMPEL, N. PICARD, C. NICHOLAS, *C. PRIEST;
Neurona Therapeutics, Inc, South San Francisco, CA

Abstract: Approximately one-third of people with epilepsy do not achieve adequate seizure control with current anti-seizure drugs, and treatment of drug-resistant epilepsy remains a significant unmet clinical need. Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy, and is characterized by mesiotemporal seizures and hippocampal sclerosis. Hippocampal sclerosis involves damage to several cell types and layers, including dentate granule cell dispersion, inhibitory interneuron and excitatory neuron cell loss, gliosis, mossy fiber sprouting, tissue atrophy, and inflammation (Blümcke et al., 2013, Houser, 1990, Devinsky et al., 2013). Long-term longitudinal characterization of hippocampal sclerosis in animal models of TLE may aid in the development of more effective anti-seizure therapies. In this study, hippocampal histopathology and inflammation were examined for up to 12 months during the chronic epileptic phase in the intrahippocampal kainate mouse model of mesiotemporal seizures and sclerosis. Eight-10 week old immunocompromised NOG mice received kainic acid into the right dorsal hippocampus to induce status epilepticus. Brain tissue was collected 1-2, 8, and 11-13 months post-induction (MPI). Quantitative analysis of hippocampal pathology was performed. Hippocampal neuronal loss in CA1, CA3, and the hilus was scored semi-quantitatively using hematoxylin and eosin staining. Granule cell dispersion was measured using PROX1 immunofluorescence labeling. Inflammation was

assessed using quantitative immunofluorescence labeling for reactive astrocytes (GFAP), and microglia (IBA1). For all measures, the ipsilateral epileptic hippocampus was compared to the contralateral hippocampus and to the hippocampi of naïve, age-matched mice. By 8 MPI, significant dispersion of the dentate granule cell layer, neurodegeneration, and inflammation were observed in the ipsilateral epileptic hippocampus while the contralateral hippocampus was largely spared. In conclusion, the epileptic hippocampus in a mouse model of chronic TLE exhibits histopathological hallmarks of human mesiotemporal sclerosis. By conducting an extended time course in the model, we have established an important baseline progression of hippocampal damage that will facilitate the future investigation of anti-seizure therapeutic candidates.

Disclosures: D. Traver: A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M.B. Parekh:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **E.T. Sevilla:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **W. Blankenberger:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **H. Kim:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **P. Hampel:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **N. Picard:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C. Nicholas:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C. Priest:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc.

Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.02

Topic: B.10. Epilepsy

Title: Co-administration of anti-seizure drugs with NRTX-1001 GABAergic interneuron therapy is well-tolerated and effective in mice

Authors: *E. SEVILLA, P. HAMPEL, W. B. BLANKENBERGER, H. K. KIM, D. A. TRAVER, J. LI, M. B. PAREKH, C. PRIEST, C. R. NICHOLAS;
Neurona Therapeutics, Inc., South San Francisco, CA

Abstract: The inhibitory cell therapy candidate NRTX-1001 is derived from human pluripotent stem cells and is being developed for the potential future treatment of drug-resistant focal epilepsy. The product is a clinical-grade cellular therapeutic comprised of human post-mitotic GABAergic interneurons of an MGE/pallial-type lineage. NRTX-1001 persists in the epileptic mouse hippocampus and provides stable seizure freedom in a chronic temporal lobe epilepsy (TLE) mouse model of mesiotemporal seizures and sclerosis. Here, preclinical studies were conducted to understand potential effects of anti-seizure drugs, levetiracetam and diazepam, on transplanted NRTX-1001 engraftment and disease-modifying activity.
Levetiracetam was infused chronically at 400 mg/kg/d, and control animals received vehicle injections for comparison. Stable therapeutic plasma levels of levetiracetam were confirmed. All of the mice received an intrahippocampal transplant of NRTX-1001 on day 3. At 30 days post-transplant (PT), histological analysis was conducted to assess human cell distribution, persistence, fate, and local inflammatory tissue

response. NRTX-1001-treated animals that received levetiracetam or vehicle had similar human cell persistence and hippocampal distribution, with appropriate interneuron fate and minimal host inflammatory response at 30 days PT. Mice were healthy throughout the study, and no behavioral abnormalities were detected in either group that received NRTX-1001.
In a second study, acute doses of the anti-seizure drug diazepam were administered several months PT in NRTX-1001-treated or vehicle-injected epileptic mice that model chronic TLE. To examine potential drug-cell therapy interactions, mesiotemporal seizures were measured by EEG in cell-treated and vehicle-injected cohorts. Most epileptic animals that received NRTX-1001 were seizure-free by 7 months PT, and the administration of two doses of diazepam did not impair the disease-modifying activity of the interneuron therapy.
In summary, combination treatment with the GABAergic interneuron therapy NRTX-1001 and two anti-seizure drugs, with different mechanisms of action, is well-tolerated and does not affect cell engraftment or disease-modifying activity.

Disclosures: E. Sevilla: A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **P. Hampel:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **W.B. Blankenberger:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **H.K. Kim:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **D.A. Traver:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **J. Li:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M.B. Parekh:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C. Priest:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C.R. Nicholas:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc..

Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.03

Topic: B.10. Epilepsy

Support: CIRM TRAN1-11611

Title: Preclinical development of the human inhibitory interneuron cellular therapeutic NRTX-1001 for the treatment of chronic focal epilepsy

Authors: *P. HAMPEL, M. B. PAREKH, W. B. BLANKENBERGER, E. T. SEVILLA, D. A. TRAVER, H. K. KIM, N. PICARD, A. BATES, D. CHERKOWSKY, A. ADLER, L. FUENTEALBA, S. LEE, S. KRIKS, N. SALTER, M. WATSON, M. BERSHTEYN, Y. MAURY, S. HAVLICEK, A. BULFONE, G. BANIK, C. PRIEST, C. R. NICHOLAS;
Neurona Therapeutics, Inc., South San Francisco, CA

Abstract: Objective:
Approximately 30% of people living with mesial temporal lobe epilepsy (TLE) do not achieve adequate seizure control with currently available pharmacological treatment options. A cellular therapeutic targeted to the temporal lobe could potentially restore balanced neural activity in the seizure focus, avoid the

unwanted side effects common to systemic drugs, and provide an alternative to tissue-destructive lobectomy and laser ablation surgery. NRTX-1001 is a clinical-grade cellular therapeutic comprised of post-mitotic GABAergic interneurons of an MGE/pallial-type lineage derived from human pluripotent stem cells. The product candidate is efficacious and safe across a broad dosing range in a chronic mouse model of TLE. The current study examined the reproducibility of safety and efficacy across independently manufactured lots of NRTX-1001.
Design/Methods:
NRTX-1001 was evaluated in the intra-hippocampal kainate mouse model of chronic TLE that displays key aspects of human TLE pathology, including pharmacoresistant mesiotemporal seizures and sclerosis. In the chronic epileptic stage, animals received intra-hippocampal transplantations of independent lots of NRTX-1001, or vehicle control. EEG was recorded continuously to determine focal electrographic seizure frequency, and animals were observed for potential behavioral abnormalities, hippocampal pathology, and human cell engraftment for 7-9 months post-transplant.
Results:
NRTX-1001 matured into appropriate interneuron subtypes, distributed throughout the epileptic mouse hippocampus, and stably persisted for the study duration. Overall, approximately two-thirds of mice that received cell transplants became stably seizure-free by 5 months post-transplant. Cell transplantation reproducibly led to stable seizure suppression with ~75% fewer electrographic seizures recorded than in vehicle-injected control animals. The cumulative duration of focal seizures was also reduced. Hippocampal neurodegeneration and dentate granule cell dispersion were significantly decreased in the cell-treated mice. No ectopic human tissues or teratomas were found, and no adverse behavioral effects were detected.
Conclusions:
NRTX-1001 persisted in the epileptic mouse hippocampus, was well tolerated, and resulted in stable seizure freedom. These findings support further development of NRTX-1001 for chronic focal epilepsy.

Disclosures: P. Hampel: A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M.B. Parekh:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **W.B. Blankenberger:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **E.T. Sevilla:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **D.A. Traver:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **H.K. Kim:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **N. Picard:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **A. Bates:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **D. Cherkowsky:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **A. Adler:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **L. Fuentealba:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **S. Lee:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **S. Kriks:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **N. Salter:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M. Watson:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M. Bershteyn:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **Y. Maury:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **S. Havlicek:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **A. Bulfone:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **G. Banik:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C. Priest:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C.R. Nicholas:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc..

Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.04

Topic: B.10. Epilepsy

Support: German Research Foundation: HA 1443/11-1
BrainLinks-BrainTools Center Freiburg

Title: Hippocampal low-frequency stimulation prevents seizure generation in a mouse model of mesial temporal lobe epilepsy

Authors: *E. PASCHEN[1,2], P. KLEIS[1,2], J. LINK[1,2], D. VIEIRA[3,4], K. HEINING[3,2,4], P. JANZ[1], U. EGERT[3,4], U. HÄUSSLER[1,5], C. HAAS[1,5];
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Abstract: Mesial temporal lobe epilepsy (MTLE) is the most common form of focal, pharmacoresistant epilepsy in adults and is often associated with hippocampal sclerosis. For MTLE patients, one alternative to surgical resection of the epileptic focus is electrical deep brain stimulation in the hippocampus. Due to the low duty cycle, low-frequency stimulation (LFS) may be advantageous over high-frequency stimulation, as it requires less electric current injection, thus allowing for longer battery life. In an *in vivo* mouse model of MTLE, we showed previously that optogenetic LFS in the hippocampus (1 Hz and 0.5 Hz) interfered with the generation of spontaneous epileptiform activity. Stimulation at higher frequencies (5-20 Hz) often resulted in the induction of behavioral seizures. Here, we aimed at successful seizure control by the application of electrical LFS (eLFS) in chronically epileptic mice. We injected kainate (KA) unilaterally into the hippocampus and a channelrhodopsin2-encoding viral vector into the entorhinal cortex of C57BL/6 mice. We implanted one electrode for local field potential recordings in each hippocampus and an optic fiber parallel to a stimulation electrode in the sclerotic hippocampus. This way we could optogenetically induce behavioral seizures and assess the seizure-suppressive effects of eLFS. We applied unilateral 1 Hz pulses for one to three hours daily for three weeks. In addition, KA- and control mice were stimulated and subjected to behavioral tests to infer a potential impact of eLFS on cognitive performance. We found that (i) 1 Hz eLFS successfully interfered with both spontaneous epileptiform activity and evoked behavioral seizures originating from the KA-injected hippocampus; (ii) suppression of epileptiform activity during eLFS was effective over several weeks without desensitization; (iii) discontinuous (open-loop) stimulation was also highly effective. On the behavioral level, preliminary results suggest that eLFS does not impair hippocampus-related cognitive functions, since mice were (i) able to navigate successfully in the Barnes Maze and (ii) showed no increase in the anxiety level following eLFS. Our results indicate that hippocampal eLFS reliably suppresses the generation of spontaneous epileptiform activity and the generalization into behavioral seizures without losing effectiveness over prolonged treatment and without affecting hippocampus-related cognitive functions. Thus, eLFS at 1 Hz may constitute a promising approach for seizure control in MTLE.

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Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.05

Topic: B.10. Epilepsy

Support: Austrian Science Fund (FWF)

Title: Toll-like receptor inhibition reduces epileptiform activity in a mouse model of temporal lobe epilepsy

Authors: *S. RAHIMI, M. DREXEL, S. SANTOS-SIERRA;
Med. Univ. of Innsbruck, Innsbruck, Austria

Abstract: Introduction: Neuroinflammation is a significant underlying cause of epileptogenesis and epilepsy and Toll-like receptors (TLR) seem to play a key role in the inflammatory process. TLR activation leads to pro-inflammatory cytokine production what may lead to neuronal hyper-excitability. Thus, inhibition of TLR function is a promising therapeutic strategy in drug-resistant epilepsy. Our group have discovered several small-molecule inhibitors of TLR2 function (e.g. INH50) that are potential candidates to reduce epileptiform activity.**Methods:** Initial in *silico/in vitro* studies led to the selection of INH50, a small-molecule that reduced the activity of TLR2 (luciferase and ELISA assays). The inhibitory effect of the compound in immune cells (human monocytes, mouse macrophages) was further confirmed via immunoblot assays against downstream proteins in the TLR2 pathway (p-JNK, p-p38, IkBα). Further, nitric oxide assays were used to test the anti-inflammatory potential of INH50 in microglia. INH50 effects were tested *in vivo* in a kainic acid-induced epilepsy mouse model. INH50 or vehicle (DMSO) were injected in the ventral hippocampus of three to four months male C57BL/6 mice. After one hour, they received intra-hippocampal injections of kainic acid and then, they were subjected to telemetric EEG recording for two weeks. Using a customized MATLAB code, epileptiform activities were measured during the status epilepticus (initial 48 hours) and ten days afterward (for 24 hours). **Results:**INH50 is an anti-inflammatory small molecule that decreased TLR2-mediated NF-kB activation in HEK293-TLR2 cells. Further, it reduced the pro-inflammatory cytokine production (IL-6, TNFα) in activated mouse macrophages and human monocytes and the nitric oxide production in microglia. The phosphorylation status of the downstream proteins JNK, p38 and the degradation of IkBα were reduced after treatment with the compound.*In vivo*, during the status epilepticus, the group of mice treated with INH50 presented a significantly lower mean of total daily number of spikes trains ($p < 0{,}0001$), total daily duration of spike trains ($p < 0{,}0001$) and total daily number of spikes (in trains, $p < 0{,}0001$) in comparison to the vehicle group. Interestingly, the same marked difference between groups persisted even after ten days ($p < 0{,}0001$ for all three measures). **Conclusion:**These results indicate that INH50 is a promising hit to develop derivatives with anti-inflammatory properties that decrease epileptiform activity.

Disclosures: S. Rahimi: None. **M. Drexel:** None. **S. Santos-Sierra:** None.

Poster

P152. Antiepileptic Therapies IV

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Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.06

Topic: B.10. Epilepsy

Support: Collaboration Grant from Corlieve Therapeutics
Institut National de la Santé et de la Recherche Médicale (INSERM)
Aix-Marseille University
Agence Nationale de la Recherche: ANR-18-CE17-0023
Centre national de la recherche scientifique (CNRS)
Bordeaux University

Title: Cl002, an aav9 vector expressing engineered mirna targeting knockdown of gluk2-containing kainate receptors as a novel gene therapy approach for treating intractable temporal lobe epilepsy

Authors: C. BOILEAU[1], S. DEFORGES[2], A. GILES[3], A. PERET[1], D. SCAVARDA[4], F. BARTHOLOMEI[5], N. PARTOUCHE[6], J. GAUTRON[6], J. VIOTTI[2], G. PENCHET[7], C. MARCHAL[8], A. TREBUCHON[5], N. VILLENEUVE[5], J. RUMI[2], T. MARISSAL[1], R. KHAZIPOV[1], I. KHALILOV[1], A. LEPINE[5], M. MILH[5], D. FIGARELLA-BRANGER[9], E. DOUGY[9], S. TONG[9], R. APPAY[9], A. MERCER[3], J. SMITH[3], O. DANOS[3], R. H. PORTER[6], C. MULLE[2], ***V. CREPEL**[1];
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Abstract: No targeted treatments for temporal lobe epilepsy (TLE) exist, and the majority of patients are resistant to approved drug therapies. Recurrent mossy fiber sprouting from dentate granule cells (DGCs) is an anatomical hallmark of TLE, which leads to an aberrant excitatory network between DGCs that operates via ectopic kainate receptors (KARs) composed of GluK2/GluK5 heterodimers. Our prior demonstration that GluK2 knockout mice are protected from pilocarpine-induced seizures led us to explore the tractability of an anti-Gluk2 approach to address TLE therapeutically. We have designed AAV9 vectors expressing engineered miRNA designed to knockdown the *grik2* mRNA, with the goal of reducing GluK2 subunit expression in the hippocampus and thus ameliorating the epileptic phenotype. Using this approach, we observed a reduction in GluK2 protein levels following transduction into primary neuronal cultures from both mice and rats. Furthermore, direct hippocampal delivery in pilocarpine-induced epileptic mice significantly reduced the number of epileptic seizures in these mice, and normalized the pathological hyperlocomotion phenotype associated with this model. Finally, transduction of organotypic hippocampal tissue surgically resected from TLE patients showed an almost complete suppression of recorded epileptiform discharges.
These data support the pivotal role of GluK2/GluK5 in triggering the epileptic seizures human TLE, and that a reduction in their expression may be expected to reduce the epileptic phenotype. We believe that AAV-mediated RNAi targeting the expression of GluK2/GluK5-KARs in DGCs is a viable approach to reduce seizures associated with intractable TLE and to address unmet needs in this patient population

Disclosures: C. Boileau: A. Employment/Salary (full or part-time):; INSERM. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending

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Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.07

Topic: B.10. Epilepsy

Support: Section of Posgraduate Studies and Research, Academic Secretary of National Polytecnic Institute, Mexico

Title: Effect of anticonvulsant drugs on nitric oxide levels of neurons in primary culture, possible proconvulsant role of neuronal nitric oxide

Authors: *L. VEGA RASGADO[1], V. ALCÁNTARA FARFÁN[2];
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Abstract: Epilepsy affects about 50 million people worldwide, but 30% of the patients are refractory to the traditional treatments. Thus, the development of new antiepileptic drugs is necessary. Nitric oxide (NO) regulates neuronal excitability in physiological and pathological conditions, with protective as well as deleterious actions. NO participation in epilepsy is demonstrated, but its role in seizures generation is controversial. Some reports indicate that NO plays a role of anticonvulsant, while other show that it leads to proconvulsant effect. Clarification of the dual effects of NO might lead to the design of new antiepileptic drugs, but it is a great challenge. The ubiquity of NO in the central nervous system implies that drugs designed to modify the biological activity of NO may have distinct effects. The therapeutic challenge would be to succeed in manipulating the NO pathways selectively. NO levels are regulated by two constitutive isoforms of the nitric oxide synthase (NOS): neuronal NOS (nNOS) and endothelial NOS (eNOS). However, NO effects are conditioned not only by keeping its concentration between certain limits. Previous results in our laboratory suggest that the contradictory role of NO in seizures generation could depend on the NOS isoform involved. Even they could play an opposite role; one of them proconvulsant, but the other anticonvulsant. Here we study the effect of anticonvulsant drugs on neuronal NO levels (nNO). With that aim primary cultures of neurons were used as a study model, and the effect of different concentrations and time of treatment with amino-oxyacetic acid (AAOA), valproate (VALP), diazepam (DIAZ) and gabapentin (GBPT) on NO levels were investigated, using a spectrophotometric method based on Griess reaction ($N \geq 5$, observations each experiment=4, post-hoc analysis Newman-Keuls test). The effect of anticonvulsant drugs on nNO levels dependent on the concentration and time of treatment. AAOA (except for 10 and 25 mM and 72 hours of treatment), VALP (excluding 10 µM, all times of treatment tested), DIAZ and GBPT (exception of 10, 75 and 100 µM at 24 hours of treatment) decreased nNO levels. The influence of the time of treatment is diverse, depending on the concentration employed. Described results, together with the fact that convulsant drugs increased nNO levels, indicate that apparently it possesses convulsant properties. It seems to be mediated not only by its effect on glutamatergic system but also on GABAergic system, probably through $GABA_A$ receptors. However, this requires forward investigation considering the limitations of this kind of studies and the unexplored influence of inducible NO.

Disclosures: L. Vega rasgado: None. **V. Alcántara farfán:** None.

Poster

P152. Antiepileptic Therapies IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P152.08

Topic: B.10. Epilepsy

Support: Inserm
Agence Nationale de la Recherche (Eranet Neuron program grant to JCP)
Fondation pour la recherche médicale (FRM program grant to JCP and fellowship to FD)
Sorbonne University (fellowship to FD)

Title: Two candidate K-Cl cotransporter 2 (KCC2) enhancers prevent epileptiform activity in vitro and in vivo

Authors: *F. DONNEGER[1,2,3], A. ZANIN[1,2,3], Y. KADIRI[1,2,3], J. ZHANG[4], B. DEVAUX[5], F. CHASSOUX[5], S. LÉVI[1,2,3], J.-C. PONCER[1,2,3];
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Abstract: In neurons, the cation-chloride cotransporters (CCC) KCC2 and Na-K-Cl cotransporter 1 (NKCC1) control intraneuronal chloride homeostasis and, subsequently, the efficacy and polarity of gamma-aminobutyric acid (GABA) signaling. In many neurological disorders, including epilepsy, reduced KCC2 expression or function may result in depolarizing GABA signaling that may then contribute to pathological activities and seizures. Compensating for the dysregulation of CCC function in the pathology therefore appears as a promising therapeutic strategy. Bumetanide, an antagonist of the NKCC1 transporter, failed to prevent acute neonatal seizures in a clinical trial. Here, instead, we tested the effects of two compounds identified from library screening as candidate KCC2 enhancers. However, their mode of action in cortical neurons and their therapeutic potential in epilepsy remain unknown or even controversial. We first compared the mode of action of these two compounds in rat hippocampal neurons. We showed that both of them enhance KCC2 function, as detected in electrophysiological assays. This effect was accompanied by a direct modulation of GABA signaling, involving either positive allosteric modulation of extrasynaptic GABAA receptors or enhanced synaptic GABA release. Single particle tracking experiments revealed that both compounds reduce the lateral diffusion of KCC2 in the plasma membrane. This effect was associated with enhanced KCC2 clustering with no change in total or plasmalemmal KCC2 expression. Both compounds effectively suppressed spontaneous, interictal-like discharges recorded in postoperative hippocampal tissue resected from mesial temporal lobe epilepsy patients. In addition, chronic administration of a Food and Drug Administration (FDA)-approved KCC2 enhancer reduced seizure occurrence by about 67% in a lithium-pilocarpine mouse model of temporal lobe epilepsy. Collectively, our data decipher the mode of action of two candidate KCC2 enhancers in hippocampal neurons and demonstrate for the first time their antiepileptic potential in pharmacoresistant epilepsy.

Disclosures: F. Donneger: None. **A. Zanin:** None. **Y. Kadiri:** None. **J. Zhang:** None. **B. Devaux:** None. **F. Chassoux:** None. **S. Lévi:** None. **J. Poncer:** None.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.01

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant R01AG061200

Title: Aging induces asymmetric trafficking of PDE11A4 in the ventral hippocampus

Authors: *S. BRUCKMEIER, K. PILARZYK, L. PORCHER, M. KELLY;
Univ. of Maryland Sch. of Medicin Program In Neurosci., Baltimore, MD

Abstract: In the context of both regular function and disease, the hippocampus exhibits molecular asymmetries between hemispheres. Our lab studies phosphodiesterase 11A4 (PDE11A4), a hippocampally-enriched enzyme that degrades cyclic nucleotides (cAMP and cGMP). PDE11A4 expression increases with age in the human and rodent hippocampus and increasingly accumulates in filamentous "structures" resembling axons. Here, we determine if these age-related ectopic accumulations of PDE11A4 occur asymmetrically between hemispheres. Aged C57BL/6J mice show a greater age-related increase in PDE11A4-filled structures in the right versus left ventral hippocampus, with no hemispheric asymmetry observed in the hippocampi of young mice. To determine if high PDE11A expression is sufficient to drive asymmetries in PDE11 accumulation, we quantified PDE11A4-filled structures in young BALB/cJ mice as PDE11A expression in young BALB/cJ mice is equal to that of old C57BL/6J mice. Young BALB/cJ mice showed an equal number of PDE11A4-filled structures in the right versus left ventral hippocampus. Finally, we tested possible mechanisms driving age-related asymmetries in PDE11A4 trafficking. We showed phosphorylation of serine 117 on PDE11A4 correlates with asymmetric trafficking of PDE11A4 in vCA1. We also showed isoflurane mimics age-related asymmetric trafficking of PDE11A in the vSub of young C57BL/6J mice, pointing to a possible role for altered glutamatergic signaling. Together, these data suggest that the PDE11A asymmetries observed in aged C57BL/6J mice are not simply driven by higher expression levels, but rather by other aging-specific mechanisms that are unique to each subregion of the ventral hippocampus.

Disclosures: S. Bruckmeier: None. **K. Pilarzyk:** None. **L. Porcher:** None. **M. Kelly:** None.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.02

Topic: C.01. Brain Wellness and Aging

Support: DBT BT/PR6371/COE/34/19/2013
ICMR/LS/133/92183
NCBS Core Funds

Title: Motor learning deficits and SOCE-dependent gene expression changes in STIM1 Deficient mice can be reversed by reducing Septin7

Authors: *S. K. DHANYA[1,2], G. HASAN[3];
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Abstract: Calcium (Ca^{2+}) plays an important role in multiple aspects of neuronal signaling and function. In addition to ligand and voltage-gated calcium channels, Ca^{2+} entry in neurons also occurs through store-operated channels (SOCs) that consist of the pore-forming Orai proteins and the Endoplasmic Reticulum (ER) calcium sensor, the Stromal Interaction Molecule (STIM). Dysregulated Ca^{2+} signaling has been associated with many neurodegenerative disorders in humans and these findings have been replicated in

mouse models. Restoring intracellular calcium homeostasis by modulating components of Store-operated Ca^{2+} entry (SOCE) could be a therapeutic strategy for the treatment of such neurodegenerative disorders. Here we tested this idea by using a Purkinje cell specific Septin 7 knock out for modulating Store-operated Ca^{2+} entry (SOCE). Septin 7 (SEPT7) is a cytoskeletal protein and is known to be a negative regulator of SOCE in both *Drosophila* and human stem-cell derived neurons (1, 2). Our study shows that either lowering or abolishing SEPT7 exclusively in *STIM1* knockout Purkinje neurons modulates the age-dependant gene expression changes brought about by loss of STIM1 (3). Importantly, reduction of SEPT7 in Purkinje neurons could significantly rescue the motor deficits observed in *STIM1* knockout mice (3). Thus, our data identify SEPT7 as an important regulator of neuronal calcium homeostasis and gene expression, thereby modulating neural circuit functions of Purkinje neurons. Our findings are relevant in the context of identifying SEPT7 as a putative therapeutic target for various neurodegenerative diseases caused by reduced intracellular calcium signaling. References: 1) Deb, B. K, Pathak, T. and Hasan, G. (2016). Store-independent modulation of Ca^{2+}entry through Orai by Septin 7. *Nat. Commun.*, *7*, 11751. https://doi.org/10.3389/fcell.2016.001422) Deb, B. K, Chakraborty, P., Gopurappilly, R., & Hasan, G. (2020). SEPT7 regulates Ca^{2+} entry through Orai channels in human neural progenitor cells and neurons. *Cell Calcium*, *90*, 102252. https://doi.org/10.1016/j.ceca.2020.1022523) Dhanya, S. K., & Hasan, G. (2021). Purkinje neurons with loss of STIM1 exhibit age-dependent changes in gene expression and synaptic components. *J. Neurosci.*, *41*, 3777–3798. https://doi.org/10.1523/jneurosci.2401-20.2021

Disclosures: S.K. Dhanya: A. Employment/Salary (full or part-time):; Full time, National Centre for biological sciences. **G. Hasan:** A. Employment/Salary (full or part-time):; Full time, National Centre for biological sciences.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.03

Topic: C.01. Brain Wellness and Aging

Title: Automated development, monitoring, and analysis of iPSC-derived 3D cerebral organoids

Authors: *O. SIRENKO, A. LIM;
Mol. Devices, San Jose, CA

Abstract: Cerebral 3D organoids are a rapidly developing technology that has great potential for understanding brain development and neuronal diseases and can be used for testing effects of compounds and genetic mutations. There has been great progress in developing reproducible methods for culturing brain organoids from induced pluripotent stem cells, that allows characterization of later events in cortical development. Further method development needs to include adoption of the model for testing effects of compounds and drug candidates, as well development methods for testing the functional neuronal activity. We describe method for automated culture and monitoring of cerebral organoids, as well as testing functional neuronal activity by recording and analyzing Ca2+ oscillations. Cerebral organoids were developed from iPSC using Lancaster & Knoblich 2014 method and Cerebral Organoid Kit (STEMCELL Technologies). The method was adopted for partial automated workflow using media

exchanges by Biomek i7 liquid handler (Beckman) and culture monitoring using the ImageXpress Confocal imaging system. We monitored size and morphology of developing brain microtissues in transmitted light over 20 weeks of development using AI-based image analysis (IN Carta) for defining the size, shape, and density of the tissues. Selected microtissues were analyzed during the different phases of development using confocal imaging by expression of Sox2, TuJ1, and GAFP markers. For detection of functional activities calcium oscillations from selected clusters of the microtissues were recorded by imaging and analyzed using MetaXpress image analysis software for kinetic peak analysis. Oscillations were observed after day 50 in culture. Those were sporadic through the volume of micro-tissue, while significantly activated by 4-aminopyridine. Cellular viabilities and organoid morphologies were analyzed using viability markers and 3D image analysis. For assay characterization, we used several neuromodulators including 4-aminopyridine, GABA, NMDA, muscimol, and others. In addition, we tested known neurotoxins rotenone and mercury. The observed changes in oscillation patterns were consistent with expected actions of respective compounds, while the levels of baseline activities and degree of drug responses varied between different micro-tissues. The method demonstrates a promise for evaluation of effects of pharmaceutical drugs, toxins, and genetic mutations, while further method development is needed for screening applications.

Disclosures: O. Sirenko: A. Employment/Salary (full or part-time):; Molecular Devices, LLC. **A. Lim:** A. Employment/Salary (full or part-time):; Moleculr Devices, LLC.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.04

Topic: C.01. Brain Wellness and Aging

Support: NIA grant R01AG060919

Title: Antagonistic roles of ras-mapk and akt signaling in integrin-k^+ channel complexes-mediated cellular apoptosis

Authors: *E. FORZISI[1], F. SESTI[1], P. RAJWADE[2];
[1]Rutgers Univ. Grad. Program In Neurosci., Piscataway, NJ; [2]Rutgers Univ., Piscataway, NJ

Abstract: Complexes formed by α5-integrins and the voltage-gated potassium (K+) channel KCNB1 (Kv2.1), known as IKCs, transduce the electrical activity at the plasma membrane into biochemical events that impinge on cytoskeletal remodeling, cell differentiation and migration. However, when cells are subject to stress of oxidative nature, IKCs turn toxic and cause inflammation and death. Here, biochemical, pharmacological and cell viability evidence demonstrates that integrins activate an apoptotic Mitogen Activated Protein Kinase/Extracellular signal-Regulated kinase (Ras-MAPK) pathway. Simultaneously, wild type (WT) KCNB1 channels sequester Protein kinase B (Akt) causing dephosphorylation of BCL2 associated agonist of cell death (BAD), a major sentinel of apoptosis progression. In contrast, IKCs formed with C73A KCNB1 variant that does not induce apoptosis (IKC-C73A), do not sequester Akt and thus are able to engage cell survival mechanisms. Taken together, these

data suggest that apoptotic and survival forces co-exist in IKCs. Integrins send death signals and KCNB1 channels simultaneously sabotage survival mechanisms. Thus, the combined action of integrins and KCNB1 channels in IKCs advances life or death.

Disclosures: E. Forzisi: None. **F. Sesti:** None. **P. Rajwade:** None.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.05

Topic: C.01. Brain Wellness and Aging

Support: La Caixa Foundation (LCF/PR/HP17/52190001)
Centro 2020 (CENTRO-01-0246-FEDER-000010)

Title: Adenosine A_{2A} receptor over-functioning as a determinant of brain aging

Authors: *R. A. CUNHA[1,2];
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Abstract: Background: The regular consumption of moderate doses of coffee is associated with increased longevity and healthspan (N Engl J Med 2012; 366:1891). One particular component of coffee, caffeine, has been shown to attenuate memory deficits and mood deterioration through its ability to rebalance a modulation system operated by adenosine (J Alzheimers Dis 2010; 20:S1). Adenosine is a stress signal released in an activity-dependent manner and over-activation of its A_{2A} receptors ($A_{2A}R$) is paramount to trigger neuronal damage (J Neurochem 2016; 139:1019). Since neurodegenerative diseases are prevalent on aging, we now tested if $A_{2A}R$ blockade with the selective $A_{2A}R$ antagonist SCH58261 (0.1 mg/kg/daily, ip) can revert synaptic and memory deficits in aged (20-22 months-old) rats. Results: SCH58261-treated aged rats recovered performance in memory tests to the level of young rats, in which SCH58261 had no effects. Memory-impaired aged rats also displayed lower hippocampal long-term potentiation, a form of synaptic plasticity, together with a lower density of vesicular glutamate transporter type 1 (vGluT1) and increased $A_{2A}R$ density in hippocampal synapses. All these changes were reverted by treatment with SCH58261 in aged rats. In humans, $A_{2A}R$ density in the hippocampus was also increased in aged individuals (72-85 years) compared to young adults (27-35 years) and $A_{2A}R$ density was even higher in patients with early AD, mainly in hippocampal neurons.Conclusions: These findings show that $A_{2A}R$ over-function is critically required for the development of age-associated memory deficits, likely involving synaptic dysfunction. This prompts considering increased $A_{2A}R$ density as a biomarker of poorer quality of brain ageing.

Disclosures: R.A. Cunha: None.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.06

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA 1RF1AG062831-01
NIH/NIA 2RF1AG043640-06

Title: Aging compromises Oligodendrocyte Precursor Cell maturation and efficient remyelination in the aging monkey brain.

Authors: *C. DIMOVASILI, A. E. FAIR, K. V. BATTERMAN, T. L. MOORE, D. L. ROSENE; Boston Univ. Sch. Med., Boston, MA

Abstract: Non-neurodegenerative normal aging in primates does not entail loss of neurons. Instead, myelin degenerates, leading to loss of white matter volume and axons. This age-related loss of white matter occurs predominantly in the anterior regions of the corpus callosum and cingulum bundle and is tightly associated with cognitive decline, likely due to cortical disconnection. In the young brain, local oligodendrocyte precursor cell (OPC) populations respond to myelin damage by proliferation and differentiation into mature oligodendrocytes which produce new myelin. However, in the aging brain, remyelination is less effective. Here we tested whether the intrinsic differentiation potency of old OPCs is a bottleneck to remyelination in the aging brain. For this, we used frozen sections of frontal white matter from 5 young (<10 years) and 6 old (>20 years) cognitively characterized rhesus monkeys. We applied immunohistochemistry and stereological counting of BCAS1 cells, stratified by morphology into early differentiating (Type 1) and mature myelinating (Type 2) oligodendroglia. We also applied *in situ* hybridization to a subset of these subjects, to quantify the expression of transcription factor Nkx2.2, combined with anti-PDGFRa immunofluorescence as a marker of OPCs. Results were analyzed relative to age and our Cognitive Impairment Index (CII). We found that Type 1 BCAS1 cells were decreased 2.3-fold in the anterior cingulum bundle of aged monkeys ($p=0.0034$), and 2.4-fold in the rostral corpus callosum (=0.03). This change did not correlate with cognitive impairment. Interestingly, Type 2 BCAS1 cells did not differ between age or cognition groups. Nkx22 expression, which is necessary for OPC to oligodendrocyte differentiation, was decreased 2-fold in the OPC populations of the aging anterior cingulum bundle ($p<0.0001$). Nkx22 decrease was also tightly associated with cognitive impairment ($p<0.0001$). These results collectively show that with aging, OPCs fail to differentiate into new mature oligodendrocytes, likely impairing remyelination in the aging brain. Interventions to stimulate OPC differentiation and promote remyelination could potentially reduce or reverse the accumulation of age-related myelin and damage associated cognitive decline.

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Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.07

Topic: C.01. Brain Wellness and Aging

Support: 1T32GM136651-01
AHA EIA34770133
R01 AG061190-01
NSF 20,15,276
AARF-17- 533294

Title: Characterization of the molecular and morphological changes underlying synapse loss in the vulnerable aging rhesus macaque brain

Authors: *E. WOO[1], D. DATTA[4], I. PERONE[1], Y. M. MOROZOV[2], L. SANSING[3], A. F. ARNSTEN[1]; [2]Dept Neurobiol, [3]Dept. of Neurol., [1]Yale Univ. Sch. Med., New Haven, CT; [4]Yale Univ., New Haven, CT

Abstract: Loss of excitatory synapses on spines highly correlates with cognitive impairment in Alzheimer's disease (AD) and is region-specific, leaving some areas of the brain largely unaffected while devastating circuits in the association cortices. However, the underlying mechanisms leading to synapse loss, including this circuit specificity, are poorly understood. We hypothesize that vulnerable excitatory spines express high levels of calcium which become dysregulated with advancing age, and that chronically elevated cytosolic calcium leads to calcium overload of mitochondria and the generation of inflammatory, "eat-me" signals (e.g. calreticulin) to nearby glia to initiate synapse phagocytosis. This hypothesis was studied in *ex vivo* studies of the aging rhesus monkey dorsolateral prefrontal cortex (dlPFC), and in *in vitro* primary cortical cultures designed to mimic the sustained calcium dysregulation that develops in the aging dlPFC. Aging rhesus macaques naturally develop region-selective synapse loss and cognitive impairment, as well as amyloid plaques and tau pathology, and thus are an advantageous model to study the molecular and cellular events associated with age-related neurodegeneration. In particular, the circuits in deep layer III (LIII) of the dlPFC that subserve working memory are especially vulnerable to spine loss with age. These circuits are normally dependent on elevated calcium signaling to support the persistent firing needed for working memory, but lose regulation of calcium-cAMP signaling with advancing age, e.g. with loss of PDE4D from dendrites and spines (Alzh&Dem 17:920-932, 2021). Aged LIII dlPFC pyramidal cells also express dysmorphic mitochondria in their dendrites, identified as "Mitochondria-on-a-string" (MOAS), which are also seen in familial AD mouse models and human AD postmortem cortices. The current study used immunoEM in young vs. aged rhesus layer III dlPFC and found that MOAS are associated with the expression of complement C1q, while there is decreased association between MOAS and PDE4D. We next asked whether calreticulin, a known "eat-me" signal, is expressed by LIII dlPFC neurons and could mediate synaptic phagocytosis. We find that calreticulin is robustly expressed in LIII dlPFC. The explicit role of chronic calcium dysregulation in causing mitochondrial dysfunction and inflammatory C1q and calreticulin signaling is currently being tested in primary neuronal cultures. Interventions that restore regulation of calcium in higher cortical circuits may protect neuronal integrity and cognitive function.

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Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.08

Topic: C.01. Brain Wellness and Aging

Title: Identification of an age-related plasma protein with effects on cognitive function

Authors: *J. M. ADAMS[1], S. V. REGE[1], R. HARISH[1], A. T. LIU[2], R. BRITTON[1], S. S. MINAMI[1], E. CZIRR[1], M. KERRISK CAMPBELL[1];
[1]Alkahest Inc, San Carlos, CA; [2]CODA Biotherapeutics Inc, South San Francisco, CA

Abstract: In the coming decades, it is expected that people over 65 years of age will make up 15% of the global population. With that comes the challenge of addressing age-related, neurological disorders, like Alzheimer's and dementia, thus motivating the identification of new therapeutics to alleviate and improve symptoms, such as cognitive decline. Although multiple candidates for therapeutics have been proposed and proved beneficial in pre-clinical models, few have managed to translate well into the clinic. To this effort, we identified a detrimental enzyme, leukotriene A4 hydrolase (LTA4H), found at high levels in plasma of aged and cognitively impaired humans and show that an increase in this enzyme correlates with decreased cognition in Alzheimer's patients. When we dosed mice with a recombinant form of this enzyme, we were able to induce cognitive deficits. We also show in rodents that chronic inhibition of this enzyme with a small molecule inhibitor leads to improvement in cognition-based behavioral readouts and histological changes in the water-channel protein, aquaporin-4, pointing to changes along the blood-brain barrier. These data support the finding of a novel enzyme involved in age- and disease-related cognitive decline and an inhibitor that can effectively act in different species to modulate this detrimental enzyme.

Disclosures: J.M. Adams: A. Employment/Salary (full or part-time):; Alkahest Inc. **S.V. Rege:** A. Employment/Salary (full or part-time):; Alkahest Inc. **R. Harish:** A. Employment/Salary (full or part-time):; Alkahest Inc. **A.T. Liu:** A. Employment/Salary (full or part-time):; Coda Biotherapeutics Inc. **R. Britton:** A. Employment/Salary (full or part-time):; Alkahest Inc. **S.S. Minami:** A. Employment/Salary (full or part-time):; Alkahest Inc. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest Inc. **M. Kerrisk Campbell:** A. Employment/Salary (full or part-time):; Alkahest Inc..

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.09

Topic: C.01. Brain Wellness and Aging

Support: NSERC Grant RGPIN-2018-04401
ARC-NL Research Grant

Title: The role of L-type calcium channels in age-associated memory decline

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Abstract: Aging is associated with cognitive decline and memory loss in humans. In rats, age-associated impairment of spatial and olfactory learning has also been observed. We investigated the role of L-type calcium channels (LTCCs) in both the piriform cortex (PC) and the hippocampus, which may be involved in the disruption of calcium homeostasis, contributing to changes in synaptic plasticity with age. We employed spatial and olfactory behavioral tasks that involve the hippocampus and PC. In an odor-associative learning task, both intraperitoneal (i.p.) and local infusions of nimodipine into the PC (5.5mg/kg for i.p; and 1-100uM 0.5uL/side infused) prevented the ability of young Sprague-Dawley rats (6-9 months) to learn that a positive odor contained a food reward. In aged rats (>18 months), on the other hand, i.p. and local infusion of nimodipine into the CA1 layer of the hippocampus improved odor-associative learning and spontaneous location recognition compared to vehicle controls. We then examined neuronal excitability in both pyramidal neurons of the PC and in the CA1 layer of the hippocampus. In young rats (<5 months old) and aging rats (>18 months old), we used whole-cell patch clamp recording to measure intrinsic electrophysiological properties of pyramidal neurons in each region. In both regions, action potential (AP) threshold was significantly higher for aged rats, with larger fast afterhyperpolarization (AHP). Aged hippocampal neurons also displayed a reduced excitability, along with higher input resistance and a significantly larger slow AHP, suggestive of increased LTCC activity. However, AHP and excitability differences were not observed in the aged PC neurons. Indeed, immunohistochemistry reveals that the LTCC subunit Cav1.2 has significantly increased expression in CA1 soma and increased Cav1.3 in CA1 dendrites in aged rats compared to young rats. In contrast, Cav1.3 expression was lower, and Cav1.2 expression was unchanged in the soma of the aged PC neurons. Altogether our data suggests that LTCCs have increased hippocampal expression with age and play a significant role in age-related mechanisms of reduced synaptic plasticity and overall cognitive decline.

Disclosures: V. Rajani: None. **S. Ghosh:** None. **T.N. Critch:** None. **A. Maziar:** None. **Q. Yuan:** None.

Poster

P182. Molecular Mechanisms: Brain Aging, and Neurodegeneration I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P182.10

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 GM121457
NIH R01 NS107475
NIH T32 GM008541
Departmental support

Title: Age-related decline of neuronal function involves a loss of inhibitory signaling in C. elegans

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Massachusetts Med. Sch., Worcester, MA; [3]Dept. of Anesthesiology, Perioperative and Pain Med., Brigham and Women's Hosp., Boston, MA

Abstract: Neural function declines with age resulting in behavioral deficits. How this age-related decline is related to changes in neural connectivity and circuit function on the cellular level is largely unknown. The nematode worm *Caenorhabditis elegans* is well suited for the investigation of neural aging, given its fully-mapped neural connectome and tractability for functional neuronal imaging. The advent of multi-neuron functional imaging in *C. elegans* presents an opportunity to define, for the first time, the effects of aging on nervous systemwide function with cellular resolution. Moreover, this animal is a powerful model system for the genetic investigation of molecular factors influencing aging. Here we employ multi-neuronal fluorescence imaging in *C. elegans* to measure changes in neural activity and connectivity with age across the animal's nervous system. Employing transgenic pan-neuronal expression of the fluorescent calcium indicator GCaMP6s, we capture neural activity at single-cell resolution across the organism's entire head region, using light sheet microscopy. We identify substantial age-related alterations in the activity dynamics of neurons as well as changes in connectivity and functional organization of the system. As the animals age, we observe a loss of systemwide organization and a corresponding shift in individual neuron activity toward higher frequencies. We also observe a specific loss of anti-correlative (i.e. inhibitory) signaling between neurons, resulting in an overall shift in the excitatory-inhibitory (E/I) balance of the system. In support of this, we find that application of the $GABA_A$ agonist muscimol diminishes aspects of nervous system decline in aged animals. Interestingly, age-related effects are recapitulated in young animals bearing a gain-of-function mutation within the *unc-2* gene, encoding a pre-synaptic voltage-gated calcium channel. Conversely, aging effects are greatly diminished by a loss-of-function mutation in *ced-4*. *Ced-4* is a key regulator of a calcium-activated caspase pathway known to play a role in synaptic elimination across multiple species. During development, UNC-2/CaV2 activity is known to trigger the removal of inhibitory GABAergic synapses in motor neurons through a CED-4 dependent pathway. Our results suggest that a similar process is occurring as the animals age, resulting in a loss of inhibitory signaling and disruption of system dynamics. Through comprehensive multi-neuronal imaging, we measure the progressive breakdown of neural activity and system dynamics with age and begin to identify the cellular processes and changes in synaptic signaling that contribute to this decline.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P246.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Key R&D Program of China (2018YFE0203600)
Research Grants Council of Hong Kong (the Theme-Based Research Scheme [T13-607/12R] and the Collaborative Research Fund [C6027-19GF])
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NSFC-RGC Joint Research Scheme (32061160472)
Guangdong Provincial Key S&T Program (2018B030336001)

Title: Deep learning methods improve polygenic risk analysis and prediction for Alzheimer's disease

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Abstract: Recent advances in genetic sequencing have enabled comprehensive genetic analyses of human diseases, resulting in the identification of numerous genetic risk factors for heritable disorders including Alzheimer's disease (AD). Such analyses enable AD risk prediction well before disease onset, which is critical for early interventions. However, current analytical approaches have limited ability to accurately estimate the risk effects of genetic variants owing to epistatic effects, which have been overlooked in most previous studies, resulting in unsatisfactory disease risk prediction. Herein, we modeled AD polygenic risk using deep learning methods, which outperformed existing models (i.e., lasso model) for classifying disease risk. Moreover, by examining the associations between the outcomes from deep learning methods and AD plasma biomarkers in our in-house Chinese AD cohorts, we showed the polygenic risk captured by the model is associated with levels of plasma Aβ and p-tau181 in normal controls. Thus, our results demonstrate the utility of deep learning methods for modeling the genetic risks of human diseases, which can facilitate both disease risk classification and the study of disease mechanisms.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P246.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA Grant K08AG064039
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Alzheimer's Association AACF-17-524184
Spanish Ministry of Science, Innovation, and Universities FPU
Real Colegio Complutense at Harvard University Research Grant

Title: Cyclic multiplex fluorescent immunohistochemistry and machine learning reveal distinct states of astrocytes and microglia in normal aging and Alzheimer's disease

Authors: *C. MUÑOZ-CASTRO[1,2,3,4], A. NOORI[1,5], C. MAGDAMO[1,2], J. D. MARKS[1], M. P. FROSCH[1,2,3], S. DAS[1,2,3], B. T. HYMAN[1,2,3], A. SERRANO-POZO[1,2,3];
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Abstract: Background: Astrocytes and microglia react to Aβ plaques and neurofibrillary tangles in the Alzheimer's disease (AD) brain, but the consequences of such responses remain elusive partly due to the limited multiplexing capability of immunohistochemistry. We have developed a methodology of cyclic multiplex fluorescent immunohistochemistry on human postmortem brain sections followed by an analysis pipeline that enables a deep morphological quantitative characterization of these glial cells in the context of their spatial relationships with plaques and tangles. **Methods:** Single FFPE sections from the temporal association cortex (n=7 control and n=7 AD) were subjected to 8 cycles of multiplex fluorescent immunohistochemistry, including 7 astroglial, 6 microglial, 1 neuronal, Aβ, and p-tau markers. Our analysis pipeline consisted of: (1) image alignment across cycles; (2) background subtraction; (3) manual annotation of 5,172 ALDH1L1+ astrocytic and 6,226 IBA1+ microglial profiles; (4) local thresholding and segmentation of profiles; (5) machine learning models on marker intensity data; and (6) deep learning on image features. **Results:** Spectral clustering identified three phenotypes of astrocytes and microglia, which we termed "homeostatic," "intermediate," and "reactive." Reactive and, to a lesser extent, intermediate astrocytes and microglia were closely associated with AD pathology (≤50 μm). Compared to homeostatic, reactive astrocytes contain substantially higher GFAP and YKL-40, modestly elevated vimentin and TSPO as well as EAAT1, and reduced GS. Intermediate astrocytes are defined by markedly increased EAAT2, moderately increased GS, and intermediate GFAP and YKL-40 levels. Relative to homeostatic, reactive microglia show increased expression of all markers (CD68, ferritin, MHC2, TMEM119, TSPO), whereas intermediate microglia exhibit increased ferritin and TMEM119 as well as intermediate CD68 levels. Machine learning models accurately discriminated between control and AD subjects at the single-cell level, either applied on high-plex signal intensity data (gradient boosting machine) or directly on image features (convolutional neural networks). **Conclusions:** Cyclic multiplex fluorescent immunohistochemistry combined with machine learning models allow the deep phenotyping of glia at single-cell resolution in postmortem brain specimens to identify distinct states in health and

disease. Besides the homeostatic and reactive, we identified a novel “intermediate” state of astrocytes and microglia in AD, which may represent a resilience mechanism or, alternatively, a transitional state between homeostatic and reactive.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P246.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Financial support from BrainTrip Limited

Title: EEG based tool for detection of cognitive impairment - results from a large ecological trial on seniors

Authors: *J. DREO[1,2], J. JUG[2,3], B. ALJAŽ[3], D. SAKIć[2], I. AKSENTIJEVIć[4,2];
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Abstract: Dementia is fast becoming one of the leading causes of impairment in old age with major dementia advocacy groups increasingly advocating for populational screening programs. Early detection coupled with early intervention (pharmacological, social, rehabilitation), even in the absence of a disease-modifying cure, is the only way for patients to maintain quality of life and independence. However, the tools currently used to diagnose dementias in clinical practice (brain imaging, CSF biomarkers, psychometric testing, and clinical observation) are simply not adequate for large-scale, cost-effective, and practical populational screening. We have tested a new approach of screening for cognitive impairment based on fully automatic analysis of EEG signals obtained with a mobile 24-channel EEG amplifier (mBrainTrain), sponge-based EEG caps (Greentek), and custom software (BDI) for EEG recording and analysis of cognitive function (BrainTrip). The BDI software a) guides minimally-trained users through the EEG recording, b) provides online EEG data quality assessment, c) performs fully automated qEEG analysis of the recorded data and returns immediate feedback on potential cognitive impairments in the tested subject. The BDI software first analyzes EEG data by automatically labeling and correcting for common artifacts. It then calculates spectral EEG features known to be associated with poor cognitive performance and combines them into a prediction model based on density clustering and a neural net classifier. We conducted a large-scale ecological evaluation of the accuracy, specificity, and sensitivity of this EEG-based tool for cognitive assessment by performing 840 EEG recordings on 220 seniors recruited from senior care homes in Slovenia between May and October 2021. Each senior participated in 4 separate recording sessions with 1-3 weeks between sessions. In each session an 8-min long rest EEG recording (eyes open and closed) was done with the BrainTrip system. Additionally, during each session participants’ cognitive abilities were tests with one of four cognitive tests (MoCA, ADAS-Cog11, WAIS, Eurotest+Phototest). Preliminary results of BDI performance (compared to a gold standard based on a

factor-analysis of all psychometric tests on 320 recordings obtained up to July 2021) for mild cognitive impairment/dementia are: Sensitivity 74.6% / 89.3%, Specificity 93.5% / 97.0%, Accuracy 86.2% / 94.3%. Based on this performance we conclude that EEG-based assessment of cognitive function is a promising option of screening for MCI and dementia.

Disclosures: J. Dreo: A. Employment/Salary (full or part-time):; BrainTrip Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainTrip Limited. **J. Jug:** A. Employment/Salary (full or part-time):; BrainTrip Limited. **B. Aljaž:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainTrip Limited. **D. Sakić:** A. Employment/Salary (full or part-time):; BrainTrip Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainTrip Limited. **I. Aksentijević:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainTrip Limited.

Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P246.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA K99 AG070390

Title: Clinical utility of blood-based, microglial derived exosomes as biomarkers for Alzheimer’s disease

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Abstract: Background: Recent studies suggest neuronal and astrocyte-derived exosomes may serve as the source of biomarkers for many neurodegenerative diseases, include AD. However very few studies have characterized the biomarker potential of microglial derived exosomes. **Method:** Plasma exosomes were extracted and precipitated from AD, mTBI patients and age matched controls. Extracted exosomes were enriched against a microglial source (TMEM119) using magnetic immunocapture and fluorescence-activated cell sorting (FACS) sorting. MDEs were characterized by size (Nanosight) and shape (TEM). Exosome marker profiling was done by western blot. MDE cargo proteins will be quantified using ELISA. **Result:** Blood-based MDEs demonstrate similar size distributions and shape to previously reported exosome preparations. Western Blot demonstrated that MDEs were positive for exosome marker Flotilin-1; microglial markers CD68 and IBA1 and negative for astrocyte marker, GLAST. Further characterization of MDE protein cargo levels, which include AD-related (Aβ and p-tau) and inflammatory markers, will be analyzed, and presented. **Conclusion:** MDEs can be successfully isolated from human blood. MDEs may also serve as useful blood-based biomarkers for AD diagnosis, akin to other CNS-derived exosomes. Further characterization is required to determine the biomarker potential of MDEs for mTBI and AD.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

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Program #/Poster #: P246.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ZonMW TOP grant #91218018

Title: Longitudinal measurement of neuronal network activity in multiple brain regions in APP/PS1 mice

Authors: *F. C. VAN HEUSDEN[1], A. VAN NIFTERICK[2], A. A. GOUW[2], A. B. SMIT[1], R. E. VAN KESTEREN[1];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, with a long preclinical and prodromal phase. To enable the study of disease mechanisms, AD has been modeled in transgenic animal lines and over the years our knowledge on the molecular and cellular processes underlying the early stages of AD pathogenesis has expanded. However, translating these findings to the clinic has proven difficult in terms of finding good biomarkers or treatment for AD. In mouse studies, neuronal hyperactivity and interneuron dysfunction have been observed. Whereas at an early disease stage hippocampal parvalbumin (PV) interneurons seem to be hyperactive in APP/PS1 mice, a commonly used mouse model for AD-associated amyloidosis, they appear to be impaired at a later disease stage. As the balance between excitation and inhibition is crucial to the generation of oscillatory activity in the brain, and since network activity provides an opportunity for mouse-to-human translation, we here investigate longitudinal changes in network activity in APP/PS1 mice. Local field potential (LFP) recordings were performed in three different brain areas - prefrontal cortex, hippocampus and parietal cortex - in male mice from 3 months of age (moa) until 10 moa. LFP activity within brain regions and synchronization between brain regions were analyzed. We observe a shift in LFP power from the lower to the higher frequencies in APP/PS1 mice compared with wildtype controls, as well as alterations in connectivity between brain regions. Using MEG and EEG data from PSEN1 mutation carriers, patients with mild cognitive impairment (MCI) and AD patients we aim to further elucidate whether and how mouse LFP data translate to human patients, and whether mouse LFP recordings hold potential for the identification of novel biomarkers for AD.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

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Program #/Poster #: P246.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: US NIH grant AG060608
NIH grant AG028383

Title: Vascular risk biomarkers are linked to frontal memory-related neuromarkers

Authors: J. J. LATHAM[1], T. L. SUDDUTH[2], B. WANG[3], J. M. BARBER[1], M. R. KELLY[1], K. SNYDER[1], B. J. MARTIN[1], G. A. JICHA[1], D. M. WILCOCK[1], *Y. JIANG[1];
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Abstract: Vascular Risk Biomarkers are Linked to Frontal Memory-related Neuromarkers
Jeremy Latham, Tiffany L. Sudduth, Baoxi Wang, JM Barber, MR Kelly, KE Synder, BJ Martin, GA Jicha, Donna Wilcock, & Y Jiang
We reported longitudinal evidence that left frontal memory-related signals predict risk of amnestic Mild Cognitive Impairment (MCI) about 5 years before clinical diagnosis (Jiang et al., 2021) in healthy cognitively intact older adults. MCI is a prodrome of dementia. There is limited understanding of MCI due to mixed Alzheimer's disease (AD) and vascular pathologies. Identifying cause-specific MCI risk pre-symptomatically increases the ability to slow cognitive decline. The relationship between subtypes of MCI induced by vascular dementia was not clear. Here we test the hypothesis that increased vascular risk alters brain signals during a cognitive task in older adults.
20 cognitively intact healthy older adults (median age 68, 9 females) from the University of Kentucky Alzheimer's Disease (AD) Research Center participated in the study. Each volunteer was assessed with the Montreal Cognitive Assessment (MoCA) and vascular/AD plasma markers were collected. Brain activity and memory performance were recorded during the 15-min Bluegrass working memory test using a 14-channel, wireless electroencephalography (EEG) headset (eMOtiv; Borhani et al., 2021). Pearson correlations were used to assess associations between frontal EEG sites and plasma markers for Vascular risk factors.
Increased frontal F7 or F3 "difference brainwaves" (Diffs: Nontarget > target) were associated with reduced ability to hold the memory target. We found that frontal F3 Diffs are negatively correlated with MoCA scores (R= -0.457) while diastolic and systolic blood pressure were positively correlated with F7 Diffs (R=0.431 and R=0.463). Left frontal signals were also significantly correlated with multiple serum biomarkers. The most significant biomarker was serum A1C (a known risk factor for developing vascular MCI-like states), which was positively correlated with mean Diffs at F3/F7 sites, F3, and F7 (R=0.645, 0.528, and 0.313).
We report that a variety of plasma biomarkers for vascular risks, specifically changes in hemoglobin and blood pressure, were associated with decreased working memory-related neural functions. Our findings directly link increased vascular risk factors with reduced neural functions of holding items in working memory in pre-symptomatic older adults.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

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Program #/Poster #: P246.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: German Research Foundation DFG CRC 1052
German Research Foundation DFG SCHR 774/5-1

Title: Heart failure decouples the precuneus from other brain regions - A link to Alzheimer's disease?

Authors: *M. L. SCHROETER[1], F. THIEL[1], F. BEUTNER[2], A. TEREN[2], A. VILLRINGER[1], K. MUELLER[1];
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Abstract: Aging increases the risk to develop neurodegenerative diseases, most importantly Alzheimer's disease. Understanding mechanisms and strategies to prevent disease and modify its course are of uttermost importance. A proteome-wide association study identified N-terminal prohormone of brain natriuretic peptide (NT-proBNP), a biomarker for heart failure (HF), to be associated with development of dementia over five years (Walker et al.; Nature Aging 2021;1:473-489). Recently, we had investigated consequences of HF associated with coronary artery disease (CAD) for brain structure in eighty patients of the Leipzig Heart Center in Germany (Mueller et al.; Circulation Research 2020;126(6):750-764). Gray matter density (GMD) as measured with structural magnetic resonance imaging (MRI) was diminished in patients with HF due to CAD across the brain, i.e. in frontomedian, parietal, posterior cingulate cortex, and precuneus, when compared with controls. This finding was replicated and focused onto the posterior cingulate cortex and precuneus in patients with CAD with HF compared with those without HF. The impact of HF on brain structure was further supported by biomarkers for HF. Cardiac ejection fraction correlated positively with GMD across the whole frontal and parietal medial cortex, whereas NT-proBNP was negatively associated with GMD in the medial and posterior cingulate cortex, hippocampus, and precuneus. Remarkably, these brain regions have been identified meta-analytically as core hubs involved in Alzheimer's disease, and its risk state mild cognitive impairment (Schroeter et al.; NeuroImage 2009;47(4):1196-1206). Here, we investigated the impact of HF on brain connectivity with functional resting-state MRI in the same cohort. HF was associated with decreased connectivity (network centrality) in the precuneus if patients with and without HF were compared - the same brain region identified as predicting conversion from mild cognitive impairment to Alzheimer's dementia. Regional centrality was correlated with HF-related biomarkers ejection fraction and NT-proBNP. In sum, HF due to CAD decouples the precuneus as the decisive connectivity hub from other brain regions, which might indicate higher vulnerability for the development of cognitive dysfunction such as in Alzheimer's disease.

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Poster

P246. Biomarkers in Neurodegenerative Diseases V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P246.08

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: Personal founds

Title: A spreadsheet structure for an EEG/neurofeedback-based re-classification of Alzheimer-disease trajectories with a novel philosophical approach

Authors: *J. F. GOMEZ-MOLINA[1], U. M. RICOY[2], Á. L. GÓMEZ-MOLINA[1];
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Abstract: Studies (classification, monitoring, intervention) of Alzheimer's Disease (AD) should, ideally, be based on evidence, tools and concepts accessible and replicable to the patient and marginalized communities (Gomez-Molina March for Science 2017, "Unbiased Science constructed for all and for the common good", 2017, Medellín, Metro Station/Stadium). Abnormalities of activation states in EEG-rhythms and their "interrelatedness"/connectivity are present in AD (Babilony, GBC-group 2021; Gomez-Molina et. al 1999, 2003). They show, in simple terms, "sleep-like slowing". See details in Gomez-Molina SfN-J-abstract. RESULTS. I.Classification arrays of AD progression based on chrono-biological issues (24 h, 7 days, 360 days, 3-11 years?) and "real-time" responses to treatments (drugs, nutrition, neuromodulation, neurofeedback, behavioral/cognitive therapies, sleep-pattern therapies). II.Algorithms: "If h[(alpha+ k*beta/gamma)/g(delta+theta)] have increased, then try to repeat what you did recently (7 days); 0<k<1, g(.) corrects for normal aging, h[.]: spectral band corrections for alpha-peak/theta-minima periodicity"."Calculate pijr, the probability of having the result r given lifestyle/treatment i and environmental condition j"."Given patient's preferences (weights) for i, r, calculate expected total risks, costs, benefits on a week-by-week basis and projected to the future". With their physician, patients propose treatments and AD-trajectory. CONCLUSIONS: I. Participation in the design of their own AD-trajectories may give sense of autonomy, freedom and dignity to patients. Contribute to mind exploration, science and other patients gives them existential meaning. II. Additional use of portable low-cost accelerometers can be useful. III. Multiple membership fuzzy-functions allows jumps across AD-classifications. IV. MRI/MEG, if available, can correct for skull and gray matter distance/co-alignment of pyramidal cells (see YouTube keywords: neurolectric minds Gomez-Molina). Conception/initiative/develop/writing/analysis: JFGM. Comment/Anal.: ALGM

Disclosures: J.F. Gomez-Molina: None. **U.M. Ricoy:** None. **Á.L. Gómez-Molina:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.01

Topic: C.10. Brain Injury and Trauma

Support: CONACyT-FOSISS No. FIS/IMSS/PROT/1769

Title: Environmental enrichment promotes cognitive recovery after a pediatric traumatic brain injury in rats

Authors: *J. ZAMUDIO FLORES, A. SALINAS GARCÍA, J. MEJIA OLIVA, N. LAJUD;
Ctr. de Investigación Biomédica de Michoacán, Inst. Mexicano del Seguro Social, Morelia, Mexico

Abstract: Pediatric traumatic brain injury (TBI) is a global public health concern that represent one of the main causes of death and disability in children and adolescents. Studies have reported that TBI-related disabilities in early life are worse than those that occur after a TBI in adult life. Environmental enrichment (EE) is a rodent model of rehabilitation which has been shown to efficiently simulate the recovery observed in clinical practice. EE confers motor and histological benefits and restores cognitive performance after adult TBI. Therefore, we consider that EE can be a useful tool to promote functional recovery after pediatric TBI. To prove this, male Sprague-Dawley rats undergoing controlled cortical impact surgery at PND 21 were used (depth: 2.5 mm, velocity: 4 m/s; n=20). They were later divided into groups with standard (STD) or EE conditions and allowed to recover for 14 days. We evaluated cognitive performance in the Morris water maze (MWM) test from post-injury day 14 to 19. The results indicated that TBI+STD significantly impaired cognitive performance in the training phase of the MWM when compared to Sham+STD; however, no differences were observed between TBI+EE and Sham groups. There was no effect of EE or injury on the probe trial performed at P19. In conclusion our data indicate that EE improves cognitive outcome after pediatric TBI.

Disclosures: J. Zamudio Flores: None. **A. Salinas García:** None. **J. Mejia Oliva:** None. **N. Lajud:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.02

Topic: C.10. Brain Injury and Trauma

Support: CONACyT-FOSISS No. 289897
Coordinacion de Investigación Científica - UMSNH

Title: Immune Tolerance to Neural- Derived Antigens Does not Improve Cognitive Deficits After Traumatic Brain Injury in Rats

Authors: *E. MELÉNDEZ HERRERA[1], J. C. MEJÍA-OLIVA[1], J. ZAMUDIO FLORES[2], F. SALINAS GARCÍA[2], M. ROMÁN LÓPEZ[1], N. LAJUD[2];
[1]Inst. de Investgaciones Sobre los Recursos Naturales, Univ. Michoacana de San Nicolás de Hidalgo, Morelia, Mexico; [2]Inst. Mexicano del Seguro Social, Morelia, Mexico

Abstract: Inflammation is a key event after traumatic brain injury (TBI). Chronic inflammation is triggered and sustained by brain tissue-derived molecules (B-Ag) recognized as self-antigens by T and B

cell receptors. This work explored the possibility of avoiding the negative consequences of chronic inflammation by the induction of tolerance to B-Ag through anterior chamber associated immune deviation (ACAID) prior to TBI. To do this, 46 female rats (postnatal day 75-80) were randomly allocated to two experimental groups and injected in the anterior chamber of the eye with vehicle (PBS) or B-Ag. Both groups were then divided into two subgroups (SHAM and TBI). The sham groups were only craniotomized (SHAM-PBS n=12; SHAM-B-Ag n=12), while the TBI groups were also injured by a controlled cortical impact 7 days after anterior chamber injection (TBI-PBS n=11; TBI-B-Ag n=11). Motor recovery was evaluated 5 days post-injury with the beam-balance test. Cognitive performance was evaluated in the Morris water maze during post-injury days 14-18 (5 days of training to find the escape platform and then a memory test without platform). Induction of immune tolerance was evaluated at the end of the behavioral trials by delayed hypersensitivity tests. The results showed an effect of injury ($F_{(1, 42)}$=31.32, p<0.001) and the day of training on the latency to find the platform ($F_{(4,168)}$=42.94, p<0.001). However, there was no effect of immune tolerance to B-Ag on the time to find the platform during training (p>0.05), or during the memory test (p>0.05) or an effect of the interaction between factors (p>0.05). Delayed hypersensitivity tests confirmed the induction of immune tolerance to B-Ag ($F_{(1,42)}$=16.07, p<0.001). Together, the results show that immune tolerance to B-Ag does not improve cognitive defects produced by TBI. More studies should evaluate the inflammatory profile induced by B-Ag and its effect on lesion size and on the number of preserved cells

Disclosures: E. Meléndez Herrera: None. **J.C. Mejía-Oliva:** None. **J. Zamudio Flores:** None. **F. Salinas García:** None. **M. Román López:** None. **N. Lajud:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.03

Topic: C.10. Brain Injury and Trauma

Support: NIH NS094950, NS099683, NS110609 (COB)
UMPC Rehabilitation Institute pilot grant (COB)
NIH T32 NS007433-22 to Alan Sved (EHM)

Title: Effects of positive allosteric modulation of α7 nicotinic acetylcholine receptors on sustained attention and cholinergic neurotransmission after experimental traumatic brain injury

Authors: *T. RANELLONE[1], E. H. MOSCHONAS[1], N. RACE[1], P. RENNERFELDT[1], R. REDDY[1], B. WEHRMEYER[1], S. BALAJI[1], J. P. CHENG[1], S. W. CARLSON[2], C. E. DIXON[2], A. E. KLINE[1], C. O. BONDI[1];
[1]Physical Med. & Rehabil., [2]Neurosurg., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Introduction: Traumatic brain injury (TBI) is a leading cause of cognitive disability. Impaired attention and memory are due, in part, to cholinergic dysregulation, which suggests that pharmacological strategies that amplify activation of acetylcholine (ACh) receptors may ameliorate behavioral deficits. Hypothesis: NS-1738, a novel type-I positive allosteric modulator at the α7 nicotinic ACh receptors (α7

nAChRs) will normalize cholinergic neurotransmission and restore sustained attention after TBI. Methods: Rats were trained on the abbreviated 3-choice serial reaction time task (3-CSRT) using a 2-s cue presentation. Anesthetized adult male rats received either a cortical impact of moderate severity or sham injury and then randomly assigned to NS-1738 (3 mg/kg) or vehicle (1.0 mL/kg). Treatments began 24 h after surgery and were given once daily for either 7 or 28 days. Assessment of sustained attention, which consisted of percent accuracy, percent omissions (i.e., distractibility), and premature responses (i.e., impulsivity) was performed on days 14-24. On post-injury day 30, markers of cholinergic neurotransmission were examined in the medial prefrontal cortex, a region previously implicated in mediating sustained attention via Western blot. The data were analyzed by two-way ANOVAs with repeated measures, followed by Newman-Keuls post hoc tests when appropriate. Results: Deficits on sustained attention, demonstrated by decreased percent accuracy and increased percent omissions, in the 3-CSRT were observed after TBI relative to the pooled sham group. Subacute NS-1738 did not improve accuracy or omissions when compared to the vehicle TBI group ($p>0.05$), however chronic NS-1738 significantly restored sustained performance and reduced distractibility ($p<0.05$). The lack of differences in the subacute group may have resulted from a drug wash-out period. Western-blot analysis reveals a general injury effect toward the reduction of cholinergic modulation after TBI. Conclusions: The data suggest that subacute augmentation of cholinergic modulation via NS-1738 after TBI was not effective in restoring higher-order attention long-term, while chronic, steady-state treatment was effective at restoring sustained attention. We are now evaluating the possibility that chronic NS-1738 may further improve cognitive function when co-administered with enriched environment. Significance: To date, there are no FDA approved pharmacotherapies for the amelioration of TBI-induced cognitive deficits. Hence, examining the efficacy of NS-1738 after experimental TBI is imperative to improve translatability of pharmacological interventions.

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Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.04

Topic: C.10. Brain Injury and Trauma

Support: Supported by the Office of the Assistant Secretary of Defense for Health Affairs through The Defense Medical Research and Development Program under Award No. W81XWH-19-1-0329.

Title: Lipoxygenase inhibitors for the treatment of traumatic brain injury

Authors: *J. ROGERS[1], X. LIU[1], L. JONG[1], Y. LIU[2], Y. WANG[2], M. BAUDRY[2];
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Abstract: Multiple reports suggest that neuroinflammation plays a significant role in traumatic brain injury (TBI), a condition that can turn a minor head injury into life-long cognitive, behavioral, and motor deficits. Nonetheless, no consensus treatment for the neuroinflammatory sequelae of TBI has been recognized. Cyclooxygenase (COX) and lipoxygenase (LOX) pathways provide an important non-steroidal alternative for controlling innate inflammatory responses. Because COX inhibitors (e.g., ibuprofen, naproxen) are associated with gastrointestinal and cardiovascular adverse reactions, we have developed lipoxygenase (LOX) inhibitors that simultaneously inhibit 5-, 12-, and 15-LOX at low nM levels. In cell cultures (THP-1 differentiated macrophages) and mouse animal models, these compounds showed little to no toxicity, high CNS penetration when given orally or by intraperitoneal (ip) injection, and inhibition of a broad range of pro-inflammatory cytokines, chemokines, and growth factors. To evaluate the effect of LOX inhibition on TBI, wild-type C57/Bl6 mice were subjected to controlled cortical impact (CCI) followed by daily ip injection of vehicle or a proprietary LOX inhibitor, SRI 31291 (40 mg/kg), for seven days. Compared to vehicle-treated controls, mice treated with SRI 31291 exhibited enhanced recovery of weight, reduced spread of brain damage, enhanced recovery of long-term potentiation in CA1 of hippocampal slices, and reduced cognitive impairment (novel object recognition, fear conditioning context and tone tests) 30 days after CCI. SRI LOX inhibitors do not act by chelating iron, the mechanism of action for the only FDA- approved LOX inhibitor, Zileuton, and may thereby avoid its adverse reactions. Collectively, our findings suggest that further evaluation of LOX inhibitors in general, and our LOX inhibitors in particular, may be warranted as potential treatments for TBI.

Disclosures: J. Rogers: None. **X. Liu:** None. **L. Jong:** None. **Y. Liu:** None. **Y. Wang:** None. **M. Baudry:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.05

Topic: C.10. Brain Injury and Trauma

Support: NIH Grants CA033572, CA216142-01 (MG)
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The UMPC Rehabilitation Institute (COB)
P30CA033572 (City of Hope Pathology Core)

Title: Spatial learning is enhanced in brain injured rats after intranasal administration of L-Myc immortalized human neural stem cells

Authors: *E. H. MOSCHONAS[1], M. GUTOVA[3], J. P. CHENG[2], L. TSATURYAN[3], V. ADHIKARLA[4], R. A. REDDY[2], R. C. ROCKNE[4], C. O. BONDI[1], A. E. KLINE[1];
[1]Physical Med. & Rehabilitation, Safar Ctr. for Resuscitation Research, Ctr. for Neurosci., [2]Physical Med. & Rehabilitation, Safar Ctr. for Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA; [3]Developmental & Stem Cell Biol., Beckman Res. Institute, City of Hope, Duarte, CA; [4]Dept. of Computat. and

Quantitative Medicine, Div. of Mathematical Oncology, Beckman Res. Institute, City of Hope, Duarte, PA

Abstract: The self-renewal capacity of neural stem cells (NSCs) and the inherent ability to migrate to sites of injury and proliferate holds high therapeutic potential in attenuating functional impairments after traumatic brain injury (TBI). To explore the possibility of NSC-based therapy after TBI, isoflurane-anesthetized adult male rats received a controlled cortical impact (CCI) of moderate severity (2.8 mm deformation at 4 m/s) or sham injury (i.e., no cortical impact). Beginning 1-week post-injury, the rats were immunosuppressed and 1×10^6 human NSCs (LM-NS008.GFP.fLuc) or vehicle (VEH) (2% human serum albumen) were administered intranasally (IN) on post-operative days 7, 9, 11, 13, 15, and 17. To evaluate the spatial distributions of the LM-NSC008 cells, half of the rats were euthanized on day 25, one day after completion of the cognitive task, and the other half were euthanized on day 46. 1 mm thick brain sections were optically cleared (CLARITY), and volumes were imaged by confocal microscopy. In addition, LM-NSC008 cell migration to the TBI site by immunohistochemistry for human-specific Nestin was observed at day 39. Acquisition of spatial learning was assessed in a well-established Morris water maze task on six successive days beginning on post-injury day 18. IN administration of LM-NSC008 cells after TBI (TBI + NSC) significantly facilitated spatial learning relative to TBI + VEH rats ($p < 0.05$) and had no effect on sham + NSC rats. Overall, these data indicate that IN-administered LM-NSC008 cells migrate to sites of TBI damage and that their presence correlates with cognitive improvement. Future studies will expand on these preliminary findings by evaluating other LM-NSC008 cell dosing paradigms and evaluating mechanisms by which LM-NSC008 cells contribute to cognitive recovery.

Disclosures: E.H. Moschonas: None. **M. Gutova:** None. **J.P. Cheng:** None. **L. Tsaturyan:** None. **V. Adhikarla:** None. **R.A. Reddy:** None. **R.C. Rockne:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P356.06

Topic: C.10. Brain Injury and Trauma

Support: US Veterans Administration Merit Grant I01BX004344.

Title: Simultaneous targeting of ER stress and oxidative stress by a tri-combo drug therapy confers neuroprotection following traumatic brain injury in mice

Authors: *C. KOZHIKKADAN DAVIS[1], S. BATHULA[1], R. VEMUGANTI[1,2];
[1]Univ. of Wisconsin Madison, Madison, WI; [2]William S. Middleton Veterans Admin. Hosp., Madison, WI

Abstract: TBI pathophysiology is multifactorial. Therefore, a drug combination therapy that targets multiple events in the pathogenesis of TBI may confer better outcomes. TBI leads to oxidative as well as ER stress, and they play a crucial role in its pathophysiology; moreover, they potentiate each other. In this study, we tested if a combination of drugs that prevent oxidative and ER stress promotes better outcomes after TBI. Male and female C57BL/6 mice aged 12 to 13 weeks were subjected to moderate (1mm impact

depth) controlled cortical impact-induced TBI. The treatment group received a combination of apocynin (10 mg/kg; NADPH oxidase inhibitor), tert-butylhydroquinone (tBHQ) (25 mg/Kg; Nrf2 activator), and salubrinal (3 mg/kg; eIF2α phosphatase inhibitor) at 5 min, 24h, and 48h after TBI compared to DMSO in the vehicle group. Rotarod and beam walk tests were carried out on days 2, 4, 7, 30, 60, and 100 after TBI. Morris water maze experiment was performed on weeks 4 and 10 following injury. Subsequently, 14 weeks after TBI, animals were euthanized, and lesion volume was measured. In a different cohort of animals, qualitative measurement of activated microglia and oxidative DNA damage, and expression levels of some of the proinflammatory genes were carried out at 72h after TBI. The tri-combo treatment significantly improved motor function, spatial memory, and reduced lesion volume compared to the sex-matched vehicle group. Further, compared to vehicle treatment, the number of activated microglia, cells with oxidative DNA damage, and expression levels of pro-inflammatory genes (TNFα, MIP-1α, IL-1β, and CD206) were seen reduced by the tri-combo treatment in the ipsilateral cerebral cortex of injured animals. In conclusion, post-TBI treatment with a drug combination of apocynin, tBHQ, and salubrinal that target ER stress and oxidative stress conferred neuroprotection in mice by suppressing inflammation.

Disclosures: C. Kozhikkadan Davis: None. **S. Bathula:** None. **R. Vemuganti:** None.

Poster

P356. Traumatic Brain Injury: Pre-Clinical Therapeutic Strategies II

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Program #/Poster #: P356.07

Topic: C.10. Brain Injury and Trauma

Support: NIH Grants HD069620, NS099674, NS08496 (AEK),
NIH Grants NS094950, NS099683, NS110609 (COB)
T32 NS007433-22 to Alan Sved (EHM)

Title: Evaluation of music medicine to ameliorate traumatic brain injury-induced neurobehavioral and cognitive deficits

Authors: V. J. VOZZELLA[1], I. N. COOPER[1], E. H. MOSCHONAS[1], J. P. CHENG[1], J. M. JARVIS[1], E. L. FINK[2], C. O. BONDI[1], *A. E. KLINE[1];
[1]Physical Med. & Rehabil., [2]Pediatric Critical Care Med., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability for children and adults worldwide. In the USA there are approximately 2.8 million TBI-related emergency department visits each year. The majority of TBI survivors have long-lasting disturbances in motor, cognitive, and emotional health (e.g., anxiety) that negatively impact their long-term academic, occupational, and social functioning. Despite the individual, medical, and societal burden of TBI, interventions to remediate the TBI sequelae and promote recovery are lacking and/or have not successfully translated from the bench to the hospital, thus strongly supporting the need to test and implement novel, safe, effective, nonpharmacological strategies. Music holds untapped potential for improving cognition and neurobehavior after TBI as evidenced by clinical studies in adults with brain injury where music-based interventions were associated with improved physical, cognitive, and emotional

functioning. Basic science data in non-TBI rats also show that music enhances cognition. The aim of this study was to increase our understanding of how music affects the brain when used as a therapy to confer cognitive and neurobehavioral recovery after TBI. Hypothesis: Classical music provided to adult rats after TBI will ameliorate TBI-induced deficits in cognition and neurobehavior. Methods: Adult male rats received a TBI of moderate severity, or sham injury, and 24 h later were randomized to classical or no music (i.e., ambient room noise), which consisted of exposure for 3 h/day from 7:00 pm to 10:00 pm (rat awake period) for 32 days (last day of behavior). Motor (beam), cognitive (spatial learning and executive function), anxiety-like behavior (open field and shock probe defensive burying), histology (lesion volume), and Iba1 were evaluated. The behavioral data were analyzed by two-way ANOVAs with repeated measures over testing days, followed by the Newman-Keuls post-hoc test, which corrects for multiple comparisons. Results: The data showed that classical music improved motor, cognitive, and anxiety-like behavior, reduced lesion volume, and increased Iba1+ staining vs. no-music. Conclusions and Significance: These findings support the role of music as a beneficial therapy for TBI that can be implemented by the 8000 certified music therapists in the USA.

Disclosures: V.J. Vozzella: None. **I.N. Cooper:** None. **E.H. Moschonas:** None. **J.P. Cheng:** None. **J.M. Jarvis:** None. **E.L. Fink:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Mary Tucker Currie Professorship, Awarded to J.W. Grau, TAMU

Title: Positivity in the spinal cord: Learning promotes adaptive responding in the face of uncontrollable stimulation

Authors: *K. E. HUDSON[1,2], M. M. TARBET[1], J. W. GRAU[1];
[1]Texas A&M Univ., College Station, TX; [2]Texas A&M Col. of Med., Bryan, TX

Abstract: Prior studies have shown that neurons within the spinal cord can support instrumental learning (Grau et al., 1998, Behav. Neurosci., 112, 1366). In a typical experiment, rats undergo a thoracic (T2) transection and are subsequently tested for 30 min by applying electrical stimulation (shock) to one hind leg. Animals given shock whenever the leg is extended (controllable stimulation) quickly learn -often within the first 6 min- to maintain the stimulated leg in a flexed position that minimizes net shock exposure over the remaining 24 min of testing. Yoked rats, that are given shock whenever the master rat is shocked (uncontrollable shock), do not learn, suggesting that controllability is essential for learning to occur. Exp. 1 examined whether trained rats would continue to maintain the learned response after 6 min of training in the absence of response-contingent stimulation. Rats underwent a spinal transection and were trained for either 6 min or 30 min with controllable shock the next day. After training, maintenance of the learned response was assessed for 30 min. Animals were then challenged with 6 min of uncontrollable shock. Just 6 min of training was sufficient to induce a lasting increase in flexion duration.

Pre-trained animals continued to maintain a flexion response when stimulated with uncontrollable shock. Interestingly, the few animals that did not maintain a lasting flexion response re-acquired this behavior during uncontrollable shock. Recognizing that exposure to uncontrollable shock should drive a learned helplessness effect rather than learning, animals in Exp. 2 were pre-trained in the same manner and then tested with controllable/uncontrollable shock applied to the opposite leg. Minus pre-training, only controllable shock brought about an increase in flexion duration during testing. In contrast, animals pre-trained for 30 min with controllable shock exhibited a learning-like increase in flexion duration when challenged with uncontrollable shock to the contralateral leg. This suggests that initial stimulation can prime (bias) the spinal cord to interpret stimulation as adaptive and may have significant therapeutic implications in spinal cord injury.

Disclosures: K.E. Hudson: None. **M.M. Tarbet:** None. **J.W. Grau:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant

Title: Targeted modulation of spino-reticulo-cerebellar circuit to determine effects on recovery of skilled forelimb function after spinal cord injury

Authors: *T. J. CAMPION, III[1], R. D. SMIT[3], R. STINGEL[4], J. CHEN[5], G. M. SMITH[2];
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Abstract: Reestablishing functional connections in the central nervous system (CNS) after spinal cord injury (SCI) continues to be a primary goal for scientists and physicians. One way this is being probed is by modulating existing CNS circuits that were spared from injury, with the goal of inducing axonal sprouting and synaptic plasticity to compensate for lost motor pathways. The corticospinal tract (CST) provides a major source of supraspinal motor input into the spinal cord, controlling goal-directed forelimb function and skilled reaching behavior. In the rat, selective lesioning of the dorsal column at the C5 spinal cord effectively severs this descending CST input and leads to a corresponding decrease in skilled forelimb function. However, rats recover almost complete forelimb function after 4 - 6 weeks of rehabilitative training. Our group recently showed that this spontaneous recovery is largely facilitated through a group of C3-C4 propriospinal interneurons (PNs). Interestingly, these C3-C4 PNs bifurcate and divergently project, with one branch descending towards C6-T1 motor pools and the other branch ascending to the lateral reticular nucleus (LRN) in the medulla. The LRN receives both sensory and motor input from different CNS structures and relays this information predominantly to the cerebellar cortex. This spino-reticulo-cerebellar circuit is hypothesized to mediate an internal motor copy of the original supraspinal motor command that is processed through the cerebellum to make real-time error corrections

in limb trajectory during skilled motor tasks. Using chemogenetic tools that allow us to both silence (hM4Di) or excite (hM3Dq) specific neuronal populations, we modulated this circuit following C5 dorsal column lesion (DCL) to study its effects on behavioral recovery. Furthermore, as the connections that make up this circuit are not well defined, we used a combination of anterograde and retrograde tracers, including those that act transsynaptically such as AAV1, to further characterize the various afferents and efferents involved in this pathway. We are presently examining the neurotransmitter specificity of these post-synaptic neurons, using RNA scope. This study characterizes some of the reticular connections emanating from the spinal cord neurons and attempts to define the functional attributes of these connections.

Disclosures: T.J. Campion: None. **R.D. Smit:** None. **R. Stingel:** None. **J. Chen:** None. **G.M. Smith:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.03

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Novel candidates in exercise-induced plasticity: exercise training reduces aggrecan mRNA expression and fine tunes perineuronal nets in the male rat hippocampus.

Authors: *N. E. DOODY[1], E. C. AKAM[2], G. N. ASKEW[1], J. C. F. KWOK[1,3], R. M. ICHIYAMA[1]; [1]Univ. of Leeds, Leeds, United Kingdom; [2]Loughborough Univ., Loughborough, United Kingdom; [3]The Czech Acad. of Sci., Prague, Czech Republic

Abstract: Studies exploring the effects of exercise in the healthy central nervous system (CNS) mainly focus on the increase in neurotrophic factors that facilitate plasticity. However, much less is known regarding the modulation of molecules that restrict neural plasticity with exercise training. This project investigated the expression of inhibitory molecules, which are known to restrict neural plasticity, following exercise training, and whether such modulation enhanced structural plasticity. Male Wistar rats (~200g) underwent six weeks of either moderate intensity continuous training (MICT) or high intensity interval training (HIIT) on a motorised treadmill and were compared to a sedentary control group. RT-qPCR was used to measure the gene expression of 26 genes involved in the RhoA/ROCK pathway. Exercise reduced the mRNA expression of inhibitory molecules within the hippocampus; specifically, aggrecan ($F(2,17)=16.902$, $p=0.002$; MICT: -0.61 Log2 fold-change compared to controls $p<0.05$, HIIT: -1.21 Log2 fold-change $p<0.05$), and Nogo-Receptor-2 ($F(2,17)=8.383$, $p=0.014$; HIIT: -1.38 Log2 fold-change $p<0.05$) (n=4). Aggrecan is a component of perineuronal nets (PNNs): lattice-like structures that enwrap subsets of neurons, restrict plasticity, and are implicated in learning and memory. We used immunohistochemistry to label PNNs with anti-aggrecan and Wisteria floribunda agglutinin (WFA) to visualise aggrecan core protein and CS-GAG chains, respectively. Exercise training did not alter total PNN counts significantly in the hippocampus. Although, MICT increased the proportion of aggrecan positive/WFA negative PNNs in the CA1 (Control: 2.43%, MICT: 11.36%, HIIT: 2.82%, $\chi^2 = 11.16$ $p<0.05$), CA2 (Control: 9.36%, MICT: 36.51%, HIIT: 34.73%, $\chi^2 = 23.72$ $p<0.0001$) and CA3

hippocampal regions (Control: 0.48%, MICT: 6.33%, HIIT: 1.54%, $\chi^2 = 7.19$ $p<0.05$) (n=3). All analyses were completed blinded to experimental groupings. This project so far has provided a novel insight into how exercise training can be implemented to modulate the expression of inhibitory molecules and alter PNN composition within the CNS. Digestion of CS-GAG chains is known to re-open a window of plasticity in the CNS. It is possible that a shift towards a higher number of PNNs that do not express CS-GAG chains following exercise may facilitate improvements in learning and memory.

Disclosures: N.E. Doody: None. **E.C. Akam:** None. **G.N. Askew:** None. **J.C.F. Kwok:** None. **R.M. Ichiyama:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Paracelsus Medical University Salzburg; PMU-FFF grant: R-20/02/130-BEN
Paracelsus Medical University Salzburg; PMU-FFF grant: R-16/04/084-BEN

Title: Hcn channel activation and intrinsic excitability of motor neurons are affected by spinal cord injury

Authors: *B. BENEDETTI[1,2,3], L. BIELER[1,2,3], C. KREUTZER[1,2,3], D. JAKUBECOVA[1,2,3], A. BENEDETTI[1,2,3], S. COUILLARD-DESPRES[1,2,3];
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Abstract: Spinal cord injury (SCI) affects the neocortex directly, and SCI-derived alteration in cortical excitability causes deranged activity and output of lower cortical layers. Controlling cortical pathophysiology after SCI may help to promote recovery. However, the cortical dysfunction ensuing SCI is poorly resolved at cellular and molecular level. Focusing on the primary motor cortex layer V (M1LV), we hypothesized that principal neurons, axotomized upon SCI, would become hyperexcitable and we questioned the role of hyperpolarization cyclic nucleotide gated channels (HCN channels) in such context. To model SCI, adult female rats underwent transection of the corticospinal tract at vertebral level C4. One week after injury, acute pharmacological manipulation of HCN channels *ex vivo* allowed to analyse the mechanisms of derangement affecting M1LV. To this end, patch clamp experiments were carried out on acute brain slices, targeting axotomized M1LV neurons (N = 21) that were identified by retrograde tracer applied at the time and point of injury. Our results revealed that HCN channels, which control the resting membrane potential and intrinsic excitability of healthy M1LV neurons, lost their relevance after SCI when the resting membrane potential of injured neurons exceeded the voltage-range of channel activation. Thus, loss of regulation by HCN channel was provoked by chronic depolarization. In conclusion, some M1LV neurons are chronically depolarized and hyperexcitable after SCI. In this regard, targeting HCN channel pharmacologically would have mixed effects because the non-homogenous dysfunction of HCN

channels in axotomized M1LV neurons combines with other root-causes of depolarization and hyperexcitability.

Disclosures: B. Benedetti: None. **L. Bieler:** None. **C. Kreutzer:** None. **D. Jakubecova:** None. **A. Benedetti:** None. **S. Couillard-Despres:** None.

Poster

P373. Plasticity: Neurophysiology I

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Program #/Poster #: P373.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2019_FI_B_00106
TV3-201736-30-31

Title: Mice with vestigial PNN present altered spinal circuits leading to motor impairment

Authors: *J. SÁNCHEZ VENTURA[1], C. CANAL[1], J. HIDALGO[1], K. FOUAD[2], A. TORRES ESPIN[3], E. UDINA[1];
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Abstract: Perineuronal nets (PNN) are a specialized extracellular matrix rich in chondroitin sulfate proteoglycans (CSPGs) that wraps neurons in the central nervous system, with a key role in stabilizing synaptic contacts and inhibiting plasticity. However, PNN activity-dependent modulation allows to rearrange their structure depending on neural activity and consequently promote or inhibit plasticity. Hence, PNN play a crucial role maintaining the right balance between plasticity and stability in the adult nervous system. A lot of insight has been gathered in the brain and thus, other functions like neuroprotection, ionic buffering, and synaptic refinement have been attributed to cortical PNN. However, in the spinal cord, their functional role is still unclear. While cortical PNN reduction is linked to several neurological pathologies, spinal PNN removal by the enzyme Chondroitinase ABC (ChABC) promotes regeneration after a spinal cord injury (SCI). Considering this apparent contradiction and the reduced information on PNN after SCI, the main goal of our study is to elucidate the role of PNN on motor function and plasticity in intact and spinal cord injured animals. Hence, we have used transgenic mice with vestigial PNN due to the lack of the link protein 1 (LP1), which is implicated in the assembly of PNNs. First, we histologically corroborate the absence of LP1 around lumbar motoneurons, which consequently generates a vestigial PNN with an altered proportion of their components. Then, these transgenic mice were subjected to different behavioral and electrophysiological tests and finally were histologically evaluated. In addition to reduced body weight, the functional test revealed that LP1-KO mice present hypoactivity, altered motor coordination and hyperreflexia in the spinal circuits compared to WT mice. This hyperreflexia could be attributed to an increase in excitatory synapses around lumbar motoneurons and the dorsal horn in LP1-KO mice. Altogether, the lack of LP1 generates a non-functional

PNN that disrupts synapses and alters spinal circuits, thereby producing motor impairments. These data highlight the importance of PNN as well as the relevance of a more precise modulation of these nets after injury. Further steps would be focused on studying the role of PNN in the plasticity of the injured corticospinal tract determining whether the sprouting of spared axons in LP1-KO mice differs from WT mice.

Disclosures: J. Sánchez Ventura: None. **C. Canal:** None. **J. Hidalgo:** None. **K. Fouad:** None. **A. Torres Espin:** None. **E. Udina:** None.

Poster

P373. Plasticity: Neurophysiology I

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Program #/Poster #: P373.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH-NINDS Grant R01NS115470
The Travis Roy Foundation

Title: Sensorimotor paired stimulation targeted to spinal cord is more effective than cortex in rats with and without spinal cord injury

Authors: *A. PAL[1], A. S. ASAN[1], J. B. CARMEL[1,2];
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Abstract: To strengthen sensory and motor system interactions, pairs of stimuli have targeted their integration, but the best site of convergence is not known. The most common human protocol, paired associative stimulation, targets the cortex. We have developed a protocol, spinal cord associative plasticity, that pairs motor cortex stimulation (MCS) with spinal cord stimulation (SCS). Here we compared convergence in MC with convergence in the SC by altering the timing of stimulation. We hypothesized that spinal convergence would have the largest effect on convergence. All experiments were done in awake, freely moving adult rats. For paired stimulation, we implanted three sets of electrodes: epidural screw electrodes over each MC, EMG electrodes in each biceps muscle, and spinal epidural electrodes over the dorsal C5-C6 SC. We stimulated the MC and recorded from the SC and vice versa. To compare the effectiveness of convergence in the SC and MC, we stimulated them using 110% or 90% of their MEP thresholds. We further tested this hypothesis in two rats with a moderate C4 contusion injury. Subthreshold SCS augmented suprathreshold MC MEPs at multiple time points with a strong peak when both stimuli converge in the SC (155% ± 27%, $p < 0.0001$ compared with MCS only). There were also smaller increases in MEPs when both stimuli converge in the MC (17% ± 6%, $p = 0.019$, compared with MCS only). When compared directly, the spinal convergence was significantly stronger than the cortical convergence ($p = 0.003$). When tested for subthreshold stimulation of both MC and SC, these subthreshold stimuli did produce an MEP, when timed to converge in the SC only. Finally, in SCI rats, we observed a similar augmentation in MEP as observed in uninjured rats with peak effect when both stimuli converge in the SC (134% ± 20 %, $p = 0.0001$) with no effect at cortical convergence. Thus, the

circuits spared by SCI are sufficient to enable this strong effect of convergence. Together, these results support the hypothesis that timing paired stimulation to converge in the SC was optimal.

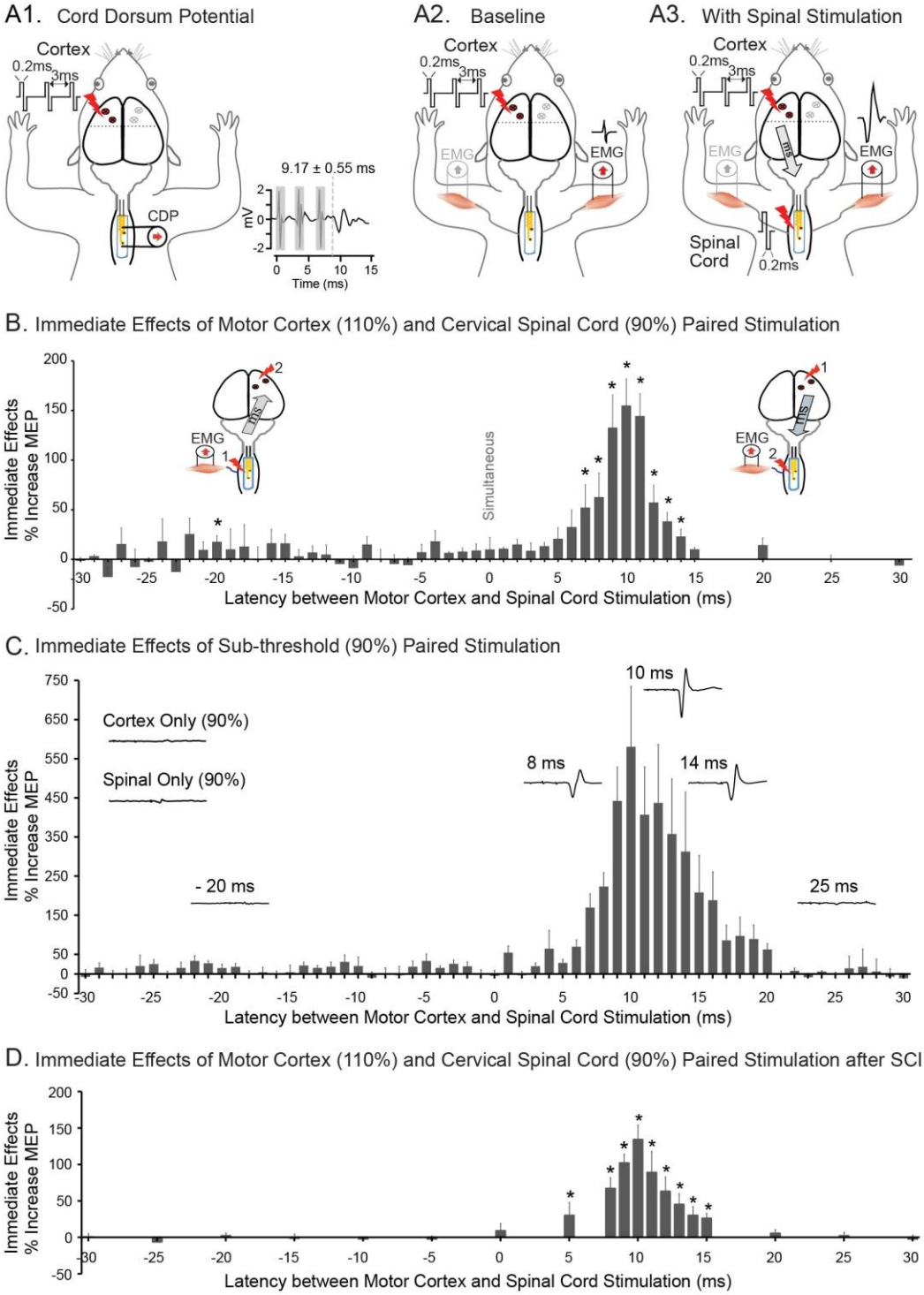


Figure: A. Schematics; A1. CDP recording from dorsal spinal cord, A2. Baseline MEP testing and A3. Motor cortex and spinal cord paired stimulation.
B. Effects of suprathrehold cortical and subthreshold spinal paired stimulation
C. Effects of both subthreshold paired stimulation.
D. Effects of suprathreshold cortical and subthreshold spinal paired stimulation in SCI rats.

Disclosures: A. Pal: None. **A.S. Asan:** None. **J.B. Carmel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jason Carmel is a co-inventor of a patent for the use of softening spinal electrodes. He also has equity in Backstop Neural, which seeks to commercialize the devices for humans..

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.07

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Functional electrical stimulation therapy facilitates corticospinal excitability of the soleus muscle

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Abstract: Partial disruption of corticospinal tract by injury such as incomplete spinal cord injury (iSCI) could result in impairments in the leg muscles resulting in frequent falls. Recently, paired corticospinal-motoneuronal stimulation (PCMS), has been used to increase the corticospinal excitability and improve motor function in upper extremities. As individuals with iSCI have imperfect transmission in the spinal cord, PCMS could facilitate the transmission and lead to positive changes in corresponding motor functions, like increasing the bandwidth of an internet connection between a computer and servers. Similarly, repetitive application of functional electrical stimulation on upper extremities with voluntary efforts, known as functional electrical stimulation therapy (FEST), has been shown to increase the corticospinal excitability resulting in improved motor functions. Although its mechanism of action remains poorly understood, it is hypothesized that it is a similar mechanism to PCMS. Further, FEST has yet to be utilized on the plantarflexor muscles which are critical to maintaining upright posture. Here, we investigated the effect of FEST on the corticospinal and spinal reflex excitability of the soleus muscle. We utilized two stimulation frequencies, 40Hz in condition 1 (three participants) and 100Hz in condition 2 (four participants). The participants were instructed to exert plantarflexion torque at 20% maximum voluntary effort with FEST on soleus muscle 200 times (~33mins). Motor evoked potentials (MEPs) and H-reflex recruitment curves were recorded prior to, immediately after and 40 minutes after the intervention as a measure of corticospinal and spinal reflex excitability, respectively. MEPs significantly increased immediately after (Condition 1: 24.4±9.78%, $p = 0.005$; Condition 2: 38.3±26.8%, $p = 0.030$) and stayed increased up to 40 minutes (Condition 1: 41.6±19.7%, $p = 0.009$; Condition 2: 56.2±16.5%, $p = 0.002$) after FEST. Spinal reflex excitability appeared unchanged in both conditions as no changes were observed for the peak H-reflex amplitude immediately after (Condition 1: -0.03±15.8%, $p = 0.960$; Condition 2: (-4.36±11.3%, $p = 0.573$) or 40 minutes (Condition 1: 6.07±12.2%, $p = 0.393$; Condition 2: (-2.94±8.98%, $p = 0.628$) after FEST. We also demonstrated that FEST with different frequencies (40 Hz and 100Hz) had similar effects on the corticospinal excitability, as determined by similarly sized MEPs immediately after ($p = 0.308$) and 40 minutes after ($p = 0.239$) FEST. Therefore, we conclude that FEST

has the potential to reduce the degree of impairment after iSCI, by enabling more rehabilitation opportunities for these individuals.

Disclosures: K. Fok: None. **N. Kaneko:** None. **S. Tajali:** None. **K. Masani:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS110577 (JRW,YW,JC, AV)
NICHD/1P41EB018783(JRW)
NIH HD36020(XYC)
NIH NS22189(JRW)
NIH NS061823(XYC&JRW)
NYS SCI Research Trust Fund C32241GG(BJH)
Stratton VA Med Center, Albany, NY

Title: Short-term and long-term effects of weak electrical stimulation of sensorimotor cortex on soleus H-reflex in rats.

Authors: *Y. CHEN[1], X. Y. CHEN[1], Y. WANG[1], L. CHEN[1], X. Y. PU[1], T. FAKE[1], A. VATO[1,2], J. S. CARP[1,3], J. R. WOLPAW[1,3,2];
[1]VA, Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr., Albany, NY; [2]Electrical and Computer Engin., [3]Biomed. Sci., State Univ. New York, Albany, NY

Abstract: Operant conditioning of the H-reflex (HR), the electrical analog of the spinal stretch reflex, is associated with plasticity in brain and spinal cord (for review: Curr Op Behav Sci 20:138-144, 2018). HR conditioning requires the corticospinal tract and sensorimotor cortex (SMC) (J Neurophysiol 78: 1730-1734, 1997; 87:645-652, 2002; 96: 119-127, 2006). Weak electrical cortical stimulation of SMC (ECS) also changes HR size (J Neurophysiol 98: 878-887, 2007). We are further exploring the short- and long-term effects of ECS on spinal physiology, anatomy, and genomics.
The Stratton IACUC approved this study. Under anesthesia, Sprague-Dawley rats are implanted with EMG electrodes in right and left soleus (SOL) muscles, volley recording electrodes over dorsal surface of spinal cord at T12, nerve stimulating cuffs on both posterior tibial nerves, and epidural stimulating electrodes over left SMC. After control H-reflex data are collected, Experimental rats receive weak SMC ECS (25 <30 μA 40-ms pulses for 1s every 10s) for 30 d. ECS amplitude is continually adjusted to maintain a stable small descending volley. ECS causes no visible distress and produces no visible responses in the rats. Rats are perfused either 4 days after ECS ends (short-term) or up to 109 days after (long-term). Control rats receive comparable surgery but no ECS, and are simply perfused 30-60 days later. HR data are collected 24/7 throughout. Just prior to perfusion, SOL motoneurons (MNs) are retrogradely labeled with cholera toxin subunit B (CTB). The lumbar spinal cord is sectioned for anatomical, histochemical, and genomic analyses.

Data from six rats studied to date show bilateral increases in SOL HR just after ECS ends. HR averaged 194.7(±42.6SE)% of pre-ECS baseline on the right ($p=0.02$) and 182.6(±18.8)% ($p<0.01$) on the left. These HR increases were associated with decreased $GABA_{B1}$ receptor immunoreactivity (IR) in both right (93±2.0% of control, $p<0.01$) and left (93±2.1%, $p=0.01$) SOL MNs. In two rats studied to date 15 weeks after ECS ended, HR size remained elevated. Further immunohistochemical and initial genomic data analyses are underway.

If confirmed in additional rats, these early results confirm and extend previous data on the spinal effects of ECS and the likely role of $GABA_{B1}$ receptor decrease in HR increase. Ongoing analyses and more data should provide further insight into the neurotransmitter and genomic mechanisms of these short and long-term spinal effects of weak SMC ECS. The results offer new understanding of cortical impact on spinal function and suggest novel therapeutic approaches for improving sensorimotor function impaired by CNS injury or disease.

Disclosures: Y. Chen: None. **X.Y. Chen:** None. **Y. Wang:** None. **L. Chen:** None. **X.Y. Pu:** None. **T. Fake:** None. **A. Vato:** None. **J.S. Carp:** None. **J.R. Wolpaw:** None.

Poster

P373. Plasticity: Neurophysiology I

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Program #/Poster #: P373.09

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH1R01 NS110577(JRW, YW, JC)
NIH/NIBIB/P41/EB018783(JRW)
NYS SCI Research Trust Fund NS22189(JRW)
NYS SCI Research Trust Fund C32241GG(BJH)

Title: Electrocortical stimulation (ECS) of rat sensorimotor cortex (SMC) may regulate glutamate ionotropic AMPA receptors and their associated mRNA in spinal cord motoneurons

Authors: *B. J. HERRON[1,2], Y. WANG[2], X. Y. CHEN[2], Y. CHEN[2], A. VATO[2,1], J. S. CARP[2,1], J. R. WOLPAW[2,1];
[1]Univ. At Albany, Sch. of Publ. Hlth., Albany, NY; [2]Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr., Albany, NY

Abstract: Several weeks of weak electrocortical stimulation (ECS) of rat sensorimotor cortex (SMC) increases soleus H-reflex (SOL HR) size. This increase persists for at least 3 months after ECS ends. It correlates with a transient increase in GAD67 terminals on SOL motoneurons (MNs) and an equally persistent decrease in GABA receptors in these MNs [J Neurophysiol 98: 878-887, 2007; 108: 2668-2678, 2012]. We are now exploring the impact of ECS on spinal cord excitatory neurotransmission by comparing ECS rats to Control (unstimulated) rats in: (1) expression of SOL MN glutamate receptor 2 and 3 ($GluR_{2/3}$-IF); and (2) expression of SOL MN *Gria2*, the mRNA for glutamate receptor 2. Rats are implanted with SOL EMG electrodes and a posterior tibial nerve stimulation cuff in both legs, and ECS electrodes over left hindlimb SMC. ECS (1-s 25-Hz train of 0.1-ms biphasic <30-uA pulses every 10 s) is

delivered 24 hr/d X 30 days, with no visible effect on behavior. The Stratton IACUC approved this study. SOL HRs are recorded throughout. Right and left SOL MN are retrograde-labeled with cholera toxin subunit B (CTB) either on Day 1 after ECS ends (ECS_{early} rats) or on Day 105 (ECS_{late} rats). All rats are perfused 3 days after CTB injection; L4-L5 spinal cord are removed and sections are processed for $GluR_{2/3}$-IF or single molecule *in situ* hybridization targeting *Gria2*, and are photographed. $GluR_{2/3}$-IF and *Gria2* expression in SOL MNs are quantified in a double-blind manner. Results for ECS rats are expressed in % of average values from Control rats. Intergroup differences are compared by ANOVA.To date, we have analyzed results from 5 Control, 3 ECS_{early}, and 2 ECS_{late} rats. In ECS_{early} rats $GluR_{2/3}$-IF was not significantly changed in right & left SOL MNs of (94±4%(right), 95±3%(left); nor was *Gria2* mRNA expression (96±5%(right), 87±6%(left)) (all $p>0.05$ vs control). In contrast, in ECS_{late} rats, $GluR_{2/3}$-IF was significantly decreased (80±4%(right), 87±6%(left) ($p<0.001$, $p=0.041$)); and so was *Gria2* mRNA expression (66±6%(right) and 69±6%(left) ($p<0.0001$ for each)). These initial results suggest that ECS does not alter MN spinal excitatory function (measured by $GluR_{2/3}$ receptor density & *Gria2* gene transcription) immediately following stimulation, but it does significantly decrease it several months later. Confirmation of these initial results and recent genome-wide expression studies will provide new insight into the long-term impact of SMC stimulation on spinal cord function.

Disclosures: B.J. Herron: None. **Y. Wang:** None. **X.Y. Chen:** None. **Y. Chen:** None. **A. Vato:** None. **J.S. Carp:** None. **J.R. Wolpaw:** None.

Poster

P373. Plasticity: Neurophysiology I

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Program #/Poster #: P373.10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH1R01 NS110577-01A1(JRW, YW, JSC)
NIH/NIBIB/P41/EB018783(JRW)
NS22189(JRW)
NYS SCI Research Trust Fund C32241GG(BJH)
Stratton VA Med Center, Albany, NY

Title: Electrocortical stimulation (ECS) of sensorimotor cortex (SMC) in rats decreases expression of G-protein-coupled inwardly rectifying potassium channel 2 (GIRK2) in spinal cord motoneurons

Authors: *Y. WANG[1], B. HERRON[2,3], Y. CHEN[1], X. Y. CHEN[1], T. FAKE[1], J. CARP[1], A. VATO[1,3], J. R. WOLPAW[1,3];
[1]VA, Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [2]Wadsworth Center, NYSDOH, Albany, NY; [3]State Univ. of New York, Albany, NY

Abstract: Electrocortical stimulation (ECS) of sensorimotor cortex (SMC) in rats for several weeks increases soleus (SOL) H-reflex (HR). HR increase correlates with $GABA_B$ receptor decrease and GAD67 terminal increase on soleus motoneurons (SOL MN), showing that ECS affects spinal cord GABAergic function (Chen et al. 2007; Wang et al. 2012; 2021). G-protein-coupled inwardly rectifying

potassium channel 2 (GIRK2) is a key effector of $GABA_B$-mediated synaptic input (Trends Neurosci 37: 20-29, 2014; Mol Genet Metab 105:64-72, 2012). We are exploring the impact of ECS on GIRK2 expression in SOL MNs. The Stratton IACUC approved this study. Rats are implanted with SOL EMG electrodes and a posterior tibial nerve stimulation cuff in both legs, and ECS electrodes over left hindlimb SMC. ECS (1-s 25-Hz train of 0.1-ms biphasic <30-uA pulses every 10 s) is delivered 24 hr/d X 30 days, with no visible effect on behavior. SOL HRs are recorded throughout. Right and left SOL MN are retrograde-labeled with cholera toxin subunit B (CTB) either on Day 1 after ECS ends (ECS_{early} rats) or on Day 105 (ECS_{late} rats). All rats are perfused 3 days after CTB injection; L4-L5 lumbar cord is sectioned and assayed for $GABA_{B1}$ or GIRK2 immunofluorescence (IF) or hybridized with GIRK2 *in situ* probes. In a double-blind manner, $GABA_{B1}$-IF and GIRK2-IF in SOL MNs on right and left sides are measured, and SOL MN GIRK2 mRNA is quantified by single molecule *in situ* hybridization. Results from ECS rats are expressed in % of average values from Control (CNTRL) rats. Intergroup differences are compared by ANOVA. Consistent with previous data, ECS increased SOL HR (232±78(SD)% of initial size (p<0.05, n=6; paired t-test); $GABA_{B1}$-IF in SOL MNs decreased to 89.6±4% (right) and 92.4±1.3 %(Left) of Control (each vs CNTRL: p<0.001). SOL MN GIRK2-IF in ECS rats decreased to 82±3% (right) and 86±3% (left) (each vs CNTRL: p<0.001). GIRK2 mRNA number/MN decreased to 73±5% (right) and 85±4% (left) (p=0.0001 and p=0.023 vs CNTRL). These initial results show that ECS-induced SOL MN $GABA_{B1}$ reduction is associated with GIRK2 channel and gene transcription decreases; they are consistent with GIRK2 functional properties and suggest that GIRK2 has a key role in ECS effects on spinal motor function. Combined with the evidence that ECS decreases MN $GABA_B$ receptors without affecting *Gabbr1* mRNA (Wang et al 2021), these results suggest that the $GABA_B$ receptor depletion underlies the GIRK2 expression decrease.

Disclosures: Y. Wang: None. **B. Herron:** None. **Y. Chen:** None. **X.Y. Chen:** None. **T. Fake:** None. **J. Carp:** None. **A. vato:** None. **J.R. Wolpaw:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Paralyzed Veterans of America grant #3168

Title: Reliability and face validity of the modified Function In Sitting Test (mFIST) in Veterans with spinal cord injury

Authors: *M. N. HATCH[1,2], V. CHAVEZ[1], J. JUDY[2], B. M. SMITH[3];
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Abstract: Objectives: Seated balance is essential for individuals who perform their daily activities from a wheelchair. Current outcomes available to test seated balance abilities in individuals with SCI are unidimensional or cost and time prohibitive for the clinical setting. We investigated reliability and face

validity of a new seated measure developed by our team, the modified Function In Sitting Test (mFIST), for use in a SCI clinical rehabilitation setting.
Design/Methods: The mFIST was administered on 46 Veterans with SCI (C4-L2; AIS grades A-D) twice within 1 week by the same evaluator while being video-recorded for spectator scoring. Intra-rater reliability (test re-test) was determined from in-person scoring; inter-rater reliability was determined by comparing spectator to in-person. To test the effect of video rating, reliability between video raters, and self-reliability (rescoring ones' own via video at least 2 months after in-person) were performed. Reliability was determined using intra-class correlations (ICC). Face validity was performed on 20 SCI consumers who completed reliability procedures. Likert-based and open-ended questions were used to assess item difficulty, clarity of instructions, and appropriateness.
Results: Our cohort was predominantly Caucasian (n=34, 72%), male (n=43, 91%), mean age of 62(SD $\pm$ 13), with equal distributions of motor incomplete (n=26, 54%) and complete injuries (n=21, 44%). Test re-test reliability was strong (ICC = 0.87, CI: 0.78 – 0.93): inter-rater reliability was slightly lower (ICC = 0.80, CI: 0.66 – 0.90)). Reliability between video raters was very high (ICC = 0.90, CI: 0.80 – 0.95) and self-reliability was almost identical to inter-rater reliability (ICC = 0.80, CI: 0.35 – 0.94). All ICC displayed p's < 0.001. A total of 95% thought the mFIST properly tested their balance ability, thought the directions were clear, and took the appropriate time. Overall, 45% indicated that the mFIST made them aware of balance issues, 35% thought it would be useful in clinic, 10% believed it confirmed their ability, and 10% didn't think it was useful. The largest variability in self-reported difficulty were retrieving items from the floor or behind them, and leaning. All interviewees agreed that balance was an important part of their daily life.
Conclusions: High levels of acceptability and initial reliability confirm use of the mFIST on individuals with SCI in clinical rehabilitation setting. Use of 2 individuals (one guarding, one scoring) is recommended for the highest reliability. Reproducibility in an Australian SCI cohort is ongoing and will help confirm these results.

Disclosures: M.N. Hatch: None. **V. Chavez:** None. **J. Judy:** None. **B.M. Smith:** None.

Poster

P373. Plasticity: Neurophysiology I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P373.12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYSDOH grant C32248GG
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Title: Transspinal stimulation actions on reflex excitability and locomotor muscle activity during walking in individuals with and without SCI

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Abstract: Proprioceptive feedback and spinal reflexes refine locomotor muscle activity during stepping and contribute to recovery after spinal cord injury (SCI). Activity-based rehabilitation, like locomotor training, is thus widely used to improve stepping for individuals with SCI. Recent studies have also supported the potential benefits of non-invasive spinal (termed here transspinal) stimulation in enhancing locomotor rehabilitation. However, stepping-related feedback and spinal reflexes share similar neuronal pathways to those activated by transspinal stimulation. Consequently, transspinal stimulation may interact with stepping-induced feedback and reflexes. In this study we investigated the neuromodulatory effects of transspinal stimulation on the modulation of soleus H-reflex excitability and electromyographic (EMG) muscle activity during stepping in humans with and without SCI. Thirteen able-bodied adults and 5 individuals with SCI participated in the study. Locomotor muscle EMG activity was recorded bilaterally from steps without, during, and after single pulse or pulse train transspinal stimulation delivered during stepping randomly at different phases of the step cycle. The modulation pattern of the soleus H-reflex was recorded in both subject groups under control conditions and following single pulse transspinal stimulation at an individualized positive and negative conditioning-test interval. The locomotor muscle EMG activity was decreased in both subject groups during transspinal stimulation, while intralimb and interlimb coordination was altered only in SCI subjects. Immediately after transspinal stimulation, the phase-dependent EMG modulation pattern remained unaffected in able-bodied subjects. The conditioned soleus H-reflex was depressed throughout the step cycle in both subject groups. The soleus H-reflex modulation pattern was nearly completely absent in individuals with SCI. Transspinal stimulation modulated depolarization of motoneurons over multiple segments, limb coordination, and soleus H-reflex excitability during stepping. The soleus H-reflex depression may be the result of complex spinal inhibitory interneuronal circuits activated by transspinal stimulation and collision between orthodromic and antidromic volleys in the peripheral mixed nerves. The soleus H-reflex depression by transspinal stimulation may suggest an interaction between proprioceptive reflexes that could have negative consequences for functional recovery after SCI, and should be examined in future studies. Conversely transspinal stimulation may be applied to normalize spinal reflex excitability after SCI.

Disclosures: A. Islam: None. **T.S. Pulverenti:** None. **M. Zaaya:** None. **M. Knikou:** None.

Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P432.01

Topic: D.06. Auditory & Vestibular Systems

Support: DFG Lu622/13-1

Title: Auditory localization in the chicken - neurophysiology and behavior

Authors: G. MALDARELLI, U. FIRZLAFF, L. KETTLER, J. M. ONDRACEK, *H. LUKSCH;
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Abstract: The ability to locate a sound source is crucial for the survival of birds. During the last decades, research in avian auditory neuroscience has mainly focused on the barn owl, which has unique peripheral specializations and hypertrophied brain structures which enable outstanding localization performances. However, in generalist birds without these specializations, the behavioral capabilities and the neuronal processing for orientation responses are only insufficiently characterized. We used the chicken as an animal model in order to 1) characterize auditory processing in specific structures of the avian midbrain and 2) measure the accuracy of sound source localization in behaving chickens.
First, we conducted *in vivo* extracellular recordings of single units in the deep layers of the OT (a presumably multimodal midbrain area involved in the avian auditory pathway) and in the *formatio reticularis pars externa* (FRLx) - a brain structure described as a relay between the inferior colliculus (IC) and the OT - of anaesthetised chickens, while presenting binaurally broadband (BB) noise filtered by the head-related transfer function (HRTF). We found two main types of auditory spatial receptive fields (aSRFs): the round and annular aSRFs. The round aSRFs responded to lateral positions of the auditory space and were mainly present in the OT, while the annular aSRFs had a ring-like shape, responded to areas around the interaural axis, and were mainly present in the FRLx. Altogether these results suggest that, in the midbrain of generalist birds, the auditory space is represented by aSRFs arranged in a concentric manner around the interaural and visual axis.
In the second experiment, chickens were trained to discriminate the location of BB noises presented from different directions with free field loudspeakers. This study allowed us to measure the sound localization accuracy by calculating a minimum audible angle of 20°.This result, compared with data from other bird species, provides evidence that the sound localization accuracy in generalist birds is affected by both the head size and the lack of auditory specializations.
The electrophysiological and behavioral data suggest that generalists like the chicken, who are not relying on sound localization for prey capture or intraspecific communication, adapted their auditory system to align with the visual axis. We also hypothesize that the auditory localization does not rely on a snapshot of the auditory stimulus as it is perceived by the animal, but rather on searching movements where the head is successively brought into a position that aligns the visual axis with the sound source.

Disclosures: G. Maldarelli: None. **U. Firzlaff:** None. **L. Kettler:** None. **J.M. Ondracek:** None. **H. Luksch:** None.

Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: P432.02

Topic: D.06. Auditory & Vestibular Systems

Support: DC003180

Title: Location-specific facilitation in marmoset auditory cortex

Authors: *C. CHEN, X. WANG;
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Abstract: It has been well established that responses of neurons in auditory cortex are influenced by stimulus context. Contextual modulations can occur in spectral, temporal or spatial domain. However, comparing to spectral and temporal contextual effects, much less is known on spatial contextual effects in auditory cortex. In this study, we explored how spatial contextual modulations evolve over time by stimulating neurons in awake marmoset auditory cortex with sequences of sounds either randomly from various spatial locations (equal probability mode) or repeatedly from a single location (high probability mode). To our surprise, instead of inducing adaptation as expected from well documented stimulus-specific adaptation (SSA) literature, repetitive stimulation in the high probability mode from spatial locations away from the center of a neuron's spatial receptive field evoked lasting facilitation observed by both extracellular and intracellular recordings from single neurons in auditory cortex. Nearly half of the sampled neuronal population exhibited this spatial facilitation, irrespective of stimuli type and visibility of the test speaker. Facilitation with longer duration occurred when the repetitive stimulation was delivered from speakers with firing rates ranked lower than the best speaker's firing rate under the equal probability mode. The extent of the facilitation decreased with decreasing presentation probability of the test speaker. Interestingly, the induced facilitation did not change spatial tuning selectivity, tuning preference and spontaneous firing rate of the tested neurons. Taken together, our findings revealed a location-specific facilitation (LSF) instead of SSA to repetitively presented sound stimuli which has not been observed in auditory cortex. This form of spatial contextual modulation may play an important role in supporting such functions as auditory streaming and segregation.

Disclosures: C. Chen: None. **X. Wang:** None.

Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: P432.03

Topic: D.06. Auditory & Vestibular Systems

Support: NIH-NIDCD

Title: Decoding the location of attended talker in a spatial multi-talker setting from invasive neural signals

Authors: *V. CHOUDHARI[1,2], P. M. PATEL[1,2], S. BICKEL[3,4], A. D. MEHTA[3,4], N. MESGARANI[1,2];
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Abstract: Motivation: Hearing-impaired listeners experience difficulty in attending to a specific talker in the presence of interfering talkers. Cognitively-controlled hearing aids address this problem by decoding the attended talker from neural signals using auditory attention decoding (AAD) algorithms, separating the speech mixture into clean streams and selectively amplifying the attended speech stream. In most

AAD algorithms, a representation (envelope or spectrogram) of the attended speech is reconstructed from neural signals. The decoded attended talker is considered as one whose speech representation yields the highest correlation with the reconstructed speech representation. As talkers in a cocktail party environment are often spatially separated, a supporting approach for an AAD algorithm could be decoding the location where attention is directed, i.e., the location of the attended talker. Recent deep learning-based multi-channel speech separation algorithms preserve location information (interaural cues) in the separated binaural speech streams. The attended location decoded from neural signals can then be compared with the locations of talkers (estimated from their binaural speech streams) to improve the attended talker decoding accuracy. In this study, we attempt to decode the location of attended talker in a spatially separated multi-talker setting using neural signals recorded from intracranially implanted electrodes. Approach: We recorded from seven epilepsy patients using depth electrodes (sEEG) as they listened to spatial multi-talker speech stimuli via headphones. Head-related transfer functions (HRTFs) were used to ensure two parallel speech streams (one male, one female) arrived at the subject from two locations at different azimuthal angles: -45 degrees (front-left) and +45 degrees (front-right). The locations of the male and the female speech streams switched randomly between trials. The subjects were asked to attend to a particular gender throughout a block. Results: We find electrodes whose steady-state mean response levels (MRLs) are modulated by attention to a talker location. Such electrodes have significantly higher steady-state MRLs when attending to a talker on the contralateral side than the ipsilateral side. Attended location can be decoded significantly above chance levels on a window-by-window basis, with a window duration as small as 500 milliseconds. Decoding accuracies improve with an increase in window durations. Significance: The ability to reliably decode attended location suggests a potential for improving the performance of existing AAD algorithms by incorporating spatial information.

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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: P432.04

Topic: D.06. Auditory & Vestibular Systems

Support: Otolaryngology T32 DC012280

Title: Spatial Hearing Deficits in a Guinea Pig Model of Noise-Induced Cochlear Synaptopathy

Authors: *M. A. BENSON[1], J. PEACOCK[1], N. T. GREENE[2], D. J. TOLLIN[1];
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Abstract: Hearing loss is typically characterized by permanently raised auditory thresholds due to cochlear dysfunction. However, recent animal studies have shown that brief and moderate noise exposure can cause a temporary threshold shift that recovers within a couple of weeks, but a permanent loss of ribbon synapses between inner hair cells and auditory nerve fibers. Such noise-induced cochlear

synaptopathy has therefore been called ‘hidden hearing loss’ because while there is a degeneration of ribbon synapses (up to 50%), the resulting hearing dysfunction is hidden from typical clinical assays. Here we used Guinea pigs to study the mechanisms leading to hearing deficits resulting from synaptopathy caused by a 2-hour 106 dB SPL 4-8 kHz octave band noise. We measured auditory brainstem responses (ABRs), distortion product otoacoustic emissions (DPOAEs), tested spatial hearing behaviorally through the prepulse inhibition (PPI) of the acoustic startle reflex, and performed immunohistochemistry. ABR and DPOAE recordings were made prior to noise exposure, 24 hours post-exposure, and 1, 2, 4, and 8 weeks following exposure. Brainstem circuits subserving spatial hearing were assessed physiologically via the binaural interaction component (BIC) of the ABR and also behaviorally through PPI (pre-noise and 8 weeks post-noise). PPI was used to measure hearing-in-noise ability, or spatial release from masking, by having the animal detect a target sound (broadband chirp) at varying SPLs from one spatial location in the presence of background noise presented from other spatial locations. This test relates theoretically to our daily hearing requirements, as we focus on someone while trying to ignore the background noise around us, like in a classroom or cocktail party.
Results show that the noise exposure induces no persistent hearing threshold shift, as measured by the DPOAEs and ABR thresholds, but results in a depleted BIC amplitude relative to control animals. Spatial hearing deficits were seen in the PPI measures. Cochlear synaptopathy was objectively confirmed by visualizing the loss of ribbon synapses in the cochlea. Labeling for the presynaptic ribbon (Ctbp2) and post synaptic ribbon (GluA2) allowed us to visualize any permanent changes to synapses in the cochlea induced by the noise exposure.
The results demonstrate that cochlear synaptopathy can cause deficits in brainstem circuits known to be critical for sound localization and that this can lead to deficits in hearing abilities that require integration of inputs from both ears.

Disclosures: M.A. Benson: None. **J. Peacock:** None. **N.T. Greene:** None. **D.J. Tollin:** None.

Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: P432.05

Topic: D.06. Auditory & Vestibular Systems

Title: Neural dynamics of spatial auditory attention in multi-talker speech perception

Authors: *P. PATEL[1], S. BICKEL[2], J. L. HERRERO[3], A. D. MEHTA[4], N. MESGARANI[1];
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Abstract: The ability to track and attend to a moving talker is important for communication in naturalistic multi-talker speech perception. The previous studies have used EEG to show that a switch in target’s location suppresses the ERP components from the target’s stream and disrupts alpha band lateralization. Other studies have used fMRI to show transient activation of parietal cortex following spatial shift in auditory attention. Due to limitations in the resolution of non-invasive methods and the use of

unnaturalistic stimulus, some questions remain unanswered. What are the cortical signatures of spatial attention switch throughout the auditory cortex as well as in the proposed dorsal and ventral attentional networks? How does the neural dynamics enable a change in spatial attention for successful tracking of a moving target's speech? We recorded intracranially from neurosurgical patients while they performed a naturalistic spatial attention task of following a target talker in multi-talker scene where the target randomly switches their location in each trial among the two possible azimuthal locations (45 and -45). Thus, we mimic a naturalistic everyday scenario where listeners need to track and attend to a moving talker in a simulated multi-talker scene. We report a neural signature of increased high-gamma envelope activity localized in time during the trial onsets for spatial auditory attention switch throughout the primary and secondary auditory cortex. The neural responses in dorsal and ventral attention network areas show distinct dynamics. We show higher high-gamma activity when the spatial direction of attention switches compared to when the spatial attention is sustained. This contrastive response which appears at the onset of attention switch is present for both dorsal and ventral attention networks but the dorsal network shows transient response to the stimulus that goes down to baseline after 1s and the ventral network shows longer sustained response to the stimulus. Furthermore, a switch in target's location momentarily disrupts the encoding of the target speech features until the attention switch is completed, highlighting the temporal dynamics of spatial attention switch and its consequence in encoding the target speech. These findings provide insights into temporal dynamics of spatial auditory attention control in the auditory cortical population and sheds light on the role of the dorsal and ventral attention networks in tracking and maintaining listener's focus on a moving talker in multi-talker acoustic scenes.

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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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University of Macau Grants MYRG2018-00146-AMSV, MYRG2019-00056-AMSV

Title: A Spiking Neuronal Network Model of the Auditory Brainstem for Sound Localization

Authors: *B.-Z. LI[1,2,3,4], S. PUN[3], M. VAI[3,4], T. C. LEI[1,2], A. KLUG[1];
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Abstract: Spatial hearing relies on the accurate detection and extraction of binaural cues performed in the auditory brainstem. In this process, the neural activity from the two auditory nerves initially propagates

through separate monaural nuclei and subsequently converges onto the superior olivary complex, where the interaural time difference (ITD) is processed in the medial superior olive (MSO), and the interaural level difference (ILD) is analyzed in the lateral superior olive (LSO). Even after propagating across several neurons, fiber bundles, and synaptic stations along this pathway, the temporal precision of the neural activity remains preserved enough such that binaural cues can still be precisely extracted by the binaural neurons in the MSO and LSO. The involved neural circuit shows multiple mechanisms designed to preserve the timing of neural activity, some of which are not completely understood. Here, we present a computational model of the auditory brainstem using spiking neuronal networks. In the model, the LSO and MSO circuits are modeled and stimulated with complex sounds presented under multiple binaural conditions. The resulting neuronal activity was further analyzed on a single cell and population level with a decoding model to estimate the precision of spatial hearing and the transformation of the binaural spatial information. Based on these in silico experiments, the simulated neural responses and ITD/ILD tuning curves are comparable to experimental findings. Correspondingly, the model exhibits acute sensitivities to ITD and ILD cues that match the behavioral performance. Moreover, the model was also used to demonstrate the influence of axon myelination and hyperexcitability on the sound localization process. These results suggest that the proposed model is capable to encode binaural cues in a biologically plausible manner. Furthermore, the model can be used to explore the functioning of the auditory brainstem under various conditions, such as developmental stages or pathological alterations.

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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Topic: D.06. Auditory & Vestibular Systems

Support: F31 DC019291
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Title: Comparison of click vs. chirp stimuli in evoking the binaural interaction component (BIC) of the auditory brainstem response (ABR)

Authors: *Z. L. OWRUTSKY, J. PEACOCK, D. J. TOLLIN;
Physiol. and Biophysics, Univ. of Colorado, Aurora, CO

Abstract: Comparison of click vs. chirp stimuli in evoking the binaural interaction component (BIC) of the auditory brainstem response (ABR)
Zoe Owrutsky, John Peacock, Daniel J. Tollin*Department of Physiology and Biophysics, University of Colorado School of Medicine, Aurora, CO 80045*
Chirp stimuli are specifically designed to enhance temporal synchrony in the responses of the auditory nerve and brainstem by accounting and compensating for the frequency- and level-dependent delays accrued by the traveling wave in the cochlea. Chirps have been shown to produce larger amplitude responses in specific waves/peaks of the auditory brainstem response (ABR). Here we test the hypothesis

that chirp stimuli can increase the amplitude of the binaural interaction component (BIC) of the ABR. The BIC of the ABR is a potential biomarker for binaural hearing. However, clinical use of the BIC has been limited because it is unreliably measured using click stimuli in humans. Here we generate and compare different chirp stimuli methods to maximize the BIC.
ABR peak latencies were measured in response to tone bursts over a range of stimulus frequencies and intensity levels in seven chinchillas. Stimuli consisted of 5-ms tone bursts (1, 2, 4, 8, 16, 24 kHz) presented via sealed and calibrated insert earphones from ~10 dB below to 50 dB above ABR detection threshold. Latencies of ABR waves I-IV and the BIC DN1 wave (the largest amplitude peak in the BIC) were plotted against frequency and then fit to a power function: Tau=k*f^(-d), where tau is latency in seconds, f is frequency, and k and d are constants. The values of k and d were then used to construct a series of sound level-specific chirps for three above-threshold stimulus intensity levels based on 1) monaural ABR wave I and 2) BIC DN1.
Monaural ABR peak latencies decreased systematically with increasing sound frequency as expected from the corresponding latencies due to cochlear delay. Consistent with other studies, our results show that monaural ABR peak amplitudes were enhanced by chirps which compensate for that latency relative to those measured with clicks. Surprisingly though, BIC DN1 peak latencies did not show a similar frequency-dependent latency shift. Rather BIC DN1 latencies appeared to be relatively constant despite increases in stimulus frequency.
Traditional chirp stimuli designed to optimize monaural ABR peak amplitudes by accounting for frequency-dependent cochlear delays appear ill-suited for eliciting optimal BIC peak amplitudes. Traditional broadband clicks or other non-traditional chirp stimuli may be preferable for eliciting an optimal BIC.
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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Topic: D.06. Auditory & Vestibular Systems

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T32-AG021890 to Wollet M

Title: Brain-derived neurotrophic factor is required for the structural and physiological refinement of MNTB neurons along the tonotopic axis

Authors: *M. WOLLET[1], E. KIM[1], E. A. GOULD[1], J. KIM[2];
[1]Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [2]Physiol., Univ. of Texas Hlth. Sci. Ctr. San Antonio Sch. of Nursing, San Antonio, TX

Abstract: In the mammalian brain, central auditory nuclei are arranged topographically according to acoustic frequency responsiveness, called *tonotopy*. The medial nucleus of the trapezoid body (MNTB) is

one of auditory brainstem nuclei responsible for sound localization. During postnatal development, the axon initial segment (AIS), a key axonal domain responsible for action potential initiation, of MNTB neurons undergoes structural refinement depending on neuron location along the tonotopic axis within the MNTB. However, the molecular mechanisms underlying the structural differentiation of the AIS along the tonotopic axis in the auditory brainstem have not been explored. In this study, we investigate BDNF as a potential mediator responsible for structural development and refinement of the MNTB in activity-dependent manner. We hypothesized that BDNF, a key factor for activity-dependent plasticity, is necessary for structural refinement of MNTB neurons after hearing onset. Using *BDNF* heterozygous (*BDNF*$^{+/-}$) mice, we examined impact of global BDNF reduction on structural and functional development of MNTB neurons by assessing AIS structural properties and intrinsic properties. *BDNF*$^{+/-}$ mice had no differentiation of AIS length or location along the tonotopic axis unlike WT mice. BDNF reduction inhibits the establishment of the structural differentiation of the AIS along the tonotopic axis in the MNTB and impacts their AP firing properties. These data suggest BDNF is essential for structural and physiological development of MNTB neurons after hearing onset. Sound deprivation and enhancement have been shown to dynamically modify length and location of the AIS in MNTB neurons. However, in *BDNF*$^{+/-}$ mice, sound enhancement (16kHz, 3 hrs, 7 days) did not impact structural dynamics of the AIS nor neuronal excitability tonotopically in the MNTB, indicating that structural plasticity of MNTB neurons in response to increased sound input requires BDNF signaling. Taken together, structural development and functional refinement of auditory neurons within the auditory brainstem requires physiological levels of BDNF in order to establish proper tonotopic organization that allows for precise binaural sound processing.

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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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RNID S55_King

Title: Adaptation to unilateral conductive hearing loss and its generalization to different acoustical conditions in the adult ferret

Authors: *A. I. SANCHEZ JIMENEZ, K. WILLARD, V. M. BAJO-LORENZANA, A. J. KING, F. R. NODAL;
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Abstract: Accurate sound localization relies on the ability of the brain to extract spatial information embedded in the auditory signal. To that effect, the brain integrates information provided independently by each ear (monaural spectral cues) or correlated between them (binaural cues). Unilateral conductive hearing loss (UCHL) produces an asymmetric input, which compromises the binaural computations

required for sound localization, whilst leaving intact the monaural spectral cues available at the normally functioning ear. Previous studies have shown that training in a sound localization task enables individuals with UCHL to partially recover their spatial accuracy and that the auditory cortex plays an essential role in such adaptation.
It remains unclear to what extent this adaptive process generalizes beyond the training stimuli to other sounds. Seven ferrets were trained to localize broadband noise bursts in a silent background. All animals showed a severe reduction in localization accuracy when one ear was plugged, which then recovered with training. Over the course of adaptation, the operant approach-to-target response accuracy reached 70-90% from an initial 20% and the response precision improved with a decrease in the error size from 47.9 ± 14.3 to 11.1 ± 10.7 degrees. Similarly, the accuracy of head orienting responses, which were initially biased toward the side of the non-occluded ear, recovered in two of the animals, suggesting the likely involvement of adaptation of neural responses at subcortical levels.
We also measured localization accuracy before and after adaptation using noise bursts of different bandwidth or amplitude modulated noise (AM) against a background of either constant or AM noise presented from an overhead loudspeaker. A positive correlation was observed between the degree of adaptation achieved and the generalization to other stimulus types. Animals that achieved an almost complete recovery of response accuracy with the broadband training stimulus showed a similar degree of improvement with the other stimuli. Thus, while localization accuracy varied with stimulus type depending on the cues available and the masking effects of the background noise, the relative performance of the animals for different sounds was unaffected by UCHL. However, those animals that adapted less with broadband noise also performed less well in the other sound conditions. Overall, these results suggest that the recovery in spatial hearing can generalize to other sounds and that adaptation and generalization may occur simultaneously.

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Poster

P432. Auditory Processing: Sound Localization and Binaural Interactions

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Topic: D.06. Auditory & Vestibular Systems

Support: FRAXA

Title: Auditory brainstem specific binaural hearing ability in Fragile X Syndrome mice

Authors: A. CHAWLA, S. ALAM, I. RAY, *E. MCCULLAGH;
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Abstract: Binaural hearing is critical for parsing sound streams into individual spatial locations and is the basis for more complex listening situations. Binaural hearing begins in the auditory brainstem, where the brain computes interaural intensity and timing differences (IID and ITD respectively), which are both crucial aspects of binaural hearing ability. One of the dominant sensory issues described in patients with

Fragile X Syndrome (FXS) is hypersensitivity to sound. FXS is the most common monogenic form of autism. We, and others, have shown that there are indeed anatomical, physiological, and behavioral changes to the auditory brainstem in *Fmr1* knockout (KO) mice. In this study, we explored whether *Fmr1* KO mice have impaired binaural hearing as measured by the binaural interaction component (BIC) of the auditory brainstem response (ABR). The ABR is a non-invasive electrophysiological measure recording a pattern of waveforms that is directly related to the different brain areas that encode sound processing in the auditory brainstem. The BIC, especially as it varies with ITDs, is a direct measure of physiological auditory brainstem mediated binaural hearing. We examined latency and amplitude of ABR waves, BIC amplitude and latency across ITDs, and hearing thresholds between 1 kHz - 64 kHz in male and female C57BL/6J wildtype, *Fmr1* KO and heterozygote female mice. Our preliminary data shows that while the overall ABR waveforms do not show changes to ABR latencies, there is a decreased latency for the BIC, in *Fmr1* KO mice compared to controls. Further studies will show when during development brainstem specific phenotypes arise in this *Fmr1* KO strain to help better target treatment timepoints and efficacy specific to auditory phenotypes. The BIC and ABR is a measurement that can be directly translated to humans and is likely a good candidate for testing mechanistically how the auditory brainstem is changed in FXS and autism.

Disclosures: A. Chawla: None. **S. Alam:** None. **I. Ray:** None. **E. McCullagh:** None.

Poster

P464. Human and Non-Human Primate Visual Representations and Perception

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P464.01

Topic: D.07. Vision

Support: ZIA-MH-002909

Title: Grating orientation information tolerant to stimulus contrast revealed by directional analyses of BOLD fMRI activity patterns of human primary visual cortex

Authors: *F. M. RAMIREZ, C. REVSINE, E. P. MERRIAM;
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Abstract: Multivariate pattern analyses are widely used in neuroimaging studies. However, it is unclear what these analyses reveal about neural coding. Such approaches often obfuscate the link between neural measurements and the stimulus, limiting their utility. Linear classification, a highly-popular approach, exploits the Euclidean distance among pattern vectors. Our recent theoretical work suggests that information regarding tuning properties is best captured by angular distances, not Euclidean distances. Specifically this is the case because the former distances, but not the latter, are explicitly sensitive to the relative direction of pattern-vectors in a high-dimensional space. The goal of this experiment was to relate specific aspects of multivariate measurements to parametrically defined dimensions of visual stimuli. We used primary visual cortex as a model system to test the following predictions: (i) Euclidean distances conflate information regarding response amplitude and selectivity, (ii) angular distances best reflect information about selectivity. In particular, if these predictions are correct, one might expect that angular,

but not Euclidean distances, might reveal information about grating orientation that is tolerant to changes in stimulus contrast. fMRI BOLD activity was measured from 5 participants (7T, 32-channel coil, 1.2x1.2x1.2 mm resolution). Stimuli consisted of Cartesian sinusoidal gratings multiplied by flower-shaped apertures. The orientation of the "petals" was controlled by the phase of the radial frequency (RF) used to generate the aperture. In a fully crossed experimental design, the compound stimulus varied along three dimensions: grating orientation, contrast, and RF-phase, resulting in a total of 96 unique conditions. We found that the Euclidean metric was sensitive to stimulus contrast and relatively insensitive to grating orientation and aperture phase. In contrast, Angular distances proved sensitive to grating orientation and aperture phase. Crucially, angular distances were also found to be significantly more robust to changes in stimulus contrast than the Euclidean distance. We propose a biologically-inspired computational model to provide a theoretic account of these observations. Our results have fundamental implications for the interpretation of MVPA, and serve to inform the development of data analysis strategies more readily interpretable in terms of the underlying neurophysiology.

Disclosures: F.M. Ramirez: None. **C. Revsine:** None. **E.P. Merriam:** None.

Poster

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HFSP RGP0036/2016
BMBF FKZ 01GQ1704
SSTeP-KiZ BMG: ZMWI1-2520DAT700
NVIDIA Corp

Title: A norm-based neural model for the recognition of dynamic facial expressions across species

Authors: *M. STETTLER[1], N. TAUBERT[2], R. SIEBERT[3], S. SPADACENTA[4], P. DICKE[5], P. THIER[6], M. A. GIESE[7];
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Abstract: Dynamic facial expression recognition is an essential skill of primate communication. While the neural mechanisms of the recognition of static facial expressions have been extensively investigated, it remains largely unclear how dynamic facial expressions are neurally encoded. We studied physiologically plausible neural encoding mechanisms exploiting highly-controlled and realistic stimulus sets generated by computer graphics. The stimulus set showed dynamic human and monkey expressions, and it allowed to study how the perception of facial dynamics interacts with changes of head shape. In psychophysical experiments, we found that the perceptual encoding of facial dynamics was largely

independent of facial shape (human vs. monkey). This raises the question how such independence can be explained in terms of neural mechanisms. Testing standard deep neural network models, we did not find a good generalization of expression recognition between different head shapes. We then developed a model based on *norm-referenced encoding*. This model assumes that snapshots of the facial movies are represented by neurons that encode the vector differences between the neutral face (norm pattern) and the actual frame in a high-dimensional face space. The output of these face neurons were then processed by temporal differentiator neurons, resulting in selective responses to dynamic faces.The model was tested with movies of human and monkey avatars that showed human and monkey expressions, and morphs between them. The proposed neural model recognizes reliably the tested dynamic facial expressions of humans and monkeys and correlates with behavioral finding, that dynamic facial expressions perception is largely independent of the basic face shape. Specifically, the model reproduces that dynamic expressions can be recognized on the face of the other species, even if the model was trained only with dynamic expressions of the head model of the other species. In addition, the neuron responses in the model show a highly gradual, almost linear dependence on the expressivity of the stimuli and good generalization to morphed expressions. Some of these characteristics match initial observations in dynamic face-selective neurons in the Superior Temporal Sulcus (STS) of macaque monkeys.

Disclosures: M. Stettler: None. **N. Taubert:** None. **R. Siebert:** None. **S. Spadacenta:** None. **P. Dicke:** None. **P. Thier:** None. **M.A. Giese:** None.

Poster

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Title: Temporal Mechanisms of Binocular Rivalry and Perception in the Human Brain

Authors: *V. RANGARAJAN[1,2], D. KING-STEPHENS[3], K. D. LAXER[4], P. WEBER[4], J. J. LIN[5], K. AUGUSTE[6,7], E. F. CHANG[6], R. T. KNIGHT[1];
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Abstract: Binocular rivalry (BR) is a striking form of perception where different images are presented concurrently to each eye and conscious perception alternates between the images. This provides a unique opportunity to disentangle conscious perception from sensory processing since perception alternates, while the sensory input remains static. We leveraged intracranial recordings in patients with refractory epilepsy to study how F-P regions support rapid shifts in conscious perception. Subjects (n=9) were

implanted with intracranial electrodes and participated in 2 experiments: Exp 1 was a category localizer in which subjects saw faces, houses, words, bodies, and scrambled images while performing an odd-ball paradigm; Exp 2 was a face/house BR paradigm in which the (red/blue) stimuli were presented independently, but simultaneously to each eye. Subjects reported when a perceptual switch occurred during 2 conditions: *rivalry*, in which perceptual switches were endogenous or self-driven, and *replay*, in which switches were replayed based on previous behavior. Behaviorally, subjects reported perceptual alternations between stimuli every 2-6 seconds with subjects reporting an average of 49.5 percepts (± 19.7 std). During *rivalry*, we found that high-frequency broadband activity (HFB: 70-150 Hz) was active during 3 main temporal response windows: (i) at the onset of stimulus presentation, and (ii) time-locked or (iii) immediately after the perceptual switch. First, we found that the initial perception of a BR stimulus is largely driven by the visual cortices, with earlier activation than associative areas. Notably, HFB activity in these regions predicted subsequent behavioral reports of the subject's perception. In contrast, later changes in perception during switching in BR are initiated by associative cortices revealing HFB activity onsetting before later sensory reactivation after a change in perception. Peak timings for occipital electrodes (avg peak=278 ms) were significantly later than frontal (avg Δ = 228 ms, *ks*-test=0.72, $p=9.1x10^{-8}$), parietal (avg Δ =225 ms, *ks*-test=0.72, $p=1.91x10^{-9}$), and temporal (avg Δ = 125 ms, *ks*-test=0.43, $p=3.55x10^{-4}$) electrodes. These patterns were not mirrored during *replay*, indicating that BR does not merely reflect perceptual decision making. Together, these findings support a bi-directional relationship between sensory and F-P associative areas providing insights into the neural substrates of conscious perception.

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Poster

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Title: Cortical magnification in human primary visual cortex correlates with contrast sensitivity

Authors: *M. HIMMELBERG, M. CARRASCO, J. WINAWER;
New York Univ., New York, NY

Abstract: The size and organization of primary visual cortex (V1) varies within and between individuals. The overall size of V1 varies up to threefold in neurotypical observers. Within an individual, the cortical magnification (mm^2 of cortex per deg^2 of visual field) varies with eccentricity and polar angle. This variation in cortical anatomy has important consequences for visual perception. Averaged across observers, contrast sensitivity and cortical magnification co-vary with eccentricity, as shown by Virsu and Romano (1979), who hypothesised that contrast sensitivity is limited by the number of activated V1 neurons. Here, we extend this logic to contrast sensitivity asymmetries as a function of polar angle -

contrast sensitivity is higher along the horizontal than vertical meridian, resulting in a horizontal-vertical asymmetry - and across individuals.
In 22 observers, we employed an orientation discrimination task to measure contrast sensitivity (Gabor patches; 4 cycles per deg, 4.5º of eccentricity, 3º diameter) at the four cardinal meridians, and used fMRI to measure their V1 maps. We then calculated the surface area of four wedge-regions-of-interest (ROIs) in each observer's V1 that matched the angular location of the contrast sensitivity measurements. Each wedge-ROI represented a wedge in the visual field that was centered along one of the four cardinal meridians and spanned ±15° of polar angle and 1-8° of eccentricity.
We used Spearman's correlations to assess the relation between contrast sensitivity and V1 surface area measurements across observers at multiple scales. First, contrast sensitivity was positively correlated with the overall size of V1 (n=22, r_ρ=0.4); observers with higher contrast sensitivity tended to have a larger V1. Second, contrast sensitivity measurements were positively correlated with the surface area of the wedge-ROIs centered at the corresponding meridians (n=22 observers x 4 locations, r_ρ=0.6); this indicated that the link between contrast sensitivity and surface area holds at a finer scale. Third, we computed the horizontal-vertical asymmetry for contrast sensitivity and for V1 surface area (i.e., the difference between horizontal and vertical measurements divided by their sum). The two measures were correlated (n=22, r_ρ=0.6); a stronger horizontal-vertical asymmetry in the distribution of V1 surface area corresponded to a stronger horizontal-vertical asymmetry in contrast sensitivity.
These data confirm that contrast sensitivity is linked to V1 surface area, and we extend this link to explain both individual variation and polar angle asymmetries in visual performance.

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Poster

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NIH P41 EB027061
NIH P30 NS076408
NIH S10 RR026783
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Title: Evidence for a ventral visual stream in the human pulvinar

Authors: *D. R. GUEST[1], E. J. ALLEN[1], Y. WU[1], T. NASELARIS[2], M. J. ARCARO[3], K. N. KAY[1]; [1]Univ. of Minnesota, Minneapolis, MN; [2]Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [3]Univ. of Pennsylvania, Philadelphia, PA

Abstract: The pulvinar is a major thalamic nucleus that is highly interconnected with visual cortex and supports a range of visual functions such as visual attention. Work in non-human primates has shown that inferior and lateral portions of the pulvinar connect predominantly to early visual cortex, have clear retinotopic organization, and are sensitive to low-level visual features such as contrast. However, less is understood about the role the pulvinar may play in processing high-level visual stimuli such as scenes, faces, and objects. To address this gap, we investigated subcortical activity in the Natural Scenes Dataset (NSD). In NSD, 8 human participants completed a visual fMRI experiment during which they were exposed to 9,000-10,000 unique natural scenes. Whole-brain fMRI data were collected at ultra-high field strength (7T) with 1.8-mm spatial resolution, ensuring high-quality measurements from subcortical regions. We fit population receptive field (pRF) models to individual voxels, systematically evaluating different stimulus features (contrast, saliency, faces, bodies, foreground, background, words) that might be encoded in voxel responses. This analysis confirmed that the LGN and inferior-lateral pulvinar respond selectively to contrast located in the contralateral visual hemifield and are retinotopically organized. Notably, the analysis also revealed a portion of the pulvinar, located medial and posterior to the contrast-selective portion, that responds selectively to bodies and faces located in the contralateral visual hemifield. To further explore these findings, we performed a thalamocortical correlation analysis in which stimulus-evoked responses in the thalamus are correlated with stimulus-evoked responses in cortex, where stimulus representations are better understood. This analysis revealed that pulvino-cortical correlations are largely restricted to the visual cortex. The contrast-selective portion of pulvinar correlates most with early visual cortex while the body- and face-selective portion of pulvinar correlates most with face- and body-selective cortical regions (e.g., FFA, FBA). More generally, we find a gradient of pulvino-cortical correlations in which the progression from anterior-lateral to posterior-medial in the pulvinar recapitulates the posterior-to-anterior organization of visual cortex. While emphasis is often placed on the pulvinar's role in visual attention, our results indicate that the pulvinar also plays a role in high-level vision and illustrate that principles of cortical organization (e.g. functional clustering and hierarchical organization) hold for the thalamus as well.

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Poster

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Topic: D.07. Vision

Support: NEI R01 EY023915

Title: A spatiotemporal pRF model of sensory suppression in human visual cortex

Authors: *E. R. KUPERS[1], I. KIM[1], K. GRILL-SPECTOR[1,2];
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Abstract: When multiple visual stimuli are presented simultaneously in the receptive field the neurophysiological response is surprisingly lower compared to when the identical stimuli are presented sequentially. The prevailing hypothesis suggests this suppression is due to competition effects within the receptive field (Kastner et al. 1998, 2001; Kim et al.; 2021; Reynolds, Chelazzi & Desimone, 1999). Alternatively, this suppression may be due to nonlinear, compressive summation within the receptive field—nonlinearities may be spatial (compressive spatial summation, CSS, Kay et al. 2013), temporal (compressive temporal summation, CTS, Zhou et al. 2017; Stigliani et al. 2019), or both. Here, we built a new spatiotemporal population receptive field (pRF) model and tested CSS and CTS models using fMRI. We collected data from two experiments: (i) retinotopic mapping with cartoon stimuli (Finzi et al. 2021) to define visual areas in ventral, dorsal, and lateral streams, as well as to estimate spatial pRF parameters for each voxel, and (ii) simultaneous vs sequential presented stimuli. Each trial contained 4 colorful squares (2x2°) presented in the upper right quadrant (3-9° eccentricity). In sequential trials, each square appeared for 250 ms and the 4 squares appeared in random order. In simultaneous trials, the identical 4 squares appeared at once for 250 ms followed by 750 ms blank. Each sequential and simultaneous block had 8 trials with random stimuli followed by 8 s blank. Results replicate prior findings of lower BOLD responses for simultaneous vs sequential blocks in individual voxels as early as V2 in all 3 observers. We then tested which model best predicts these suppressive effects: (i) linear temporal + spatial summation, (ii) compressive spatial + linear temporal summation (CSS), (iii) linear spatial + compressive temporal summation (CTS, 2-channel temporal model by Stigliani et al. 2019). Both nonlinear models predict lower responses for simultaneous than sequential blocks in single voxels, but the linear model predicts the same level of response across sequential and simultaneous blocks. Across the visual hierarchy, the CTS model explains most variance in the data (27±5.2%, up to ~60% in ventral and lateral areas), and significantly more than both the CSS (23±4.3%, up to ~50%) or linear model (24±4.6%, up to ~54%). These results indicate that a linear pRF model cannot explain the observed sensory suppression and the underlying mechanism involves nonlinear summation. Our new spatiotemporal pRF model offers a quantitative approach to study dynamic visual stimuli and provides insight into neural computations of sensory suppression in the human visual pathways.

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Poster

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Support: NEI R01 EY023915
Marie Sklodowska-Curie grant H2020-MSCA-IF-2017-795807

Title: Spatiotemporal population receptive field model of human visual cortex

Authors: *I. KIM[1], E. KUPERS[1], G. LERMA-USABIAGA[2], W. SHIM[3], K. GRILL-SPECTOR[1,4];
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Sebastian, Spain; [3]Biomed. Engin., Sungkyunkwan Univ., Suwon, Kyunggi-Do, Korea, Republic of; [4]Wu Tsai Neurosciences Inst., Stanford, CA

Abstract: Computational modeling to predict neural responses to stimuli varying in basic visual dimensions of space and time is crucial for understanding how we perceive dynamic visual scenes. However, standard population receptive field (pRF) models only characterize neural responses to the spatial aspects of the stimulus (Dumoulin & Wandell, 2008; Kay et al., 2013). Currently, no pRF model explains responses across both space and time in the human visual system. Here, we built and tested a stimulus-referred spatiotemporal pRF model using simulated and experimental fMRI data. The spatiotemporal model derives fMRI time series from spatial 2D gaussians and nonlinear temporal neural impulse functions in millisecond resolution (Stigliani et al., 2019; Zhou et al., 2019). First, we developed simulation software to ensure computational reproducibility and validity of our spatiotemporal model. The software (i) generates synthetic fMRI time series from a stimulus and spatiotemporal pRFs, (ii) solves spatiotemporal pRF parameters, and (iii) tests the solution to the ground truth parameters used to synthesize the fMRI time series. The ground truth parameters were accurately recovered from the synthetic fMRI time series. Second, we tested how well the spatiotemporal pRF model predicts experimental fMRI data (n=10). The visual stimuli consisted of bar apertures systematically traversing across the visual field (12° radius, 4 directions, 9 discrete steps) with varying temporal dynamics (33 ms to 5 s duration, 33 ms to 200 ms interstimulus intervals). We found that the spatiotemporal pRF model had higher cross-validated accuracy than the standard pRF in all the tested visual areas (V1, hV4, and TO1). Interestingly, the spatiotemporal model showed substantially higher accuracy for brief, transient visual stimuli compared to the standard pRF model. Overall, the spatiotemporal pRF model quantitatively predicts each voxel's responses to a wide range of visual stimuli that vary in spatial location, size, timing, and duration ranging from milliseconds to seconds. These results suggest that incorporating stimulus components of space and time in pRF models is important for modeling a wide range of spatiotemporal stimulus evoked responses in the human visual cortex.

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Poster

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Title: Neural tuning modulation modeling in R: A software package for inferring the form of neuromodulation from fMRI tuning functions

Authors: *P. SADIL, R. A. COWELL, D. E. HUBER;
Psychological and Brain Sci., Univ. of Massachusetts, Amherst, MA

Abstract: Many neuroscience theories assume that changes in human cognition are underpinned by changes in neural tuning. However, neural tuning cannot be measured directly in humans with non-invasive measurements; standard voxels from fMRI aggregate the signal of hundreds of thousands of neurons. We present a statistical framework called Neural Tuning Modulation Modeling, which allows researchers to use fMRI to infer how changes in cognitive states -- e.g., viewing a stimulus with versus without attention -- modulate neural tuning functions. The framework comprises two tools: one tool uses hierarchical Bayesian modeling and cross-validated model comparison, and the other is a nonparametric check using regression slopes. These methods exploit the fact that voxels in an fMRI dataset, like single neurons, exhibit tuning functions (e.g., the activation of a voxel in visual cortex may vary systematically with orientation), and these voxel tuning functions can be modulated across the same conditions that modulate neural tuning functions. Distinct changes in voxel-level activation are predicted by different modulations at the neural level, allowing adjudication between different forms of modulation in neural tuning with non-invasive fMRI. The framework has been validated using fMRI data collected from participants viewing oriented gratings at high- and low-contrast, which is known from electrophysiology to cause multiplicative scaling of orientation tuned neurons. Beyond orientation, this approach could be applied to determine the form of modulation in any fMRI experiment, provided that the experiment tests multiple points along a stimulus dimension to which neurons are tuned (e.g., direction of motion, pitch, stimulus location, etc.). We showcase a new R software package that aims to make it easy to apply the framework.

Disclosures: P. Sadil: None. **R.A. Cowell:** None. **D.E. Huber:** None.

Poster

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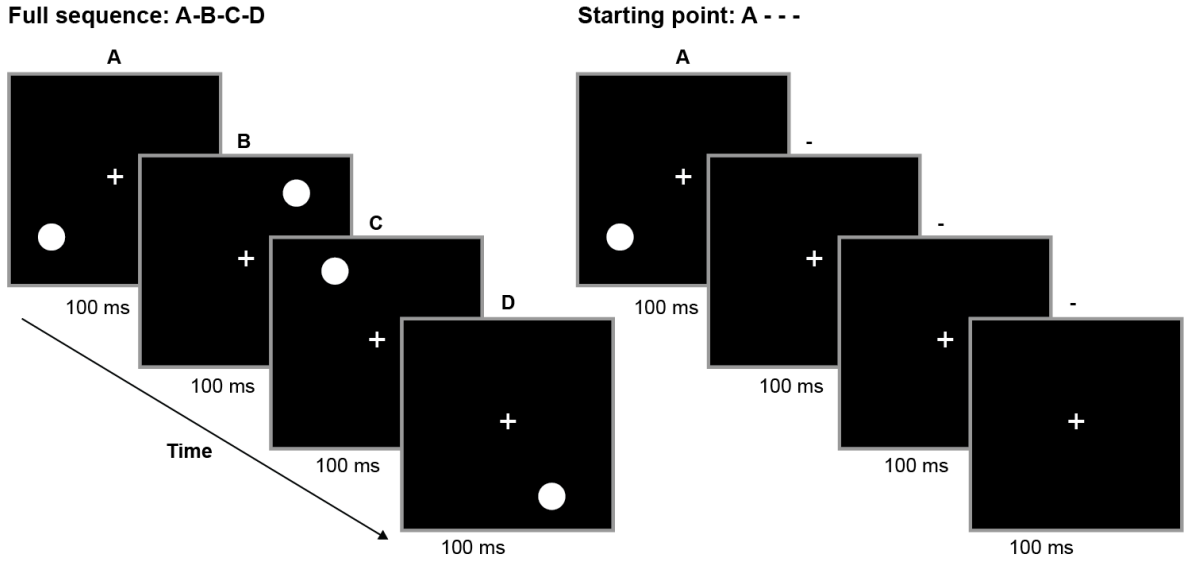
Title: V1 as a predictive map: successor-like representation of upcoming events in human visual cortex

Authors: *M. EKMAN, S. KUSCH, F. DE LANGE;
Donders Inst. for Brain, Cognition and Behaviour, Nijmegen, Netherlands

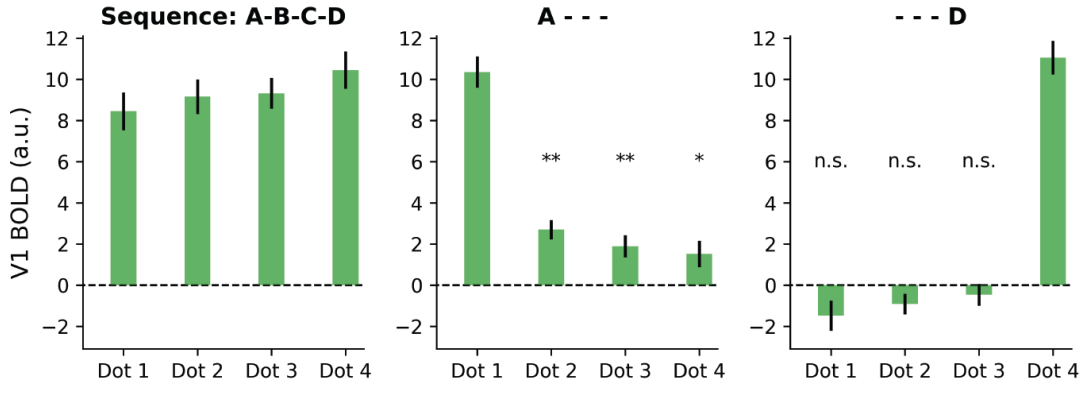
Abstract: Predictions of upcoming visual events may constitute an important mechanism to guide flexible behavior and have been observed in animal (Ji & Wilson 2007; Xu et al. 2012) and human visual cortex (Ekman et al. 2017). These predictions are based on an experience-dependent representation ('model') of our environment. However, it remains unknown what the inherent features and limitations of the model underlying our predictions are. Recently, it has been proposed that representations take the form of a map-like structure, the so-called successor representation (SR). The SR hypothesis makes two testable predictions, namely that population activity represents future states, and that these future states are discounted, such that events in the close future are more prominently represented compared to events in the distant future (Stachenfeld et al. 2017; Dayan 1993). Here we used human fMRI to probe whether

visual activity adheres to these properties of the SR. Participants were exposed to a spatio-temporal sequence consisting of four items (A-B-C-D). We found that after repeated exposure to the sequence, merely presenting the starting point of the sequence (i.e., A - - -) resulted in forward replay of the full sequence in V1, reflecting the anticipation of upcoming stimulus events. During forward replay, V1 BOLD activity decreased as a function of distance in successor space, independent of spatial distance. Further, forward replay was also observed when only intermediate sequence points were shown (i.e., - B - -, and - - C -), indicating that the relational structure of the sequence is represented in V1. Importantly, forward replay was only observed at the successor- but not at the predecessor states of the sequence. Additionally, representations of future sequence states were also observed in the anterior Hippocampus and correlated with V1 representations on behaviorally correct trials, but not on incorrect trials, suggesting an important functional relationship between V1 and Hippocampus for forming a 'predictive map-like' representation of the environment.

1. Experimental paradigm



2. V1 Stimulus representation



Disclosures: M. Ekman: None. **S. Kusch:** None. **F. de Lange:** None.

Poster

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Title: Receptive field mapping of face neurons during naturalistic viewing

Authors: W. S. ONG[1], K. N. KAY[2], M. S. LIVINGSTONE[3], *M. ARCARO[1];
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Abstract: Inferotemporal cortex (IT) contains neurons that respond selectively to complex shapes and visual categories. These neurons are thought to be critical for our ability to recognize objects in our environment. Though traditionally underemphasized, prior work has demonstrated that object representations in IT can exhibit a high degree of spatial specificity (Op de Beeck & Vogels 2000; Issa & DiCarlo 2012). However, it has remained challenging to assess spatially specific responses under naturalistic viewing conditions. Here, we recorded multi-unit spiking activity from multielectrode arrays implanted in fMRI-defined macaque posterior (PL), middle (ML), and anterior (AL) lateral face patches during viewing of naturalistic scenes and used model-based receptive field mapping methods to estimate the location and size of neuronal receptive fields (RF). We found that RF parameters derived from modeling the location of faces in naturalistic scenes were comparable to RFs derived from conventional mapping approaches using isolated faces on a uniform background. Interestingly, the sizes of RFs tended to be smaller for faces in naturalistic scenes. RF sizes reflected the hierarchical organization of IT. RF sizes were smallest in PL (0.5-2 degrees), larger in ML (2-6 degrees) and largest in AL (5-12 degrees). Model fits (variance explained) for faces in scenes were good for both ML and AL where face selectivity is strong, but poorer for PL likely reflecting the weaker selectivity for faces. Position and size measurements were reproducible across sessions for the same stimuli. Finally, we found that correctly identifying the visual features that drive neurons was critical for accurately measuring RFs. For example, the receptive fields of PL and ML neurons for one monkey were offset along the y-axis when modeling upright and inverted faces, reflecting specific selectivity for the eyes within a presented face. These results suggest that previously reported variation in neuronal firing to different faces (or viewpoints) may in part reflect simple shifts in the retinal position of specific facial features for which a neuron is selective (e.g., eyes). More broadly, these results illustrate that space and visual feature coding are intertwined throughout the ventral visual hierarchy and indicate a prominent role for spatial coding in object processing during natural visual experience.

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Poster

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Program #/Poster #: P464.11

Topic: D.07. Vision

Support: NIH Grant R01MH111417

Title: Spatial Tuning of Alpha Oscillations in Human Visual Cortex

Authors: *K. YUASA[1], I. I. A. GROEN[1,2], G. PIANTONI[3], S. MONTENEGRO[4], A. FLINKER[4], S. DEVORE[4], O. DEVINSKY[4], W. DOYLE[4], N. F. RAMSEY[3], N. PETRIDOU[3], J. WINAWER[1]; [1]Dept. of Psychology, New York Univ., New York, NY; [2]Video & Image Sense Lab., Inst. for Informatics, Univ. of Amsterdam, Amsterdam, Netherlands; [3]Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [4]New York Univ. Sch. of Med., New York, NY

Abstract: The alpha oscillation (8-13 Hz) is a pronounced neuronal signal measured from the human occipital lobe. Alpha oscillations are thought to reflect cognitive functions including attention and alertness, and to be synchronized across a large cortical extent. However, there is some evidence that suppression of alpha oscillations in visual cortex can be spatially specific. Here, we used intracranial electrodes (ECoG) to measure alpha oscillations in visual cortex of 9 human subjects. Subjects viewed contrast patterns masked by an aperture at different visual field locations. We used a model to separate the alpha oscillation from broadband signals that overlap the alpha range. This was essential because power in the alpha band reflects both signals, and the two tend to oppose one another. A simple measure of alpha power that does not remove the broadband signal would incorrectly quantify the alpha rhythm.

We find that for a given electrode, alpha oscillations were suppressed only when stimuli appeared in specific regions of the visual field. We fit a 2D Gaussian population receptive field (pRF) model to the time series of the alpha response and compared the solutions to pRF models fit to broadband responses measured from the same electrodes at higher frequencies (70-180 Hz). The pRF centers were similar for the two measures, but the sizes differed, with alpha pRFs several times larger. The results demonstrate that alpha suppression in human visual cortex is spatially tuned and is in agreement with the underlying retinotopic map.

To complement analyses of the alpha amplitude, we examined the coherence of the alpha oscillation between electrodes on a high-density ECoG grid (1 mm diameter, 3 mm center-to-center spacing). When the stimulus was in an electrode's pRF, coherence with neighboring electrodes decreased, compared to a blank screen. Overall, we found a modest correlation such that when the alpha oscillatory amplitude decreased, coherence with neighboring electrodes also tended to decrease. We extrapolate that when coherence with neighboring electrodes decreases, coherence within the neural population under the electrode decreases. This would imply that neural coherence contributes to the changes in amplitude we observe during the mapping experiment.

Our findings support the possibility that the alpha suppression reflects part of the computations in generating neural responses to visual stimulation. We speculate that suppression of alpha oscillations to stimuli within or near the receptive field of a patch of cortex increases the responsivity of that cortical location, consistent with psychophysically measured benefits of attentional cueing.

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Poster

P464. Human and Non-Human Primate Visual Representations and Perception

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P464.12

Topic: D.08. Visual Sensory-motor Processing

Support: CIHR

Title: Visual receptive fields in the posterior parietal cortex of the common marmoset

Authors: *K. JOHNSTON[1], S. EVERLING[2], J. SELVANAYAGAM[3];
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Abstract: The common marmoset (*Callithrix jacchus*), is an emerging model in visual neuroscience. This species possesses comparable oculomotor behaviour and visual and frontoparietal areas homologous to the rhesus macaque, which has historically been the standard model for electrophysiological investigations of oculomotor and cognitive control. The locations and sizes of visual receptive fields (RFs) reflect a fundamental aspect of the organization of cortical visual and oculomotor areas. In the marmoset, RF properties have been investigated in primary and tertiary visual areas, and frontal cortex in anesthetized preparations, but knowledge of the properties of RFs areas in the awake, behaving marmoset, and in posterior parietal cortex (PPC), encompassing areas LIP, MIP, and VIP, remain limited. Here we investigated RF properties of PPC neurons in the awake marmoset by recording with high density Neuropixels laminar probes in a receptive field mapping paradigm. In this paradigm, black dots (radius 0.3 deg) were briefly flashed (SOA: 100-200ms) on a grey background at one of 24 locations (5x5 grid in +/-10 deg). To determine whether units exhibited visual responses and spatial tuning, we conducted a two-way mixed ANOVA (Epoch x Location) comparing activity 50-100ms post-stimulus onset to a 50ms prestimulus period for each location. Of 3727 total units recorded, 698 showed a significant interaction of Epoch and Location. To investigate the receptive field properties of these units, we fit their responses to a 2D elliptical gaussian to estimate RF center and extent. 23.5% of all RFs were located in the contralateral hemifield and 4.3% in the ipsilateral hemifield, with the remaining RFs extending bilaterally. 64.8% of all RFs were located in the upper visual field. RF eccentricities ranged from 1 to 19 deg (median=3.35 deg). RF widths ranged from 3 - 20 deg (median=7.25). In 25 of 30 penetrations, we observed similar RFs across units. Altogether, we observed large bilateral RFs and smaller contralateral RFs similar to those observed in macaque PPC. In addition, RF widths resembled those found in macaque PPC at comparable eccentricities. These data suggest that RF properties and organization are similar in macaque and marmoset PPC, and provide further support for the marmoset model in investigations of the neural circuitry of the primate PPC and it's role in visual and cognitive processes.

Disclosures: K. Johnston: None. **S. Everling:** None. **J. Selvanayagam:** None.

Poster

P464. Human and Non-Human Primate Visual Representations and Perception

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Program #/Poster #: P464.13

Topic: D.08. Visual Sensory-motor Processing

Support: Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council

Title: Cortical microcircuitry underlying target discrimination in the posterior parietal cortex of the common marmoset

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Abstract: The concept of a "canonical circuit", derived from investigations in primary sensory cortex, suggests a basic local, laminar cortical structure shared by all areas of neocortex. Investigations in rhesus macaques have revealed functional classes of cells in the frontoparietal network that play an important role in oculomotor control and visual attention. However, due to the difficulty in accessing key nodes of this network that are embedded within sulci (e.g., FEF and LIP) in the macaque, knowledge of the laminar microcircuitry of these areas and its function in cognitive tasks remains limited. To address this gap, we exploited the relatively lissencephalic cortex and homologous frontoparietal networks of the common marmoset (Callithrix jacchus). We carried out ultra high-density laminar recordings from one node of the frontoparietal network, the posterior parietal cortex (PPC), in two adult marmosets, targeting regions identified using fMRI as having strong BOLD responses in a saccade task. Recordings were conducted with high density laminar neuropixel probes (384 electrodes spanning 3.84mm), as the animals completed a visual target selection task, in which the animal was required to make a saccade to a target stimulus in the presence or absence of a distractor presented in the opposite hemifield. The animals correctly made a saccade to the target in the absence of a distractor faster (median RT: 158.5ms) and more accurately (mean accuracy: 82.5%) than in the presence of a distractor (median RT: 164.1ms; mean accuracy: 68.8%). We recorded from 3913 units, of which 945 units showed significant visual or saccade related activity. Of these units, 262 units discriminated between target and distractor stimuli prior to making a correct response; 66.7% of these units showed increased activity for the target stimulus. For these units, we computed the latency at which each unit's discharge activity selected for its preferred stimulus. The earliest discrimination time varied as a function of depth, occurring at approximately 60ms for units in more superficial locations (500 μm from the surface of the brain) followed by 80ms in deeper units (1500 and 2500 μm). Altogether we found that marmoset PPC neurons discriminated between target and distractor stimuli and that the latency to discriminate between target and distractor stimuli was shortest in superficial units followed by longer latencies in deeper units. These data provide novel insight into the laminar organization of visual responses in primate PPC.

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Poster

P464. Human and Non-Human Primate Visual Representations and Perception

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Program #/Poster #: P464.14

Topic: D.07. Vision

Support: NIH Grant EY029703
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Unrestricted grant from Research to Prevent Blindness

Title: Interocular suppression in primary visual cortex in strabismus: Impact of sequential rather than simultaneous stimulation

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Abstract: Diplopia, or double vision, results from strabismus because misalignment of the visual axes causes images to fall upon non-corresponding locations in the two retinas. In children who develop strabismus early in life, this noxious sensation is prevented by suppression of the image originating from one of the eyes. Our goal is to elucidate the neural mechanism of diplopia suppression. In a recent study directed at this question, we recorded neurons in primary visual cortex of two Rhesus macaques raised with exotropia (an outwards ocular deviation) induced by surgical weakening of the medial rectus muscles. Remarkably, simultaneous display of stimuli to each eye in the alert, behaving monkeys did not induce suppression in V1 neurons. Puzzled by this negative result, and guided by previous evidence suggesting that the timing of stimulus presentation may have a critical impact on receptive field interactions, in this present study we modified our protocol to display stimuli in a staggered sequence, rather than simultaneously. Additional recordings were made in the same two macaques, following two paradigms. In Trial Type 1, as the monkeys performed a simple fixation task, the receptive field in one eye was stimulated for 5 seconds with a drifting sinusoidal grating while the other eye was occluded. The occluder then was removed and the neuron was stimulated for another 5 seconds. The effect of uncovering the eye, which potentially exposed the animal to diplopia, was quantified by the peripheral retinal interaction index (PRII). In Trial Type 2, the receptive field in the fixating eye was stimulated with a drifting grating during binocular viewing. After 5 seconds a second grating appeared in the receptive field of the non-fixating eye. The impact of adding the second grating, which had the potential to generate visual confusion, was quantified by the receptive field interaction index (RFII). For 82 cells recorded from calcarine cortex in the two monkeys, the mean PRII was 0.48 ± 0.05 (0.50 = no suppression) and the mean RFII was 0.46 ± 0.08 (0.50 = no suppression). These values suggest a mild net suppression in V1, but the modest decline in spike rate registered during the second epoch of visual stimulation might have been due to neuronal adaptation, rather than interocular suppression. In a few instances neurons showed unequivocal suppression, but overall, these recordings did not support the contention that staggered sequential stimulus presentation is more effective than simultaneous stimulus presentation at evoking interocular suppression in primary visual cortical neurons.

Disclosures: J.R. Economides: None. **M.D. Dilbeck:** None. **D.L. Adams:** None. **J.C. Horton:** None.

Poster

P477. Visual Plasticity in Humans and Disease Models

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Program #/Poster #: P477.01

Topic: D.07. Vision

Support: NIH Grant EY014999
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Research to Prevent Blindness

Title: Adaptation to retinal blur occurs in monocular channels

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Abstract: Adaptation is a canonical function that shapes behavior from experience. In vision, retinal images are the primary source of information for visual perception but subject to blur from the eyes' imperfect optics. Would long-term experience with the native blur patterns contribute to vision? We asked this question in relation to stereovision, because it was counterintuitive that stereo-performance did not always improve with optical correction. Two out of seven of our human participants - those with the very best optics - performed worse instead. The mean stereoacuity, or the smallest discriminable depth given in terms of disparity in arcsecs, was 18.61arcsec through their own eyes but 33.34arcsec with the improved optics when tested with three-dimensional wave stimuli cycling at 1cpd. Likewise, stereoacuity with narrower waves of 2cpd was 28.22 and 53.82arcsec respectively, and 46.30 vs 85.50arcsec with the narrowest waves at 3cpd. This suggested that familiarity to one's own blur patterns is important. In a separate experiment, evidence that the visual system had adapted to maximize stereovision came from manipulating the native blur using adaptive optics. We replaced our participants' optics with someone else's so that everyone would have the same blur patterns. Stereoacuity was also poorer in everyone compared to the person from whom the optics came (1cpd: 53.64arcsec [mean replacement] vs 8.46arcsec; 2cpd: 101.5 vs 12.91 arcsec; 3cpd: 182.34 vs 16.76arcsec). Next, we asked about its neural locus. Did adaptation occur before or after binocular combination? To answer, we swapped the optics of the two eyes in six human participants and compared the results to the native stereoacuity where the left and right eyes each received their habitual blur. Swapping caused unfamiliarity in the monocular channels, but the binocular channels still received the same average blur as well as the same difference of the two eyes. We observed that stereoacuity was worse with the swap, indicating that adaptation had occurred in monocular channels towards the blur patterns of the individual eyes (1cpd: 28.4arcsec with the native optics vs 43.4arcsec swapped; 2cpd: 53.6 vs 123.0arcsec; 3cpd: 144.5 vs 221.9arcsec). The detriment grew with interocular difference (1cpd: $r=0.91$, $p=0.01$; 2cpd: $r=0.97$, $p=<0.01$; 3cpd: $r=0.91$, $p<0.01$) as expected because swapping would matter only if the blur patterns in the two eyes were different. These results indicate a component of adaptation that happens before binocular combination; that is, in monocular channels and towards the blur patterns of individual eyes.

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Poster

P477. Visual Plasticity in Humans and Disease Models

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Topic: D.07. Vision

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Title: Connectivity gradients as a tool for examining use-dependent plasticity in the human visual system

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Abstract: Experience-dependent plasticity in the human visual system involves complex modifications that balance maintaining a stable visual representation with the capability to change the system. Describing these multi-factorial changes in connectivity and comparing them across participants has been historically challenging. We applied the tools of connectivity gradients to this issue, an approach that allows for individual differences in the specific plastic changes, but can quantify changes in the long-range, large-scale connection patterns of individual portions of the visual cortex.

A voxel can be characterized based on its specific patterns of input and output connections to the rest of the brain, and assigned an identifier known as a connectivity fingerprint. Using voxel-wise connectivity fingerprints, we can produce valid topographic representations of functional connectivity. The Congrads method (Haak et al., 2018) is a data-driven technique for connectopic mapping within a predefined region of interest. This method involves fitting the results with a spatial statistical model that summarizes the map in terms of a limited number of trend surface model coefficients, making it possible to disentangle multiple overlapping dimensions of organization that may be present in a given a brain region (such as representations of polar angle and eccentricity in visual cortex, for example).

While the broad principle of topographic mapping of functional connectivity has been well established, quantitative study of changes in this topographical organization with experience is comparatively limited. We apply the method to data in healthy controls as well as from participants with central vision loss due to macular degeneration. These patients have well-documented patterns of vision use (well characterized retinal loss and increased use, including a “preferred retinal locus”). Using connectivity gradients in this population has the benefits of examining specific hypothesized regions of interest, but removes the requirement for examining individual connections. The method has promise as a nuanced way to examine the multidimensional changes in functional connectivity profiles that may occur as a function of differential use of vision.

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Poster

P477. Visual Plasticity in Humans and Disease Models

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MOST110-2321-B-010-004
MOST108-2321-B-010-010-MY2
VGHUST109-V1-2-2
UST X108UST05
R21EY028329
R01EY027841

Title: Both high-frequency repetitive transcranial magnetic stimulation and visual training enhanced plasticity-induced neurochemical changes in early visual areas but with different neurochemical mechanisms

Authors: *S.-H. LIN[1], Y. LIEN[1], K. SHIBATA[2], Y. SASAKI[3], T. WATANABE[3], C.-P. LIN[1], L.-H. CHANG[1];
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Abstract: It has been found that repetitive transcranial magnetic stimulation (rTMS) and visual training increase visual plasticity. This finding led some researchers to assume that rTMS and visual learning are subserved by the same or highly similar visual mechanisms. Here, we tested whether this assumption is true, by measuring the E/I ratio in early visual areas after the rTMS application in one group (n=18) and visual training in the other group (n=12). The E/I ratio refers to the concentration of glutamate as an excitatory neurotransmitter divided by the concentration of GABA as an inhibitory neurotransmitter by multiple magnetic resonance spectroscopy (MRS) and is regarded as an index of the degree of plasticity (Bang et al., 2018; Shibata et al., 2017; Tamaki et al., 2020). Although the E/I ratios changed both after the HF rTMS application and visual training reflecting visual plasticity enhancements, the time courses and major metabolites were significantly different in the two conditions. The peak E/I ratio was observed 3.5 hours after the HF rTMS with a significant decrease in GABA, whereas the peak E/I ratio occurred 30 minutes after visual training with increased glutamate. Our findings suggest that although both rTMS and visual learning increase the plasticity in early visual areas, the consequent neurochemical changes are fundamentally different. Previous conclusions in some studies examining the effect of rTMS may need to be reconsidered.

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Poster

P477. Visual Plasticity in Humans and Disease Models

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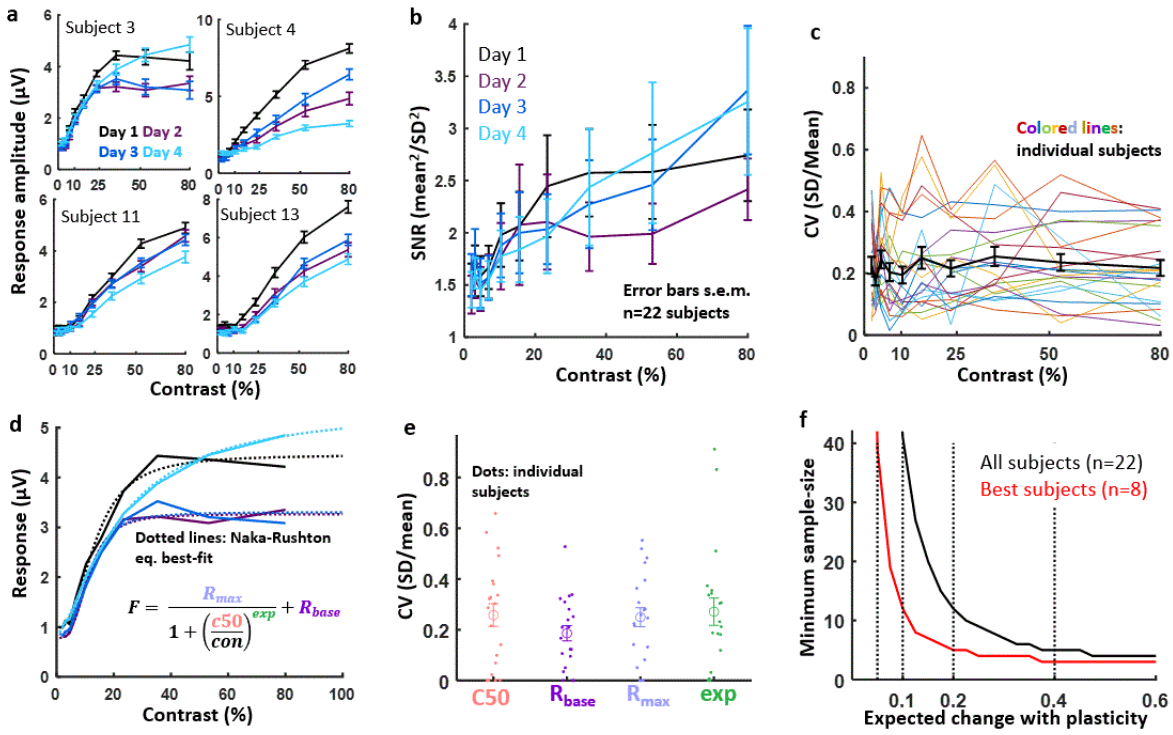
Program #/Poster #: P477.04

Topic: D.07. Vision

Title: Stability and plasticity of steady-state visual evoked potential contrast-response functions

Authors: *R. T. ASH[1], K. NIX[2], M. LEE[2], Y. CHEN[2], K. BUTTS PAULY[3], N. R. WILLIAMS[1], A. M. NORCIA[2];
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Abstract: A repeated measure of neural activity that is stable over time when unperturbed is needed to be able to meaningfully measure neuroplastic changes, e.g. following a plasticity induction protocol. We assessed the repeated-measure across-day stability of the steady-state visual-evoked potential (ssVEP), an exceptionally high signal-to-noise electrophysiological readout of neural activity in human visual cortex, in preparation for studies of visual cortical neuroplasticity. We re-analyzed data from Dmochowski et al *Neuroimage* 2015, in which ssVEP contrast-sweep responses (90 trials, 22 subjects) were measured daily for 4 days using a 128-channel EGI hydrocel EEG system and custom xDIVA software (*Fig. a*). High signal-to-noise (SNR > 1) responses were acquired from 20/22 subjects (*Fig. b*). The across-day coefficient of variation (CV= SD/ Mean) of the response was 0.22±0.13 (mean±SD) and did not significantly vary with contrast (*Fig. c*). Contrast-sweep ssVEP responses were fit well by the Naka-Rushton equation (*Fig. d*, r^2 = 0.24±0.18) Naka-Rushton parameters were also mostly stable with across-day CV<0.3 *(Fig. e*). We calculated the sample size needed to detect changes in response amplitude or contrast-response function parameters with a power of 0.8 given the measured across-day variability (*Fig. f*). Our ssVEP protocol could detect a 10% change with 40 subjects, a 20% change with 12 subjects, and a 40% change with 6 subjects. Restricting the analysis to the 1/3 most reliable subjects (*Fig. f* red line, n=8, CV=0.11±0.04) the contrast-sweep ssVEP was powered to detect a 5% change with 40 subjects, a 10% change with 12 subjects, and a 20% change with 5 subjects. Future work will partition the sources of response variability including brain state, learning/plasticity effects, physiological noise, and measurement. We are currently developing methods to induce plasticity in ssVEP contrast-response functions using repetitive transcranial magnetic stimulation, repetitive sensory stimulation, and transcranial focused ultrasound.



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Poster

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Support: DFG CRC 1233, Grant no. 276693517

Title: Sleep-independent generalization of visual texture discrimination skills

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Abstract: Sleep-dependent consolidation of visual experience has been shown to improve texture discrimination skills. This improvement is thought to be specific for the trained location in the visual field. In the current study, we tested if previously acquired texture discrimination skills can be generalized to different locations and if such generalization benefits from sleep.
We trained healthy young participants on a visual texture discrimination task in one quadrant of the visual

field before a night of sleep or daytime wakefulness. After the retention interval, participants were tested the following morning (Sleep group) or in the evening of the same day (Wake group) in both the trained as well as an untrained quadrant. Importantly, participants were explicitly informed about this testing procedure before training.
Visual texture discrimination performance was better after retention compared to training, as suggested by reduced threshold stimulus onset asynchronies. However, performance was not different between trained and untrained visual quadrants. There was also no difference between Sleep and Wake groups.
Our results suggest that, unlike previously assumed, visual texture discrimination skills trained in a specific location can generalize to other parts of the visual field. This effect appears to be independent of sleep. Additional experiments are needed to assess whether explicit prior knowledge about the generalization test may explain these findings.

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Poster

P477. Visual Plasticity in Humans and Disease Models

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Program #/Poster #: P477.06

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Support: Recherche en santé de la vision (projet pilote)
CRSNG

Title: Functional reorganization of the cortical connectivity following localized ischemic stroke in the mouse visual cortex.

Authors: *S. TISSIER[1], C. ALBERT[1], V. CHOUINARD[1], B. OLIVEIRA FERREIRA DE SOUZA[1], J.-F. BOUCHARD[2], C. F. CASANOVA[3], M. P. VANNI[1];
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Abstract: Goal : In cortical damage caused, for example, by a stroke, some of the lost cortical function can be recovered through cellular and molecular mechanisms that induce cortical plasticity. These reorganizations involve changes in the connectivity between regions as well as in the functional properties of the spared cortical areas. Thanks to the significant development of calcium imaging in recent years, the connections and functional properties of different regions of the cortex can be measured longitudinally in mice with great precision. Several studies have shown the involvement of endocannabinoid receptors, such as CB2, on plasticity and neuronal growth. The objective of this study was to first document the impact of restricted lesions on the cortical functional organization of the cortex and the demonstrate the role of endocannabinoid receptors on the observed reorganization. Methods In this study, n = 22 male and female mice (2 to 4 mo, n=10 cnr2+/+ and n=12 cnr2-/- lacking functional CB2 receptors) were injected (IV) with a virus allowing the expression of a calcium indicator throughout the entire cortex (AAV.PHPeB.Syn.GCaMP6s). Following implantation of a chronic optical chamber, calcium imaging of the dorsal cortex was assessed weekly with and without visual stimuli. After 3 weeks of baseline, a

photothrombotic stroke was induced in the primary visual cortex (V1) by photothrombotic in 12 mice (n=5 cnr2+/+ and n=6 cnr2-/-). Rose bengal was injected (IP) and a green laser was focused to achieve thrombosis in the visual cortex. The limits of cortical damage were established using Speckle imaging to spatially measure blood flow. These limits were later confirmed with histology using SYTOX Orange labelling. After induction of stroke, changes in resting state functional connectivity (using correlation between selected seeds) and visual evoked response were measured every week for 8 weeks post-stroke. Results Histological and speckle contrast imaging showed that our photothrombotic model of visual stroke induced a defined lesion of 1 mm3 associated with long-term functional deficits in the cortical circuitry. Visually evoked responses in visual cortex stimulation were impaired after a stroke and partially recovered after five weeks. The absence of CB2 receptors disrupted the functional reorganization following these lesions in the visual cortex. Conclusion: Calcium imaging proved to be a successful approach to characterize the mechanisms involved in cortical plasticity following damage to the visual cortex. In future, the impact of the environment in which an animal thrives will be explored using this experimental approach.

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Poster

P477. Visual Plasticity in Humans and Disease Models

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Topic: D.07. Vision

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NIH Grant R01EY029245
NSF GRFP 2020301419

Title: Using the visual cliff assay to detect and study recovery from amblyopia in mice

Authors: *H. DE JESÚS-CORTÉS[1], D. A. BOWEN[2,1], A. MORELLO-MEGIAS[1], S. I. TORRES-BIGIO[1], P. A. ALICEA-ROMÁN[1], A. M. ALEJANDRO-SOTO[1], F. REILLY-ANDÚJAR[1], M. F. BEAR[1];
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Abstract: Amblyopia is a neurodevelopmental disorder of the visual system caused by uncorrected refractive error, cataract, strabismus, or ptosis during infancy and early childhood. The current standard of care is to strengthen the weak eye by depriving, or patching, the fellow eye. While this treatment can improve acuity in the amblyopic eye, these gains often come at the expense of acuity in the fellow eye, are not associated with improvements in binocularity, and are typically only achieved if treatment is initiated in early childhood (within the critical period). In our lab we use a mouse model of amblyopia induced by monocular deprivation (MD) to study the pathophysiology of this disorder and test novel therapeutics. The visual cliff assay (VCA) has been used in multiple animal models, including humans, to

assess stereopsis and depth perception, two key features of binocular vision that are disrupted in amblyopia. However, to date, no study has used the VCA to assess the effects of MD and characterize the recovery from amblyopia in mice. The VCA is advantageous in that we can compare functional and behavioral deficits within animals to determine the severity of amblyopia and track subsequent recovery, and it does not require operant conditioning. We first characterized and validated multiple aspects of the VCA including contribution of binocular vision, and the test-retest reliability. We demonstrate that after long-term MD (3 weeks), mice exhibit reduced preference for the safe side and more crosses to the cliff side and take less time to cross into the cliff side compared to their "sham" (no MD) littermate controls. When mice perform the VCA with their fellow eye closed, they spend less time in the safe side, have more crosses between sides, and take less time to cross into the cliff side compared to animals with their amblyopic eye closed. We conclude that the VCA is sensitive to detect amblyopia and therefore can be leveraged to study the efficacy of various treatments targeted at curing amblyopia in mice.

Disclosures: H. De Jesús-Cortés: None. **D.A. Bowen:** None. **A. Morello-Megias:** None. **S.I. Torres-Bigio:** None. **P.A. Alicea-Román:** None. **A.M. Alejandro-Soto:** None. **F. Reilly-Andújar:** None. **M.F. Bear:** None.

Poster

P477. Visual Plasticity in Humans and Disease Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P477.08

Topic: D.07. Vision

Support: NIH Grant R01NS104776
Walt and Lilly Disney Award for Amblyopia Research

Title: Sleep and binocular experience promote optimal recovery of visual deficits in a mouse model of amblyopia

Authors: *J. D. MARTINEZ, M. J. DONNELLY, D. S. POPKE, D. TORRES, L. G. WILSON, W. P. BRANCALEONE, S. SHESKEY, B. C. CLAWSON, S. JIANG, S. J. ATON;
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Abstract: Amblyopia is a visual disorder that arises from imbalances in visual input to the primary visual cortex (V1) during childhood and leads to long-lasting visual disruption. Altered visual experience via monocular deprivation (MD) profoundly changes ocular dominance (OD) in V1, and is a well-studied experimental model for understanding amblyopia. Traditional amblyopia treatment includes patching the dominant eye, a monocular visual experience. However, the relative impact of monocular vs. a binocular experience on recovery of V1 function is not well understood, nor is the contribution of sleep timing relative to experience. We compared how binocular recovery (BR) or reverse occlusion (RO) of identical duration and visual content affects post-MD recovery of visual function in regular spiking neurons and fast-spiking (FS) interneurons within binocular mouse V1 (bV1). We find that BR is quantitatively superior to RO with respect to normalization of bV1 neurons' OD, and parvalbumin-expressing FS interneurons visual responsiveness. Sleep deprivation in the hours following BR visual experience disrupt

both the renormalization of OD and firing rate response changes in bV1. Thus a combination of BR experience and subsequent sleep together promote optimal recovery of binocular vision in a mouse model of amblyopia.

Disclosures: J.D. Martinez: None. **M.J. Donnelly:** None. **D.S. Popke:** None. **D. Torres:** None. **L.G. Wilson:** None. **W.P. Brancaleone:** None. **S. Sheskey:** None. **B.C. Clawson:** None. **S. Jiang:** None. **S.J. Aton:** None.

Poster

P477. Visual Plasticity in Humans and Disease Models

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Program #/Poster #: P477.09

Topic: D.07. Vision

Support: NIH K99 EY029326
NIH R01 EY029245
CIHR 153333
Beckman-Argyros Award

Title: Correction of amblyopia in cats and mice after the critical period

Authors: *M.-F. FONG[1,2], K. R. DUFFY[3], M. P. LEET[1], C. T. CANDLER[1,4], J. U. DEERE[5,1,6], L. MARTIN[1,7], J. S. YAO[1,8], N. T. LIANG[1], K. LIU[1], M. F. BEAR[1];
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Abstract: Monocular deprivation early in development causes amblyopia, a severe visual impairment. Prognosis is poor if therapy is initiated after an early critical period. However, clinical observations have shown that recovery from amblyopia can occur later in life when the non-deprived (fellow) eye is removed. The traditional interpretation of this finding is that vision is improved by relieving interocular suppression in primary visual cortex. However, an alternative explanation is that elimination of activity in the fellow eye establishes conditions in visual cortex that enable the weak connections from the amblyopic eye to gain strength. Here we show in cats and mice that temporary inactivation of the fellow eye is sufficient to promote a full and enduring recovery from amblyopia at ages when conventional treatments fail. Thus, connections serving the amblyopic eye are capable of substantial plasticity beyond the critical period, and this potential is unleashed by reversibly silencing the fellow eye.

Disclosures: M. Fong: None. **K.R. Duffy:** None. **M.P. Leet:** None. **C.T. Candler:** None. **J.U. Deere:** None. **L. Martin:** None. **J.S. Yao:** None. **N.T. Liang:** None. **K. Liu:** None. **M.F. Bear:** None.

Poster

P477. Visual Plasticity in Humans and Disease Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P477.10

Topic: D.07. Vision

Support: NSERC 201605049

Title: Effect of stimulus location on visually-evoked potentials (VEPs) in hearing and deaf subjects

Authors: *T. MITZELFELT, X. BAO, P. BARNES, S. G. LOMBER;
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Abstract: Cross-modal plasticity is a phenomenon in which areas of the brain are repurposed and reorganized to compensate for sensory deficits. Significant activation of auditory areas in response to visual stimuli was observed in fMRI of deaf, but not hearing, children suggesting the use of auditory cortex in processing visual input. Deaf cats, compared with hearing cats, have superior visual localization in the peripheral field and reversible deactivation of posterior auditory cortex selectively eliminated this superior visual localization ability. Given the evidence in support of auditory-visual cross-modal plasticity provided by these studies, we sought to determine changes in the peripheral visual field following deafness by examining visual evoked potentials (VEPs), a commonly used non-invasive ophthalmological technique. VEPs were recorded from lightly anesthetized adult (>6M) cats (.04mg/kg dexmedetomidine, IM): 6 hearing and 5 deaf cats (deafness induced in the first postnatal month by systemic administration of ototoxic drugs). A screen was placed 16.5 cm from the right eye, with the left eye obstructed by a black contact lens. A circular checkerboard (12° visual angle) was inverted every 0.5 s , at one of 7 different azimuth angles between 0° and 90° . At least 200 inverts were presented at each angle in total. From the averaged VEP waveforms, peak-to-peak amplitude was quantified for each angle in each subject. A threshold azimuth angle was determined for each subject by selecting the most peripheral angle in which a clear VEP signal was observable. In both groups, peak-to-peak amplitudes decreased as visual stimuli were present more peripherally. However, a larger decrease was observed for deaf cats when the checkerboard was present at the most central locations compared to hearing cats, while a smaller decrease was observed at the most peripheral locations (75° & 90°). No statistical significance was revealed for peak-to-peak amplitudes between the two groups. The threshold azimuth angles (the most peripheral angle with VEPs present) for deaf subjects were larger compared to hearing subjects (Mann-Whitney U test, p = .052). The increase in visually-evoked cortical activity shown by VEPs in deaf subjects may result from the structural change of sensory cortices and underlie their advantage in visual localization. Similar cortical plasticity in humans may to have a profound influence in the development of language. With further research (in both animal models and human), VEPs can potentially serve as an auxiliary tool in the rehabilitation after cochlear implants, given its objective, non-invasive nature. Study was funded by CIHR and NSERC.

Disclosures: T. Mitzelfelt: None. **X. Bao:** None. **P. Barnes:** None. **S.G. Lomber:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

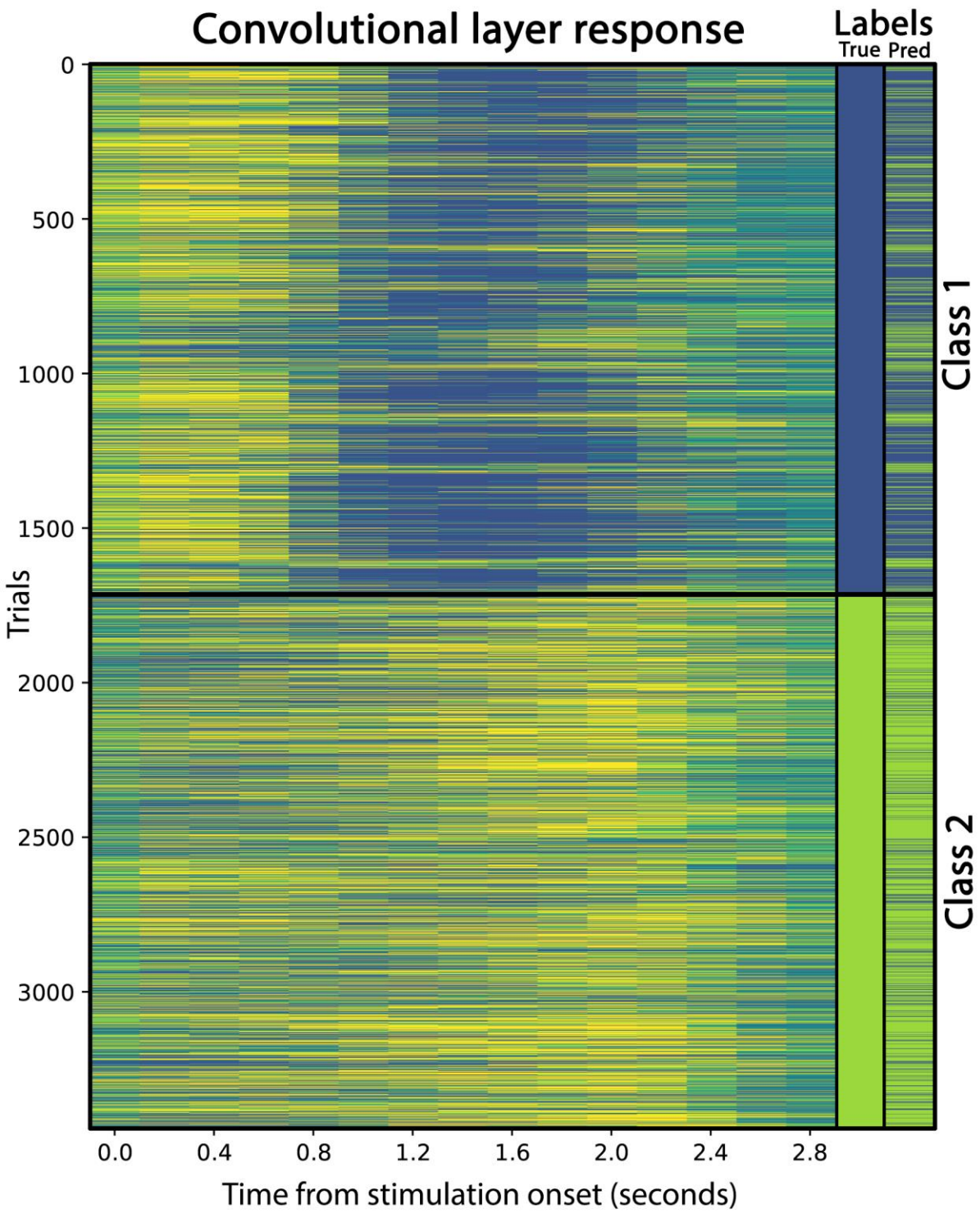
Program #/Poster #: P546.01

Topic: E.05. Brain-Machine Interface

Title: Single-trial decoding of binary communication from intracortical microelectrode arrays in a completely locked-in patient using a deep neural network

Authors: *K. LEE[1], J. RAMOS DA CRUZ[1], A. TONIN[2,1], D. IBÁÑEZ-SORIA[1], A. ESPINOSA[1], N. F. RAMSEY[3,1], J. B. ZIMMERMANN[1];
[1]Wyss Ctr. for Bio and Neuroengineering, Geneva, Switzerland; [2]Univ. of Tübingen, Tübingen, Germany; [3]Brain Ctr. Rudolf Magnus, Univ. of Utrecht, Utrecht, Netherlands

Abstract: Objective
Brain-computer interface (BCI) for completely locked-in state (CLIS) patients, who cannot move any body part including eyes, are especially challenging. In this study, we designed a deep convolutional neural network (CNN) model to automatically localize and learn task-dependent features from intracortical recordings of a CLIS patient to facilitate a YES/NO binary communication. Advanced decoders are necessary to overcome decreased performance of the original linear classifier due to high variability and decreased signal-to-noise ratio.
Method
The patient, diagnosed with amyotrophic lateral sclerosis and in CLIS, was implanted with two 64-channel microelectrode arrays in motor cortex. The patient learned to modulate multi-unit activity to control a YES/NO BCI paradigm based on a pre-trained linear classifier model with auditory feedback. We used spike-band power (SBP) features computed at 20 Hz from the 128 electrodes. We designed a CNN model by stacking 1-D temporal convolutional layers applied along the time axis with a pooling layer after each group of convolutional layers to increase the receptive field, followed by a global max pooling, fully connected layer and output layer. For training the CNN, we used the data recorded during calibration sessions of the paradigm, originally used to train the linear classifier model. The test data for CNN came from signals recorded during a cued online BCI session, where the patient received a feedback based on the daily-trained linear classifier model.
Result
The proposed model achieved 74% single-trial accuracy from 3440 testing trials (65% online accuracy with linear classifier, chance level threshold=51.4% at α=0.05). Interestingly, we observed distinct phase and amplitude responses from convolutional filters (see Figure). A clear difference can be also seen between the two conditions.
Conclusion
In this single-case study, a CNN with temporal filters met the dual purpose of achieving a higher performance compared to the previous classifier and capturing discriminative dynamics from multi-channel signals.



Disclosures: K. Lee: None. **J. Ramos da Cruz:** None. **A. Tonin:** None. **D. Ibáñez-Soria:** None. **A. Espinosa:** None. **N.F. Ramsey:** None. **J.B. Zimmermann:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P546.02

Topic: E.05. Brain-Machine Interface

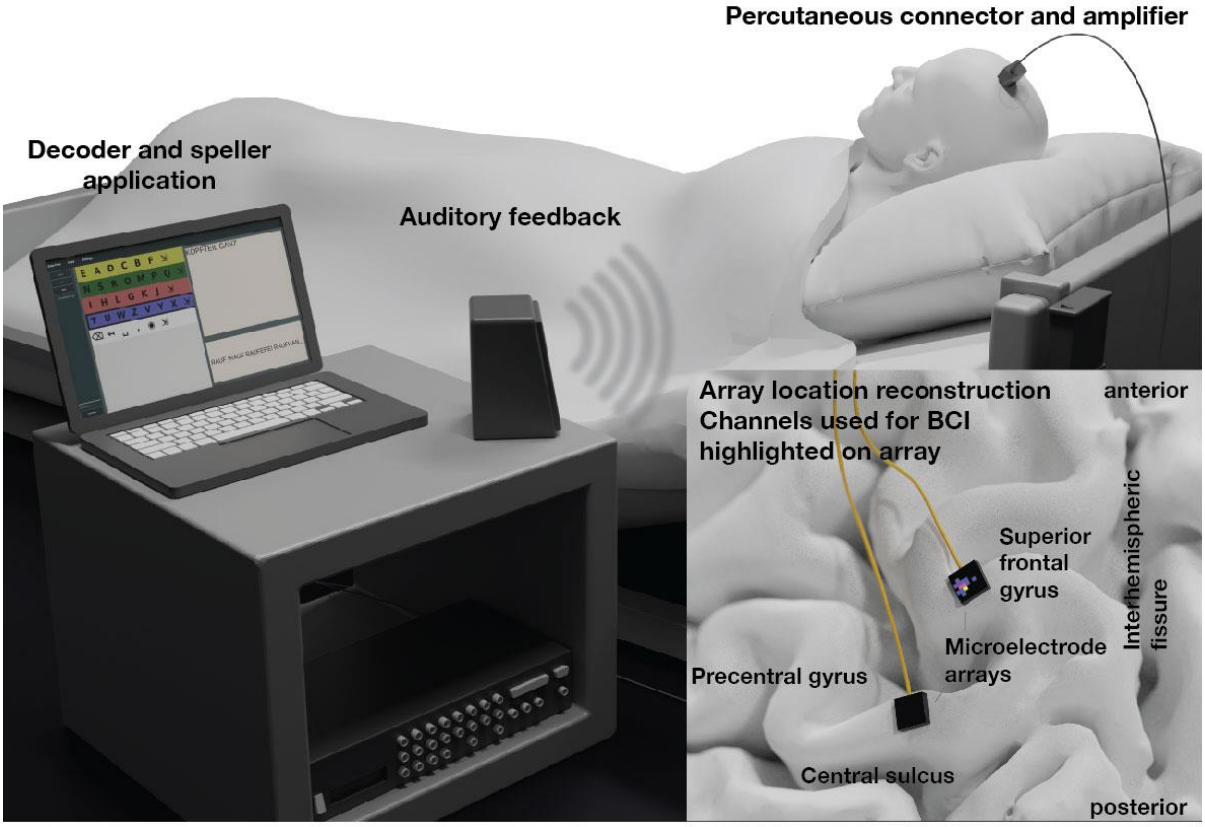
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LUMINOUS-H2020-FETOPEN-2014-2015-RIA 515 (686764)
Bogenhausen Staedtische Klinik, Munich

Title: Enabling communication using intracortical signals in a completely locked-in patient for over two years

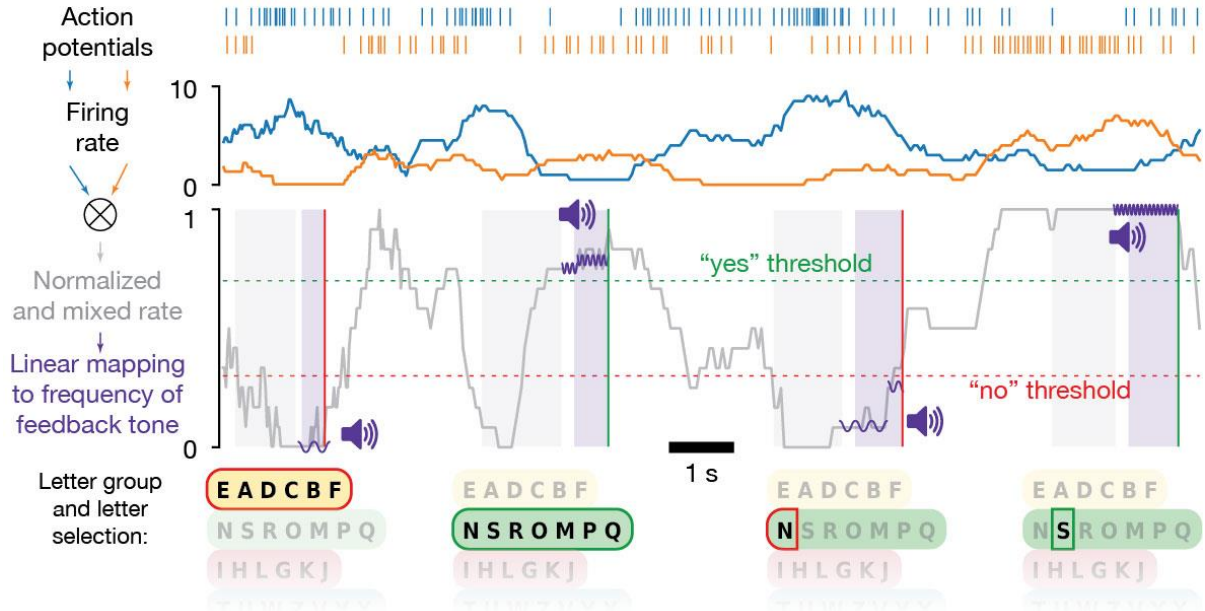
Authors: *J. B. ZIMMERMANN[1], U. CHAUDHARY[2], I. VLACHOS[1], A. ESPINOSA[1], A. TONIN[1,2], A. JARAMILLO-GONZALEZ[2], M. KHALILI ARDALI[2], H. TOPKA[3], J. LEHMBERG[4], G. M. FRIEHS[5], A. WOODTLI[1], J. P. DONOGHUE[6], N. BIRBAUMER[2];
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Abstract: Patients with amyotrophic lateral sclerosis (ALS) lose all muscle-based routes of communication as motor neuron degeneration progresses, and ultimately, they are left without any means of communication. Despite many attempts using non-invasive and intracranial brain-computer interfaces (BCI), enabling communication for people in completely locked-in state (CLIS) remains a challenge. With consent of the participant, family, and approval from legal and health authorities for this study, two 64 microelectrode arrays were implanted in the supplementary and primary motor cortex of a CLIS patient with ALS. The last successful communication session with non-invasive eye movement recordings was recorded one month prior to implantation.
We implemented a neurofeedback task in which the participant learned to modulate multi-unit activity (MUA) by manipulating feedback tone frequency with MUA changes. In a training task, the participant was asked to match the feedback frequency to one of two target tones in repeated trials. Later, high and low frequencies were assigned to 'yes' and 'no' responses in a speller task. The speller paradigm comprised two stages: first, groups of letters were presented in turn and either skipped or selected. When a letter group was selected, each letter of that group was presented in turn until one was chosen.
The participant could form words and phrases, often spelling hundreds of characters at a time, albeit slowly (~1 character / min on average). Ability to spell was variable: days of prolific speller use were followed by days on which the patient had little voluntary control of the speller. Ability to spell also decreased over time, and communication later on consisted mostly of short sequences of yes/no questions. This may be caused by the gradual deterioration of the electrodes leading to loss of MUA that was observed.
To our knowledge, this is the first case of a person in CLIS being implanted with intracranial electrodes

and regaining the ability to communicate. The implant led to meaningful and substantial communication about the participant's needs and wishes.



Schematic representation of signal processing, neurofeedback paradigm, and speller control



Disclosures: J.B. Zimmermann: None. **U. Chaudhary:** None. **I. Vlachos:** None. **A. Espinosa:** None. **A. Tonin:** None. **A. Jaramillo-Gonzalez:** None. **M. Khalili Ardali:** None. **H. Topka:** None. **J. Lehmberg:** None. **G.M. Friehs:** None. **A. Woodtli:** None. **J.P. Donoghue:** None. **N. Birbaumer:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P546.03

Topic: E.05. Brain-Machine Interface

Title: Independent Home Use of a Microarray Brain Computer-Interface in a Completely Locked In-Patient

Authors: *A. TONIN[1,2], D. IBAÑEZ-SORIA[1], J. RAMOS DA CRUZ[1], K. LEE[1], A. ESPINOSA[1], N. F. RAMSEY[3,1], J. B. ZIMMERMANN[1];
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Abstract: The translational aspect of brain computer interfaces (BCIs) - i.e. whether they can be reliably operated by patients and/or caretakers in home environments - is a major challenge of the field. Here, we describe the case of a BCI home use system that allows caretakers of a patient with Complete Locked in Syndrome (CLIS) to independently run BCI sessions without the supervision of investigators. The end-user is in his mid 30's and was diagnosed with amyotrophic lateral sclerosis (ALS). In 2019, the patient - already in CLIS - was implanted with two 64 microelectrode arrays (Blackrock Microsystems LLC) in the motor cortex. The patient learned to modulate his neural activity to control binary BCI paradigms. For home use, we developed a three-step procedure that enables caretakers to initialize BCI sessions allowing the patient to communicate using a speller or a yes/no response paradigm. This procedure comprises Calibration, Validation, and Communication. Calibration and Validation steps are used daily to automatically build a classifier; Validation is also used to train the end-user without the risk of delivering wrong communication. Caretakers were advised to proceed to communication only if Validation accuracy was at least 80% (chance level 75%). Weekly, supervised sessions were performed to evaluate the status quo. In addition, data were analyzed offline to evaluate whether parameters needed to be adjusted. After 5 months of home use, data from those sessions were used to train a grand classifier, reducing the home use procedure to Validation and Communication. When Validation performance did not meet the threshold, caretakers were advised to not start Communication. Finally, the classifier is regularly retrained offline when new sessions are available. Eight months into the home use deployment, analysis of the validation performance, number of characters spelled per session, and yes/no response results, show that the performance achieved in the home use is comparable to those achieved in supervised sessions. Recently, the patient's ability to control the BCI has deteriorated, affecting the reliability of the current paradigm in both home use as well as supervised sessions. For the first time a home use BCI system for ALS patients in CLIS has been successfully deployed. Results show that microarray implant is feasible for home use BCI: the system has been frequently used by the caretakers and it shows performance comparable to supervised sessions. Moreover, the involvement of the family led to a general positive psychological

effect. However, therefore investigators still need to be in the loop framework, at least sporadically, to ensure reliability of the system.

Disclosures: A. Tonin: None. **D. Ibañez-Soria:** None. **J. Ramos da Cruz:** None. **K. Lee:** None. **A. Espinosa:** None. **N.F. Ramsey:** None. **J.B. Zimmermann:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P546.04

Topic: E.05. Brain-Machine Interface

Title: Intracortical Eyes-Closed Steady-State Visual Evoked Potentials and Auditory Oddball Evoked Potentials in a Completely Locked-In Patient

Authors: *J. RAMOS DA CRUZ[1], K. LEE[1], A. TONIN[1,2], A. ESPINOSA[1], D. IBANEZ SORIA[1], N. F. RAMSEY[3,1], J. B. ZIMMERMANN[1];
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Abstract: Patients with amyotrophic lateral sclerosis (ALS) can progress into complete locked-in syndrome (CLIS) where muscle-based communication is not possible. We have previously shown that motor-imagery-based communication is possible in a CLIS patient implanted with microelectrode arrays. The patient uses neurofeedback modulation of multi-unit activity (MUA) to control several brain-computer interface (BCI) applications. At over two years post-implantation, only few channels record MUA, and control of activity on remaining channels appears to be difficult and unreliable. Here, we report recent attempts to identify alternative BCI channels to improve the communication with the patient. The patient is in mid 30's and was diagnosed with ALS eventually leading to CLIS. In 2019, he was implanted with two 64 microelectrode arrays (Blackrock Microsystems LLC) in the left motor cortex. As alternative communication channels, we explored two BCI paradigms: steady-state visual evoked potentials (SSVEP) and auditory oddball. In the SSVEP paradigm, light emitting diodes flickering at different frequencies were used to present visual stimuli to the patient with his eyes closed. He was instructed to attend to one of the two light sources oppositely placed at 45 degrees from the visual field center. For the auditory oddball paradigm, sequences of repetitive sounds infrequently interrupted by a deviant stimulus were presented to the participant. He was asked to count the number of attended deviant stimuli. Besides the two microelectrode arrays, data were also recorded with frontal, parietal, and temporal electroencephalogram (EEG) electrodes with a Brain Products V-Amp amplifier for comparison. Intracortical data acquisition was performed using NeuroKey software. Offline analysis confirmed that both eyes-closed SSVEP and neuronal responses to oddball auditory stimuli can be detected by not only off-occipital EEG electrodes but also the microelectrode arrays, when using the pedestal as reference. In the SSVEP paradigm, we identified increased spectral power of the attended frequencies and corresponding harmonics. In the oddball paradigm, the frequent and deviant stimuli elicited neuronal responses, with standard peak-amplitude latencies, but evoked amplitudes differed based on the stimulus category. In sum, eyes-closed SSVEP and auditory oddball evoked potentials can be recorded from

microelectrode arrays implanted in the motor cortex of a CLIS patient. Preliminary results suggest that the patient can modulate the signals with selective attention, thus opening avenues for alternative BCI communication channels.

Disclosures: J. Ramos da Cruz: None. **K. Lee:** None. **A. Tonin:** None. **A. Espinosa:** None. **D. Ibanez Soria:** None. **N.F. Ramsey:** None. **J.B. Zimmermann:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P546.05

Topic: E.05. Brain-Machine Interface

Title: Neurokey, a flexible real-time neural decoding platform to accelerate the research and development of neuroscience applications

Authors: *D. IBANEZ SORIA[1], J. BARROS[1], M. ANDERSEN[1], N. ROBERTS[2], A. TONIN[1], A. ESPINOSA[1], J. RAMOS DA CRUZ[1], K. LEE[1], T. LAABS[1], G. KOUVAS[1], C. GRAEVE[1], N. F. RAMSEY[3,1], R. FRANKLIN[4], L. CHITNENI[4], J. B. ZIMMERMANN[1];
[1]Wyss Ctr. for Bio and Neuroengineering, Geneve, Switzerland; [2]Strange Crew, Las Vegas, NV; [3]Brain Ctr. Rudolf Magnus, Univ. of Utrecht, Utrecht, Netherlands; [4]Blackrock Microsystems, Salt Lake City, UT

Abstract: Neuroscientists often need to build their own software to meet specific research requirements. Besides integration issues, it can be difficult to quickly adapt to new research conditions and developing software as a medical device for use in clinical trials can be a long, sometimes challenging, processs. Our software platform, NeuroKey (NKy), grew out of research needs. It allows neuroscientists to focus on research and spend less time on software development. NKy facilitates the translation from research tool to clinical application by providing means for scientist to design intelligent and adaptive user interfaces.NKy combines, processes and decodes electrophysiological data in real-time. It uses JUCE, an open-source C++ cross-platform library for audio processing that ensures accurate timing and low latency. Developed as a medical-grade platform, NKy is optimized for the analysis of large data streams from high channel count implantable devices and has been validated for up to 256 channels at 30000 samples/sec. NKy is also integrated with additional systems such as near-infrared spectroscopy or electroencephalographs. The software is modular allowing complex algorithms to be divided into smaller steps. Its basic units, called processors, are independent modules with specific functionalities that interface with external data sources, analyse, and decode electrophysiological data. Users can select and interconnect processors within NKy graphical user interface (GUI) to create processing pipelines. These processors include filters, spike detectors, band power estimators or machine learning-based classifiers among others. The GUI also provides the means to present information to the end-user and integrates a fully configurable keyboard widget for brain computer interface applications.NKy software development kit (SDK) written in Python allows full pipeline control and secure real-time access to all processing stages. While NKy performs the heavy real-time signal processing, the Python high-level programming language allows efficient cross-platform prototyping and development of a wide variety of neuroscience

applications.NKy BCI application is medical device software of safety class A as per IEC 62304. It is currently in home-use as part of a single case study to enable communication for a user with amyotrophic lateral sclerosis who is in completely locked-in state. NKy is also being used to explore novel closed-loop stimulation paradigms to improve recovery from spinal cord injuries. The use of NKy for stroke rehabilitation and epileptic seizure monitoring is at present at feasibility stage.

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Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P546.06

Topic: E.05. Brain-Machine Interface

Support: GE-2-2-023A (REXO)
IT-2-2-023 (VAFES).

Title: Spikedeeptector in conjunction with background activity rejector (bar) as a feature extraction technique for online invasive brain-computer interface (bci) applications

Authors: *M. SAIF-UR-REHMAN[1], O. ALI[3], J. HILGENHÖNER[1], C. KLAES[4], I. IOSSIFIDIS[2]; [1]Computer Sci. Dept., Ruhr West Univ. of Applied Sci., Mülheim An der Ruhr, Germany; [2]Computer Sci., Ruhr West Univ. of Applied Sci., Muelheim An Der Ruhr, Germany; [3]Dept. of Neurosurg., Knappschaftskrankenhaus Bochum, Germany, Bochum, Germany; [4]Neurosurg., Knappschaftskrankenhaus Bochum, Bochum, Germany

Abstract: Recently developed invasive brain-computer interface (BCI) systems showed promising results to transform the lives of severely disabled persons by successfully translating the neural activity into corresponding intended actions. The translation of neuronal activity is a two-step process: feature vectors extraction and classification or regression. Non-stationary behavior of neural signals, minor perturbation of implanted microelectrode arrays, neural activities of neurons too far away from the electrodes tip, exposure of neural signals to several surrounding noise sources and external artifacts are the main obstacles for reliable feature extraction techniques that are suitable for online BCI applications. Ideally, during recording sessions, online BCI decoding applications require feature vector extraction techniques that do not require parameter tuning, and low computational cost to reduce the latency in the decoding loop. Conventionally, raw signals are first band-pass filtered and then thresholding is applied to extract the events that represent spike activity (SA). These extracted SA events are mostly used as the features for online decoding. Majority of extracted events do not necessarily represent the neural activity, but the external artifacts. Henceforth, the extracted feature vectors are contaminated with noise. Similarly, most of the implanted microelectrodes do not record any neural data but noise. Including such electrodes for feature vectors construction adversely affects the performance of online BCI decoding. Here, we

introduced a feature extraction technique that automatically detects the channels recording neural data. Then the events representing SA on the extracted channels are selected for feature vectors construction. SpikeDeeptector and background activity rejector (BAR) are stacked together to extract channels and meaningful events. SpikeDeeptector and BAR, both are deep learning-based algorithms. Here, we used pretrained model of SpikeDeeptector and BAR algorithm. In this study, we used the data recorded from a tetraplegic patient implanted with two Utah arrays on posterior parietal cortex (PPC). The patient imagined three different hand shapes. The intended shape is successfully decoded by proposed feature extraction algorithm in combination with support vector machine (SVM) as the classification algorithm. The results of proposed algorithm are compared with the most used band pass filtering in combination with thresholding process. In the preliminary results, the proposed algorithm showed significant improvements over its counterpart.

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Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

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Program #/Poster #: P546.07

Topic: E.05. Brain-Machine Interface

Title: Long-term recording and stimulation using the Brain Interchange BCI neural interfacing system with micro-ECoG and DBS electrodes in an ovine animal model

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Abstract: Active neural implants and bi-directional brain-computer interfaces (BCIs) are increasingly used in basic and translational neuroscientific research as well as in investigational therapeutical and medical applications. As the requirements for potential applications grow in complexity, fully implantable neural interfaces and BCI devices must provide long-term implantation compatibility, a larger range of technical flexibility, and medical safety to the user and to patients. The CorTec Brain Interchange system meets these crucial requirements: flexible electrode type and recording configuration choice, open- and closed-loop stimulation functionality, biocompatible materials, and inherent safety features.
The Brain Interchange system was chronically implanted for > 6 months in female, adult sheep. The system was equipped with two 12-contact (1.3 mm diameter) micro-electrocorticographic electrode arrays (CorTec GmbH) implanted bilaterally on the prefrontal cortex and with two 4-contact deep brain stimulation (DBS) leads (Cartesia, Boston Scientific, USA) implanted bilaterally in the medial forebrain bundle area. Neural data was obtained during resting state recordings and in experiments with application

of direct cortical electrical surface stimulation and DBS, respectively, in awake behaving animals. Different stimulation paradigms were performed: single-pulse stimulation and burst stimulation with frequencies of 200 Hz (µECoG) and 130 Hz (DBS). All conducted implantations and experiments were approved by the Animal Ethics committee of the Regierungspraesidium Freiburg and followed the EU-directive 2010/63/EU.
First, we will present neurobiological data obtained from resting state recordings over the time course of the chronic implantation period to verify the long-term recording functionality of the devices. Second, we demonstrate the flexibility of the stimulation functionality and report the presence of brain responses to single-pulse stimulation, so-called cortico-cortical evoked potentials (CCEPs). In addition, we examine brain activity changes elicited by µECoG-based burst stimulation.
The presented data underpin the flexibility and robustness of the recording and stimulation functionality of the fully implantable neural interfacing system Brain Interchange from both a technical and neurobiological perspective. The outcomes from these preclinical studies in large mammals demonstrate that the system meets the desired requirements for neuroscientific and potential medical applications as a basis for the next step towards investigational device exemption studies in human patients.

Disclosures: C.A. Gkogkidis: A. Employment/Salary (full or part-time):; CorTec GmbH, Freiburg, Germany. **Y. Tong:** None. **J. Wessolleck:** None. **M. Sousa:** A. Employment/Salary (full or part-time):; CorTec GmbH, Freiburg, Germany. **H. Cristina Schmitz:** None. **C. Scheiwe:** None. **M. Schuettler:** A. Employment/Salary (full or part-time):; CorTec GmbH, Freiburg, Germany. **J. Rickert:** A. Employment/Salary (full or part-time):; CorTec GmbH, Freiburg, Germany. **V.A. Coenen:** F. Consulting Fees (e.g., advisory boards); CorTec GmbH, Freiburg, Germany. **M.D. Döbrössy:** None.

Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

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Topic: E.05. Brain-Machine Interface

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Title: Pre-surgical fMRI localization for implantation of a brain-computer interface

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Abstract: Pre-Surgical fMRI Localization for Implantation of a Brain-Computer Interface
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VANSTEENSEL, N. F. RAMSEY*Neurol. and Neurosurg., UMC Brain Center,University Med. Ctr. Utrecht, Utrecht, Netherlands*
Abstract: A prerequisite for implanting a minimally invasive brain-computer interface (BCI) is a detailed, non-invasive localization of the target location. Functional MRI is a natural choice for this step. We have previously demonstrated a close spatial correlation between the fMRI response and electrocorticography (ECoG) activity associated with hand movements in able-bodied people with epilepsy. Here, we investigated whether a similar relation exists in people with locked-in syndrome (LIS). We used data obtained within the Utrecht NeuroProsthesis (UNP) study from three individuals with LIS who were implanted with a chronic ECoG-based BCI to test feasibility of independent home use. Placement of electrode strips through burrholes in the skull was guided by pre-surgical fMRI (3 tesla). Strips were implanted over the motor cortex and electrode positions were confirmed post-surgically with a CT scan. Leads were tunneled to an amplifier (Activa ® PC+s; Medtronic plc; investigational device) that was implanted under the left clavicle. Based on CT images, electrode coordinates were aligned to the fMRI activity allowing direct fMRI-ECoG comparison. Per contact point, we compared the magnitude of task-related low and high frequency band (LFB and HFB, respectively) ECoG modulation with task-related BOLD activity. In two out of three participants, we found strong correlations between fMRI and HFB ECoG activity (participants UNP1 & UNP4 respectively: $r = 0.61$ & 0.80; $p = 0.02$ & 0.03). For UNP5, a non-significant trend was observed ($r = 0.41$; $p = 0.09$). Moreover, using fMRI, we could retrospectively confirm the optimal electrode pair for BCI control in UNP1 and UNP4. In UNP5, the optimal control pair as assessed by normal feature selection was the second best as predicted by fMRI. For this participant, the correlation may not have reached significance because only a limited number of ECoG datasets was available (4 datasets, compared to 13 and 12 for UNP1 and UNP4 respectively). We conclude that pre-surgical fMRI shows a close spatial correlation with the activity measured with ECoG-electrodes, suggesting that target locations for ECoG electrode implantation can be predicted using fMRI. We therefore recommend using pre-surgical fMRI to localize target regions in similar, minimally invasive BCI systems.

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Poster

P546. Neurophysiology: Implanted Electrodes and Other Direct Interactions with Neurons II

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Topic: E.05. Brain-Machine Interface

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Defense Advanced Research Projects Agency (DARPA) and Space and Naval Warfare Systems Center Pacific (SSC Pacific) under Contract N66001-10-C-4056

Title: The effect of visual and proprioceptive feedback on brain-computer interface control of a robotic arm

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Abstract: Vision and proprioception play important roles in regulating motor output during reaching, and brain computer interfaces (BCIs) offer a unique opportunity to study the effects of sensory feedback on motor cortex (M1) neurons. During a clinical BCI trial, we implanted two 96-channel microelectrode arrays into M1 of a person who was completely paralyzed below the neck but retained intact somatosensation. Neural firing rates were transformed into a 2-dimensional velocity control signal for a robotic arm using an optimal linear estimator. We examined how visual and proprioceptive feedback were incorporated into BCI control by having the participant move this arm left and right over a centerline as many times as possible in one minute. During this task, the participant was provided with either visual or proprioceptive feedback, both, or neither. Proprioceptive feedback was provided by moving the participant's arm to match the movement of the robotic arm. Task performance with vision or proprioception alone was better than when neither were provided. However, providing proprioceptive feedback impaired performance relative to visual feedback alone, unless the decoder was trained with both modalities. In contrast, Flesher et al. (2021) showed that tactile feedback improved BCI performance although the decoder was not trained with tactile input. These results raise the question of how different sensory feedback modalities influence M1 activity and ultimately BCI performance. We examined the kinematics of the robotic arm across different feedback conditions and found that both positional variance and average speed were highest when proprioceptive feedback alone was provided. This suggests that the participant's control strategy changes to account for lower precision in proprioceptive sensation. We then examined population-level responses by identifying the dimensions of neural activity that best captured variance for different combinations of visual and proprioceptive feedback. We computed the principal angle between the neural activity during performance and the decoder, and found that the overlap between neural activity and the decode axis was largest when sensory feedback during the task matched the modalities present during decoder training. Overall performance also improved as the overlap between the decoder and the neural activity during the task increased. Combined, these results suggest that proprioceptive feedback may have a uniquely large impact on M1 activity relative to other sensory modalities, and that training a decoder with proprioceptive feedback allows the decoder to take advantage of proprioception-driven variability in M1.

Disclosures: M.F. Liu: None. **R.A. Gaunt:** None. **J.L. Collinger:** None. **A.P. Batista:** None. **D.J. Weber:** None.

Poster

P695. Anxiety: Human and Pre-Clinical Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P695.01

Topic: G.06. Anxiety Disorders

Support: R15MH110951

Title: Gray matter volume correlates of electrocortical measures of conflict monitoring in high trait anxiety

Authors: J. FOLEY, H. GABOURY, H. M. GILBERTSON, L. FANG, *J. CARLSON;
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Abstract: Conflict monitoring is believed to play an important role in determining the circumstances in which top-down cognitive control processes are required for adaptive behavioral responding. The N2 is a negative event-related potential (ERP) peaking at 200-300 ms post-stimulus onset and maximal at frontocentral scalp electrodes. The N2 is thought to originate from the anterior cingulate cortex and/or supplementary motor area and reflect conflict monitoring-related cognitive control processes. Individuals with high levels of anxiety demonstrate increased N2 amplitudes during conflict processing, suggesting a relationship between hyperactive conflict monitoring and anxious symptomatology. Individual differences in the amplitude of the N2 have been linked to variability in gray matter volume in individuals with schizophrenia, autism spectrum disorder, multiple sclerosis, as well as other neurological and psychological disorders. Yet, the extent to which differences in regional gray matter volume relate to variability in N2 amplitudes in high trait anxious individuals remains untested. To address this knowledge gap, this study was conducted with a sample of 71 high trait anxious right-handed adults (female = 47) between 18 to 38 years of age. Participants completed a flanker task while EEG data was recorded. The task required participants to identify the center stimulus in a series of incongruent (e.g., < < > < <) and congruent arrows (e.g., < < < < <). EEG data were preprocessed using EEGLAB. Whole brain T1-weighted MRI scans were used to acquire estimates of gray matter volume. A voxel based morphometry (VBM) regression analysis was performed in SPM12 to assess the association between (delta) N2 amplitudes (Incongruent - Congruent) and regional gray matter volume. Incongruent N2 amplitudes were more negative than congruent N2 amplitudes, $t(70), = -7.60$, $p < .001$. Using a whole-brain cluster-level family-wise error (FWE) correction, we found that N2 amplitudes were correlated with gray matter volume in the bilateral inferior frontal gyri (xyz: -57, 32, 6; k = 1592 & xyz: 50, 41, -6; k = 641), anterior cingulate cortex (xyz: -3, 56, 5; k = 2134), supplementary/premotor motor area, (xyz: 35, -2, 57, k = 929), right superior temporal gyrus (xyz: 72, -32, -2; k = 754), and other frontal regions (all p_{FWE} values < .05). Larger gray matter volume in these regions was associated with greater N2 amplitudes. No regions showed the opposite association. Such findings provide a better understanding of the link between functional and structural measures of conflict processing in individuals with anxiety.

Disclosures: J. Foley: None. **H. Gaboury:** None. **H.M. Gilbertson:** None. **L. Fang:** None. **J. Carlson:** None.

Poster

P695. Anxiety: Human and Pre-Clinical Studies

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Topic: G.06. Anxiety Disorders

Support: NIMH Grant R15MH110951

Title: Prefrontal cortex based intrinsic functional connectivity is related to electrocortical measures of conflict monitoring

Authors: S. LYONS, H. GILBERTSON, C. GIRARD, J. M. CARLSON, *L. FANG;
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Abstract: Conflict monitoring is a facet of executive functioning which prioritizes task-relevant information and inhibits distractions to ensure accurate responding. Conflict is often induced using tasks such as the flanker task where participants report the central symbol regardless of the congruent (e.g., < < < < <) or incongruent (e.g., < < > < <) symbols flanking it. Elevated anxiety is associated with heightened conflict monitoring, which is often indexed by the N2, a negative event-related potential appearing ~200-350ms at frontocentral scalp locations after stimulus presentation. It is thought that this increase in conflict monitoring reflects greater cortical recruitment to compensate for impaired inhibitory control. Moreover, previous neuroimaging research has identified that, under conflict, individuals with anxiety experience elevated activity in regions such as the anterior cingulate cortex (ACC) and regions of the prefrontal cortex (PFC). At present, despite knowing the N2 emerges from the ACC, little is known about how intrinsic connectivity associates with this electrocortical response of conflict monitoring in anxiety. The purpose of this study was to assess the association between the ACC as well as regions of the dorsolateral PFC (DLPFC) seeded functional connectivity and N2 amplitude in high trait-anxious individuals. Participants included 60 right-handed adults scoring 40 or above on the State-Trait Anxiety Inventory-Trait Scale. They were asked to complete one 10-minute resting-state fMRI session and one EEG session in which N2 data was collected during an arrow flanker task. Seed-to-voxel analysis showed that, at an uncorrected $p < .001$ level, delta N2 amplitudes (difference scores between incongruent and congruent trials) were negatively correlated with the rsFC between the ACC and superior frontal gyrus (SFG), the rsFC between the left DLPFC and parahippocampal gyrus, as well as the rsFC between the left DLPFC and parietal operculum cortex. Moreover, ROI-to-ROI analysis revealed that delta N2 was correlated with the rsFC between right SFG and left superior temporal gyrus (STG) after FDR correction at the $p < .05$ level. Adding to current literature, our study provides the first evidence that enhanced N2 amplitudes in highly anxious individuals are associated with the functional coupling between regions involved in conflict detection (e.g., ACC) and attention allocation (e.g., SFG). In addition, our findings also reveal that regions involved in cognitive control/proactive inhibition and action cancellation, are associated with elevated conflict monitoring in anxiety.

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Poster

P695. Anxiety: Human and Pre-Clinical Studies

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Program #/Poster #: P695.03

Topic: G.06. Anxiety Disorders

Title: Threat Bias and Resting State Functional Connectivity of the Periaqueductal Grey and Lateral Hypothalamus in Anxiety Disorders

Authors: *K. ROBERTS[1], S. HU[1], C.-S. R. LI[2];
[1]Psychology, SUNY Oswego, Oswego, NY; [2]Dept Psychiatry, Yale Univ., New Haven, CT

Abstract: The periaqueductal gray (PAG) and lateral hypothalamus(LH) are involved in processing pain and fear. This study evaluated the resting state functional connectivity (rsFC) of the PAG and LH in patients with anxiety disorders (PAD, n=30) and healthy controls (HC, n=70). Functional magnetic resonance imaging (fMRI) and behavioral data were obtained from the Nathan Kline Institute - Rockland Sample. Participants completed a 5-minute resting fMRI scan and a dot-probe task outside the scanner. The dot-probe task consisted of two faces (threatening or neutral) appearing on a screen, one of which would be replaced by a dot that required a button press. Threat bias was computed as the difference in reaction time (RT) between trials with the dot replacing the neutral vs. threatening faces (i.e., RT in neutral - RT in threat). Thus, a positive threat bias reflected a faster response to threatening vs. neutral faces, indicative of higher anxiety. Evaluated at a corrected threshold, the whole-brain rsFC of the PAG or LH showed no differences between PAD and HC. Regression analysis showed negative correlations of threat bias with left PAG-putamen and with right LH-inferior frontal gyrus rsFC in PAD but not in HC. In addition, a positive correlation between the right LH-posterior dorsal anterior cingulate cortex rsFC and threat bias was found in PAD but not HC. These connectivity metrics may serve as important neural markers of anxiety disorders.

Disclosures: K. Roberts: None. **S. Hu:** None. **C.R. Li:** None.

Poster

P695. Anxiety: Human and Pre-Clinical Studies

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Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

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Topic: G.06. Anxiety Disorders

Support: NIH Grant MH-114026-02

Title: Accelerated exercise-induced stress resilience in females is not dependent on running distance

Authors: *M. K. TANNER[1], A. A. HOHORST[3], N. JAMIL[1], E. C. LOETZ[2], B. N. GREENWOOD[2]; [2]Psychology, [1]Univ. of Colorado Denver, Denver, CO; [3]Univ. of Colorado - Denver, Denver, CO

Abstract: Stress-related psychiatric disorders are the most common mental health disorders in the world and affect women at nearly twice the rate of men. Participation in regular physical activity is an inexpensive and readily available tool for preventing the effects of stress in both sexes. However, little research has been done to characterize exercise-induced stress resilience in females. Understanding exercise-induced stress resilience in females is critical since females are more susceptible to stress-related disorders than males. Rodents provide a useful model for studying stress resilience produced by exercise. Following exposure to inescapable stress, rats display anxiety-like behaviors, such as exaggerated fear in response to mild stimuli. In both male and female rats, 6 weeks of voluntary wheel running prior to inescapable stress exposure prevents the behavioral effects of stress. Interestingly, 3 weeks of wheel running is sufficient to produce stress resilience in females, but not males. Although female rats run greater nightly distances compared to males, it is currently unclear if running distance has a role in the rapid acquisition of stress resilience in females. The goal of the current study was to determine if 3 weeks of voluntary wheel running produces stress resilience in female rats that run similar distances as males.

Adult, female Sprague Dawley rats were randomly assigned to sedentary, unlimited running, or limited running conditions. Rats in the unlimited running group had 24 h access to voluntary running wheels, while rats in the limited running group had access to voluntary running wheels for 3 h after the start of the active cycle. Females in the unlimited running group ran up to 1.5x more than what is typically seen in males, while females in the limited group ran less than males. After 3 weeks of sedentary or running conditions, half of the rats were exposed to inescapable stress. The following day, freezing behavior was assessed immediately following 2 foot shocks. Sedentary rats exposed to inescapable stress, compared to non-stressed rats, had exaggerated freezing in response to the 2 foot shocks; indicative of exaggerated fear learning. Three weeks of both unlimited and limited running prevented stress-induced exaggerated fear, and the degree of stress protection afforded by 3 weeks of wheel running was similar between unlimited and limited females. These results suggest that running distance does not drive the rapid acquisition of exercise-induced stress resilience in females. Further research is needed to identify the mechanisms underlying the accelerated stress resilience produced by exercise in females.

Disclosures: M.K. Tanner: None. **A.A. Hohorst:** None. **N. Jamil:** None. **E.C. Loetz:** None. **B.N. Greenwood:** None.

Poster

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Topic: G.06. Anxiety Disorders

Support: NIH Grant MH-114026-02

Title: Estrous cycle modulation of conditioned fear extinction and relapse

Authors: *A. A. HOHORST[1], M. K. TANNER[1], T. J. HUBERT[1], B. N. GREENWOOD[2], E. C. LOETZ[2];
[2]Psychology, [1]Univ. of Colorado Denver, Denver, CO

Abstract: Impaired inhibition of learned fear is a feature of stress-related psychiatric disorders such as depression, generalized anxiety disorder and post-traumatic stress disorder (PTSD). Extinction-based exposure therapy is the behavioral therapy of choice for stress-related psychiatric disorders, however, it has limited long term efficacy due to the vulnerability of fear memories to later relapse. Additionally, women are up to 60% more likely to experience an anxiety disorder and up to twice as likely to experience PTSD compared to men. Although women are at a higher risk than men to develop these common stress-related psychiatric disorders, sex differences are not fully considered in the field of neuroscience. Prior research has shown that females can have enhanced fear extinction compared to males, and that the strength of fear extinction in females varies depending on phase of the estrous cycle during which fear extinction takes place. However, whether the phase of the estrous cycle during which fear extinction is learned impacts later fear relapse after extinction has not been well characterized. The goal of this experiment was to determine whether sex and phase of the estrous cycle during extinction training modulates later fear relapse. Long-Evans rats were exposed to auditory fear conditioning in

Context A, followed 24 h later by fear extinction in Context B. The next day, rats were re-exposed to the conditioned stimulus in either the same context used for extinction (Context B) to test fear extinction memory, or a different, novel context (Context C) to assess fear renewal. Spontaneous recovery of fear was assessed a week later in Context B. Female cycle progression was monitored daily. Results indicate that males and females learned auditory fear conditioning and fear extinction similarly. Levels of fear extinction retention and fear relapse were similar between males and females exposed to fear extinction during metestrus/diestrus. However, females exposed to fear extinction training during pro-estrus or estrus, had improved retention of fear extinction, as well as reduced fear renewal and spontaneous recovery compared to both males and females exposed to fear extinction training in other estrous phases. These data suggest that phase of the estrous cycle during fear extinction learning modulates fear relapse; whereby learning fear extinction during proestrus/estrus is protective against later relapse. These results could have important clinical implications for the use of exposure therapy in women.

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Poster

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Title: Glyphosate exposure induces novelty-induced anxiety in rats

Authors: *A. FIGUEROA-PÉREZ, M. RIVERA-LÓPEZ, M. CÁCERES-CHACÓN, O. MARTÍNEZ-GUZMÁN, D. SIERRA-MERCADO;
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Abstract: Glyphosate is the most common active ingredient in herbicides used in landscaping and agriculture. Glyphosate is thought to be safe for humans and animals because it acts because it acts by inhibiting a metabolic route almost exclusive to plants. However, recent studies in rodents have shown that glyphosate is capable of increasing the expression of anxiety-like behaviors in classical paradigms such as the open field test and elevated plus maze. However, the effect that glyphosate may have on novelty-induced anxiety or neophobia, has not been explored. Therefore, we aimed to evaluate the effect of prolonged oral consumption of glyphosate-contaminated drinking water on novelty-induced anxiety. To achieve this, we weighed rats weekly as well as measured their water intake to prepare a solution that

would allow us provide the rat with a target dose of 2.0mg/kg of GBH daily (chronic references dose approved by the E.P.A.) in their drinking water. Control rats were treated in the same manner but received filtered drinking water. Of note, there were no differences in neither the amounts of food or water consumption, nor body weight between the groups ($p>0.05$). After 4 weeks of exposure, we assessed for novelty-induced anxiety using a modified open field test in which an object was placed in the center of the arena. Here, glyphosate decreased the amount of time spent interacting with the object (Glyphosate: 8.71, control: 35.02, $p=0.0202$) as well as the number of interactions with the object (Glyphosate: 3.00; control: 9.42; $p=0.0255$). Next, animals were placed in an operant chamber and presented with 5 auditory tones (30 s, 4 kHz, 77 dB; 3 min intertrial interval), and the amount of time spent freezing to the tone was measured. Glyphosate significantly increased the percent time spent freezing to the tones (Glyphosate: 14.05, control: 4.95; $p=0.0201$). In conclusion, glyphosate increases novelty-induced anxiety to different types of stimuli and in different contexts. Future directions include evaluating brain regions involved in anxiety-like behaviors for changes in neuronal activity.

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Poster

P695. Anxiety: Human and Pre-Clinical Studies

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Program #/Poster #: P695.07

Topic: G.06. Anxiety Disorders

Support: ICCBS-Faculty Grant

Title: Potential of geraniol to reduce anxiety-like symptoms and abnormal EEG wave pattern

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Abstract: Research objectives To determine the changes in electroencephalogram (EEG) wave pattern of rats upon induction of anxiety-like symptoms by a single acute stressor and its possible attenuation by geraniol treatment in rats. **Rationale** Among neuropsychiatric disorders, anxiety is wide spread globally and causes 2.3% of worldwide disability. Anxiety at a glance is body's natural response to an actual or perceived threat. But the problem complicates when this response prolongs further unnecessarily. Diagnosis of anxiety is usually based on interviews and sessions with physician. However, a unique method of evaluating anxiety is through the analysis of EEG of the affected person. Therefore, our study aims to determine rat EEG fluctuations due to anxiety in rats. Moreover, this study was also designed to analyze the potential of geraniol against anxiety disorders. Geraniol is one of the monoterpenoids which has been reported to have antioxidant and anti-inflammatory effects. Furthermore, there is some evidence that geraniol has brain calming, and anti-epileptic potential. **Material and methods** Thirty male albino Wistar rats weighing between 220-250g were divided into 5 groups (n=6) comprising of control, disease

model, low dose treatment, high dose treatment and positive control (diazepam) groups. Test rats were subjected to an electric shock (1.0 mA for 1s) followed by respective drug administration after 15 min. Low dose and high dose treatment groups were treated with geraniol at the dose of 10 mg/kg and 30 mg/kg respectively, whereas diazepam was administered at the dose of 3.5 mg/kg. Half hour after dosing, anxiety was evaluated using behavioral paradigm of elevated plus maze (EPM). EEG was monitored 15 min after performing EPM. All the experimental procedures were approved by the Institutional Animal care and use committee (IACUC). **Results** The results from EPM showed significantly increased anxiety-like symptoms in disease group while reduced anxiety-like behavior was observed in treatment groups. EEG band changes were evaluated by EEG recorder system which comprised of data acquisition system from the Science Beam Company, Iran. The EEG recording demonstrated the elevated power of low beta, high beta and gamma waves in disease group, whereas, geraniol and diazepam treatment resulted in normalization of beta and gamma power in rats subjected to electric shock. These results are in parallel with the results of EPM test. Thus, it can be concluded that geraniol exhibits a potential to reduce symptoms of anxiety and normalize the associated impaired EEG wave pattern. **Funding** International Center for Chemical and Biological Sciences, University of Karachi.

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Poster

P695. Anxiety: Human and Pre-Clinical Studies

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Program #/Poster #: P695.08

Topic: G.06. Anxiety Disorders

Support: Grant from Sarepta Therapeutics

Title: Central nervous system expression of dystrophins and antisense therapy in a mouse model of Duchenne muscular dystrophy.

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Abstract: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disease caused by mutations in the dystrophin gene, resulting in muscle degeneration and a shortened life expectancy. DMD patients also have a higher prevalence of intellectual disability, anxiety, attention deficit hyperactivity disorder, and autism spectrum disorder than the general population. The presence of at least seven alternative promoters, two polyA addition sites and alternative splicing results in several dystrophin isoforms with different expression patterns and putative roles. Mutations affecting only the full-length isoforms (Dp427) have been linked to emotional behavioural problems including anxiety, depression, and hyperactivity in DMD patients. Mdx mice carry a mutation affecting only the Dp427 isoforms and display an enhanced fear response, and increased anxiety- and depressive-like behaviours. Dystrophin expression in muscle can be restored using an exon-skipping phosphorodiamidate morpholino oligomer (PMO) treatment. In

order to improve neurobehavioural phenotypes in this pre-clinical model, we aim to map the expression of Dp427 isoforms in the mouse brain in detail and develop PMO treatment strategies aimed at restoring dystrophin expression in the brain. Dp427 transcripts have been detected across the brains of male wildtype mice including in the cerebellum, hippocampus, and cortex. The 5' regions of Dp427 transcripts have been sequenced to identify the unique sequences of each isoform. Dp427 protein has been detected in the cerebellar Purkinje and molecular layers and the hippocampal pyramidal cell layer by immunohistochemistry, and has been quantified using a capillary western immunoassay. Male mice were given a single dose of a fluorescently-tagged PMO either by a intracereberoventricular (ICV) injection or an intracisternal magna (ICM) injection, and the biodistribution of the PMO in the brain was determined 48 hours later. The commonly used ICV injection into the lateral ventricle resulted in superior biodistribution of the PMO, however ICM injections are minimally invasive and require little post-surgery recovery. These results indicate that repeated or chronic ICM injections will be required to efficiently restore dystrophin in key brain regions. Several antisense oligonucleotide therapies have now been approved for treatment of DMD in muscle only. These pre-clinical studies will allow us to explore the possibility of improving life quality by also addressing neurobehavioural comorbidities in DMD patients.

Disclosures: T.E. Gileadi: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **M. Siddle:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **C. Fergus:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **D. Chambers:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **V.P. Kelly:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **J.E. Morgan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **R. Phadke:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **F. Montanaro:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics. **F. Muntoni:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sarepta Therapeutics.

Poster

P695. Anxiety: Human and Pre-Clinical Studies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P695.09

Topic: G.06. Anxiety Disorders

Support: Artelo Biosciences
Mitacs Canada

Title: Inhibition of fatty acid binding protein-5 in the prefrontal cortex reduces fear and anxiety responses by distinct endocannabinoid receptor-mediated mechanisms

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Abstract: Current pharmacological treatments for anxiety disorders are associated with significant deleterious side-effects, including dependence, withdrawal and cognitive impairments. Recently, the endocannabinoid (eCB) system has drawn attention as a promising target for novel anxiolytic pharmacotherapies. Previous evidence has revealed that genetic and/or pharmacological manipulations altering eCB signaling change fear and anxiety responses of rodents. Anandamide (AEA), the more extensively investigated eCB ligand, is synthesized on demand, activate numerous eCB receptors, and is metabolized by fatty acid amide hydroxylase (FAAH). However, water-insoluble lipids such as AEA require chaperone proteins for their intracellular transportation to FAAH, a process which requires fatty acid binding proteins (FABP). We are investigating the effects of a novel FABP-5 inhibitor, SBFI-103, on fear and anxiety-related behaviors using adult male Sprague Dawley rats. Acute SBFI-103, when administered locally into the prelimbic region of the medial prefrontal cortex of rats (mPFC), led to an anxiolytic response as well as reduced contextual fear expression in a dose dependent manner. Surprisingly, both effects were reversed when a cannabinoid-2 (CB2) receptor antagonist, AM630, was co-infused with SBFI-103. Co-infusion of the cannabinoid-1 (CB1) receptor antagonist Rimonabant with SBFI-103 reversed the contextual fear response, yet showed no reversal effect on anxiety. Co-administration of G-protein coupled receptor 55 antagonist CID16020046 partially reversed the SBFI-103-induced changes whereas co-administration of peroxisome proliferator-activated receptor gamma antagonist T0070907 showed no effect. Furthermore, in vivo neuronal recordings revealed that intra-mPFC SBFI-103 infusion reduced activity of putative pyramidal neurons in the basolateral amygdala as well as elevated activity of pyramidal neurons in the CA1 region of the ventral hippocampus and significantly reduced alpha, beta and gamma oscillation patterns, both of which were dependent on CB2 transmission. These results indicate that intra-mPFC FABP-5 inhibition, which should elevate AEA availability in the synaptic cleft, alters neuronal activity in key regions of anxiety-related neural circuitry, resulting in an anxiolytic behavioral phenotype. Our findings identify a promising role for FABP5 inhibition as a novel anxiolytic pharmacotherapy. Furthermore, we identify a novel, CB2-dependent FABP5 signaling pathway in the PFC capable of strongly modulating anxiety-related behaviours and neuronal transmission patterns.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P764.01

Topic: G.09. Drugs of Abuse and Addiction

Title: Novel virtual reality intervention reduces e-cigarette dependence and cravings in undergraduate students

Authors: *S. SKLENARIK[1], J. KELLY[1], K. THOMPSON[2], S. BOUCHARD[3], S. KRISHNAN-SARIN[4], R. S. ASTUR[1];
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Abstract: The use of electronic cigarettes (e-cigarettes), or "vaping," is highly prevalent and increasing dramatically among young adults (Schulenberg et al., 2020). Concerningly, there is limited data supporting clinical approaches to reduce vaping among this population (Berg et al., 2020). Previously, we demonstrated that immersing smokers in a virtual reality (VR) environment in which they are instructed to search for and crush virtual cigarettes significantly improved smoking cessation and decreased nicotine dependence (Girard et al., 2009). The goal of the current study is to investigate the efficacy of a similar intervention in reducing e-cigarette dependence among college undergraduates.This intervention consists of 4 lab sessions over a 2-week period as well as an online follow-up 1 week later. Each lab session involves a 20-minute VR session, during which participants use an immersive head-mounted display and controllers to navigate a virtual environment filled with either 100 floating vapes (experimental condition) or 100 floating tennis balls (control condition). Participants in the experimental condition are instructed to search for, throw, and destroy 60 vapes using a virtual hand that mirrors the participant's actual hand movements. In the control condition, e-cigarettes are replaced with virtual tennis balls that bounce upon being thrown. Throughout the intervention, participants are asked to complete validated assessments to quantify vaping dependence, including the Penn State Electronic Cigarette Dependence Index (PSECDI; Foulds et al., 2015) the Electronic Cigarette Dependence Scale (EDS; Morean et al., 2019), and the Fagerstrom Test for Nicotine Dependence (adapted for vaping; FTND; Fagerstrom & Schneider, 1989). Additionally, participants completed the Questionnaire of Vaping Craving (QVC; Dowd et al., 2018).To date, 8 participants that met PSECDI criteria for medium to high e-cigarette dependence and self-reported wanting to reduce their e-cigarette use have completed the intervention; all participants were assigned to the experimental condition. From session 1 to session 4, participants demonstrated significant ($p < 0.05$) reductions in vaping dependence and cravings. Specifically, we observed a 35% reduction in PSECDI scores, a 43% reduction in EDS scores, a 57% reduction in FTND scores, and a 31% reduction in QVC scores from baseline. Data collection is ongoing, and results from the control condition will be crucial to elucidating the efficacy of this intervention. Overall, this promising pilot data suggests that the destruction of addictive stimuli in a virtual environment may be helpful in decreasing vaping dependence.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P764.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA/NIH/DHHS 09486

Title: Testing the effects of liraglutide on nicotine-mediated behaviors in rats

Authors: *K. RAGNINI[1], R. HERMAN[1], R. MERKEL[1], S. ZEB[1], H. D. SCHMIDT[2];
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Abstract: While consumption of traditional tobacco products is declining, the recent increase in use of electronic nicotine delivery systems such as nicotine vaping devices present a new challenge to addressing nicotine use disorder. Long-term cessation of nicotine use is often difficult to achieve due to withdrawal-induced adverse effects including weight gain. Glucagon-like peptide 1 receptors (GLP-1Rs) are expressed throughout the brain including in neural circuits that regulate nicotine taking and food intake. Liraglutide is a GLP-1R agonist that is FDA-approved for treating weight gain in humans. Our pilot preclinical findings indicate that systemic liraglutide attenuates nicotine reinstatement. Here, we investigated the effects of repeated liraglutide administration on nicotine taking and seeking as well as nicotine withdrawal-induced weight gain. Male and female rats were allowed to self-administer nicotine (0.03 mg/kg/infusion) intermittently for 20 days on a fixed-ratio 1 (FR-1) schedule of reinforcement. Rats received daily systemic liraglutide (0.025mg/ml/kg) or vehicle treatments 60 minutes prior to the operant sessions. Liraglutide decreased nicotine self-administration and reinstatement in female rats. In contrast, this dose of liraglutide did not appear to be efficacious in nicotine-experienced male rats. To assess body weight changes during abstinence, nicotine-experienced rats and yoked saline controls were housed in hanging wire cages during the self-administration, abstinence, and reinstatement phases of the experiment. During abstinence, rats received either repeated daily liraglutide (0.025mg/ml/kg, i.p.) or vehicle. Body weight, ad libitum high fat chow intake, and water intake were recorded. Our preliminary data indicates that liraglutide attenuated nicotine withdrawal-induced body weight gain as compared to vehicle-treated nicotine-experienced animals and yoked nicotine-naive controls. We hypothesize that liraglutide reduces withdrawal-induced hyperphagia for nicotine-experienced animals. These experiments will include both male and female rats to identify potential sex differences. Together, these studies will determine if GLP-1Rs represent a potential pharmacological target for reducing nicotine relapse and attenuating weight gain during nicotine abstinence.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

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Program #/Poster #: P764.03

Topic: G.09. Drugs of Abuse and Addiction

Support: Igniting Research Collaborations program funded by the University of Kentucky Vice President for Research and College Deans

Title: Chronic administration of synthetic contraceptive hormones alters ethanol and nicotine intake in a co-use model in freely cycling female rats

Authors: *E. E. MAHER[1], E. BONDY[1], S. KHATRI[1], J. WEAFER[2], C. D. GIPSON[1];
[1]Family and Community Med., [2]Psychology, Univ. of Kentucky, Lexington, KY

Abstract: Tobacco and alcohol use disorders (TUD and AUD, respectively) are tremendous health liabilities, and co-use of these substances is highly prevalent in the United States. Women are particularly at risk, as AUD is increasing in women at alarming rates (an 84% increase in cases from 2002-2013) and long-term smoking cessation is more difficult to achieve in women than men. Further, ovarian hormones can affect frequency of binge drinking, as well as cigarette craving, with increases in 17β-estradiol (E2) and progesterone being associated with addiction risk and resilience, respectively. Given the role of ovarian hormones in addiction, it is also important to consider how exogenous synthetic hormones, commonly found in hormonal contraceptives, may influence motivation for alcohol and nicotine. Hormonal contraceptives contain synthetic forms of estrogen (e.g., ethinyl estradiol, or EE) and/or progesterone (e.g., levonorgestrel, or LEVO). However, despite widespread contraceptive use and the influence of hormones on addiction vulnerability, little is known regarding the influence of contraceptives on nicotine and alcohol co-use.The aim of the current study is to determine the influence of EE and LEVO on nicotine and ethanol (EtOH) intake in rats. We hypothesized that female rats given LEVO will show lower rates of nicotine and EtOH intake, whereas rats given EE+LEVO will show higher rates of intake of both drugs. Prior to nicotine self-administration (SA), rats underwent a drinking in the dark (DID) paradigm when rats were given a 4-hr session in which the water bottle was replaced with a sipper tube containing 10% EtOH or vehicle (water) three hours into the dark (active) cycle. To determine intake for the day, bottles were weighed before and after DID sessions. Following DID, rats receive a subcutaneous (s.c.) injection of either LEVO, EE+LEVO, or vehicle (sesame oil) and began nicotine SA (0.06 mg/kg/infusion) on an FR1 schedule. Results show that rats that receive EE+LEVO have a higher intake of nicotine as compared to rats that received LEVO alone or vehicle. Interestingly, there was no difference in nicotine intake with hormone treatment in animals that drank EtOH prior to nicotine SA. We also show that, contrary to our hypothesis, animals that received LEVO alone consume more EtOH then either the EE+LEVO or vehicle treated animals. Overall, we found that EE+LEVO decreased EtOH intake when EtOH was co-used with nicotine, whereas this hormone combination increases nicotine consumption when rats are not concurrently drinking. Thus, these results can inform women's care by determining safer hormonal contraceptive use when women concurrently drink and smoke.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

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Program #/Poster #: P764.04

Topic: G.09. Drugs of Abuse and Addiction

NIH, National Institute on Drug Abuse N01DA-18-8936

Title: Preclinical evaluation of FSNY-1 for tobacco use disorder

Authors: R. D. HILL, R. A. SHETTY, C. TAYLOR, *M. J. FORSTER;
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Abstract: Previous reports from this laboratory suggested that both the experimental compound FSNY-1 and the standard, varenicline, fully blocked the stimulant effects of nicotine in mice. However, nicotine-effective doses of varenicline also had locomotor depressant effects by themselves. In the current studies, FSNY-1 and varenicline were compared for their ability to diminish the reinforcing effects of nicotine, detected as an extinction-like effect in a nicotine self-administration (SA) assay. Rats previously trained to a criterion of nicotine self-administration (0.03 mg/kg/inf; FR-1) showed gradual reduction in number of responses after 3 daily sessions of extinction. After reinstatement of nicotine responding, separate groups of rats were treated with different doses of FSNY-1 or varenicline on each of three days prior to a nicotine SA session. Extinction like-effects on frequency of nicotine infusions were evident following both FSNY-1 (ongoing studies, 2.5 to 10 mg/kg) and varenicline (0.3 to 3 mg/kg). These studies provide additional evidence for clinical application of FSNY-1 in tobacco use disorder. These results also support the validity of multiple session self-administration testing for identification of drugs useful in tobacco use disorder.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

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Topic: G.09. Drugs of Abuse and Addiction

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FAPERJ Grant SEI-260003/001135/2020
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Title: Nicotine exposure in mice modeled to schizophrenia: testing the self-medication theory

Authors: *Y. ABREU-VILLACA[1], A. DUTRA-TAVARES[2], L. A. COUTO[1], A. BANDEIRA-MARTINS[1], J. O. SILVA[1], T. P. SOUZA[1], A. C. MANHAES[1];
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Abstract: The self-medication theory proposes that patients with SCHZ smoke to alleviate symptoms of the disease and side effects of treatment. Accordingly, the acceptance of this theory implies that patients are more prone to become smokers after the appearance of SCHZ symptoms. Despite that, in experimental animals, few studies simulate self-medication by modeling SCHZ before nicotine/tobacco exposure. Here, C57Bl/6 mice (60-75 days, n=9-13 per group and sex) initially modeled to SCHZ and subsequently exposed to nicotine were submitted to a protocol of locomotor sensitization and to a pre-pulse inhibition (PPI) test. Hyperlocomotion is associated with the positive symptomology of SCHZ, while deficits in PPI assess sensorimotor gating, which is impaired in SCHZ patients. Initially, mice were either assigned to a CT (s.c. saline injections) or a PCP (phencyclidine 2.5mg/kg, s.c.) group and tested in an open field arena for four consecutive days (S1-S4). Phencyclidine, a NMDA receptor antagonist, was used to model SCHZ. After that, half of CT and half of PCP mice further received daily nicotine injections (0.5mg/kg, s.c.), so that 4 groups (CT, NIC, PCP and PCP-NIC) were tested for additional 4 days (S5-S8). The day after, mice received their respective treatment and were tested in the PPI apparatus. The startle responses for pairs of a prepulse (pP: 70, 75 or 80dB) followed by a pulse (P: 120dB) were registered and the %PPI calculated. The phencyclidine dose was 10mg/kg. Phencyclidine had a major impact on locomotor activity from the first day of exposure onwards. PCP mice exhibited a progressive increase in locomotion, characteristic of behavioral sensitization (S1<S8). From S5 to S8, the analysis of the four experimental groups confirmed the effect of phencyclidine (PCP and PCP-NIC groups were hyperactive when compared to CT and NIC groups), and demonstrated that PCP and PCP-NIC mice were not different from each other. These data show that nicotine did not interfere with phencyclidine-evoked sensitization. In the PPI test, the analysis of the startle responses that followed pP70+P and pP75+P acoustic stimuli indicated that phencyclidine reduced %PPI in exposed mice when compared to non-exposed ones. Nicotine failed to interfere with these results. The analysis of the pP80+P pair indicated similar results in females. Distinctively, in males, the deficient response of PCP mice was worsened when phencyclidine was combined with nicotine. In mice modeled to SCHZ, subsequent exposure to nicotine did not interfere with locomotor sensitization but worsened the pre-pulse inhibition deficit in a sex-dependent manner. These results do not corroborate the self-medication theory.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

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Program #/Poster #: P764.06

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant DA035924

Title: Relapse-like behavior and nAChR sensitization following intermittent access nicotine self-administration

Authors: *M. A. TAPIA, X.-T. JIN, B. R. TUCKER, L. N. THOMAS, N. B. WALKER, S. E. ALBERTSON, S. R. JONES, R. M. DRENAN;
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Abstract: Tobacco smoking is the leading cause of preventable death worldwide. Rodent self-administration (SA) models have provided insights into tobacco addiction. Many of the previous SA models have used fixed-ratio (FR) schedules of reinforcement. These schedules may not capture the subtleties of human tobacco use, including intermittent smoke breaks during working hours and socialization. *Objective*: The present study aims to examine SA behavior during intermittent access (IntA) to nicotine to determine (1) how nicotine intake on an IntA schedule compares to continued access on a FR schedule and (2) whether nicotine IntA impacts cue-induced relapse behavior and alters nicotinic acetylcholine receptors (nAChRs) in the interpeduncular nucleus (IPN) during forced abstinence. *Methods*: Male Sprague Dawley rats were first allowed to self-administer saline or nicotine (0.03 mg/kg) for 10 2-hour acquisition sessions (known as ACQ) on a FR 1 schedule of reinforcement. Following ACQ, rats switched to 7 days of 4-hour IntA nicotine self-administration. Each IntA session consisted of 12 alternating Drug-Available and No-Drug Available periods lasting 5 and 15 min respectively. After completing ACQ and IntA sessions, we investigated nAChR using patch-clamp electrophysiology and non-reinforced operant responding for cue-induced nicotine seeking on Days 1 and 7 of forced abstinence. *Results*: Findings indicate that while rats had only half as much time available to administer nicotine during IntA, overall responding and nicotine intake was maintained and even enhanced relative to ACQ. Moreover, IntA enhanced cue-induced nicotine seeking and elevated IPN nAChR neuronal activity after 7 drug-free days. *Conclusion*: These data indicate that rats will readily self-administer nicotine on an IntA schedule and is sufficient to potentiate nicotine craving and neuronal activity in the IPN. Given the number of individuals who take intermittent smoke breaks during the day, our preclinical IntA model of nicotine SA is a useful paradigm for investigating nicotine intake and neurobiological changes associated with nicotine addiction.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

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Program #/Poster #: P764.07

Topic: G.09. Drugs of Abuse and Addiction

Support: DePauw University
Buehler Family Foundation
Arthur Vining Davis Foundation

Title: Nicotine-choice behavior and acetylcholine receptors in zebrafish

Authors: *H. SCHNEIDER[1], K. CHINYANYA[1], A. BUTTON[1], S. KRAUSE[1], A. PEARSON[1], D. HARRIS[1], E. KENNEDY[1], Z. CAPPEL[1], S. STEVENS[1], A. SHEMET PITCHER[1], D. ROSENE[1], S. GOLDE[1], J. ROSA[1], H. MARTON[1], K. GARDNER[1], H. AFZAL[2];
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Abstract: Nicotine-use behavior is one of the main causes of preventable diseases such as cancer, cardiovascular diseases, diabetes, and chronic obstructive pulmonary disease. Helping people quit nicotine products is a main goal of our projects. Developing a zebrafish model for nicotine use behavior could provide a tool for studying the underlying genetic, environmental and neuronal elements of nicotine use behavior. Most recently, we established behavioral nicotine-choice assays for larval zebrafish using a plus-maze and a gradient-maze. EthovisionXT (Noldus) was used for the analysis of swimming paths. The assays identified nicotine-seeking, nicotine-avoiding or nicotine-neutral larval zebrafish (6-8 dpf) based on the cumulative duration larval zebrafish spent in and the frequency at which larval zebrafish enter the compartments of the test-mazes. In a random wildtype line about 20% of tested zebrafish show nicotine-seeking behavior, 25 to 30% show nicotine avoidance behavior and 50 to 55% show nicotine-neutral behavior in the gradient maze. The nicotine-choice behavior is concentration dependent and changes with nicotine-preincubation. As a first step towards the neurogenomics of nicotine-seeking and avoidance behavior in zebrafish, we investigated single nucleotide polymorphisms (SNPs) in zebrafish acetylcholine receptor genes (chrna3, chrna5, chrnb4) that have been linked in human homologs to heavy smoking. Some of these SNPs are conserved and weakly linked to nicotine-seeking behavior in larval zebrafish. In addition, we discovered sequence variations in introns of zebrafish chrna3 and chrna5 genes that include a microsatellite region and a deletion that could have a regulatory function.
In summary, our results indicate that variations of nicotine-seeking behavior in larval zebrafish could be associated with variants in acetylcholine receptor genes. Future studies will explore acetylcholine receptor variants in nicotine-seeker and avoider lines and aim for a better understanding of the neurogenomics of nicotine-seeking and avoidance behavior and responses to pharmacotherapeutics used in smoking cessation treatment.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

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Topic: G.09. Drugs of Abuse and Addiction

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K23-DA045081

Title: A pilot study of whole-brain reactivity to flavored e-cigarettes among women smokers: The association with depressive symptoms

Authors: *A. C. KRISTICH[1], C. R. BORDNER[2], A. L. HOBKIRK[1], K. R. HOUSER[1], B. HOGLEN[1], J. FOULDS[2], D. MUKHERJEE[3];
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Abstract: A pilot study of whole-brain reactivity to flavored e-cigarettes among women smokers: The association with depressive symptoms Ava Kristich, Candace R. Bordner, Kenny R. Houser, Brianna Hoglen, Jonathan Foulds, Dahlia Mukherjee, Andrea L. Hobkirk**Background:** Clinical depression is a risk factor for nicotine dependence (Breslau et al., 2004). Electronic cigarettes (e-cigarettes) contain nicotine, a nicotinic acetylcholine receptor agonist that can improve depressive behaviors by desensitizing and increasing acetylcholine receptors (Gandelman et al., 2018). E-cigarettes with sweet flavors are popular among adults who are new users or established cigarette smokers (Schneller et al., 2018). Appealing sweet flavors in e-cigarettes have the potential to increase the risk for addiction by stimulating corticostriatal reward pathways (Small et al., 2012, Tang et al., 2012). The aim of the analysis was to assess if brain reward reactivity to sweet-flavored and unflavored e-cigarettes varied with the level of self-reported depressive symptoms among women smokers. The findings have implications for the risk of e-cigarette addiction and use of e-cigarettes as a smoking harm-reduction method for depressed smokers.**Methods:** Nine adult female daily smokers inhaled aerosolized strawberry-vanilla flavored and unflavored e-liquid with low concentrations of nicotine during two functional magnetic resonance imaging (fMRI) scans. Participants completed the Center for Epidemiological Studies Depression Scale (CES-D) to determine levels of depressive symptoms. The CES-D scores were correlated with whole-brain blood-oxygen level-dependent (BOLD) signals during each fMRI scan using voxel-wise general linear models in the FMRIB Software Library (FSL). Brain regions with significant clusters of BOLD signal were identified using the Harvard-Oxford Cortical and Subcortical atlases. **Results**: There were five significant brain clusters showing a positive correlation between CES-D scores and BOLD signal during the flavored aerosol, located in the ventromedial prefrontal cortex, cuneus, bilateral precentral and postcentral gyrus, and the cingulate gyrus. There was only one region in the cuneus with a significant positive correlation between CES-D scores and BOLD signal during inhalation of the unflavored aerosol. No brain regions showed a negative correlation. **Conclusions**: We observed that higher depressive symptoms associated with more cortical brain reactivity during flavored e-cigarette use. The results highlight potential mechanisms in which flavored e-cigarettes may increase addiction potential or alter depressive symptoms for women smokers.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P764.09

Topic: G.09. Drugs of Abuse and Addiction

Support: R37DA020686

Title: Regulation of nicotine intake by the gut hormone cholecystokinin: evidence for brain-body interactions in addiction

Authors: *K. M. BRAUNSCHEIDEL, L. WILLS, Y. R. HACHICHA, S. P. B. CALIGIURI, P. J. KENNY;
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Abstract: Nicotine addiction in the form of habitual tobacco use is the leading cause of premature death in the United States. In addition to the direct effects of nicotine on hedonic neurocircuitry, recent evidence implicates aversion neurocircuitry and peripheral structures in nicotine habit formation. For instance, circulating levels of the satiety-signaling gut-hormone cholecystokinin (CCK) is disrupted in smokers following meal consumption. The effects of CCK receptor (CCKR) activity on nicotine intake is undetermined. Here, we address this gap in knowledge and describe a potential neural mechanism for peripheral control over nicotine intake. We first confirmed that nicotine increases postprandial, but not fasting plasma CCK concentration in mice. We then found that the peripherally-restricted CCKR agonist, CCK-8 (10 $\mu*kg^{-1}$), decreased volitional nicotine intake, especially at anxiogenic nicotine doses. CCK-8 did not affect nicotine-craving or food rewards earned in an operant-based task or interfere with nicotine ($0.5mg*kg^{-1}$, SC) conditioned place preference. CCK-8 did, however, increase anxiety-like behaviors during preference testing. Taken together, these data suggest CCKR activation is involved in regulating aversive, not hedonic, properties of nicotine. We hypothesize that the presence of CCK receptors in gut-innervating vagal sensory neurons of the nodose ganglia (NG) potentiates aversive nicotine signals from the periphery similar to CCK's regulation of appetite. In support of this idea, we found that an equimolar dose of the peripherally-restricted nicotine analogue, methlynicotinium caused an enhanced place aversion relative to nicotine ($1.5mg*kg^{-1}$, SC). Next, using Targeted Recombination in Active Population (TRAP) mice, we identified nicotine-responsive populations in the NG as well as its primary target, the nucleus of the solitary tract. A final cohort of mice were injected subcutaneously with saline, nicotine, or methlynicotinium. After 90 minutes, NG were processed for single-nuclei RNA sequencing to determine overlapping changes to the transcriptome between central and peripheral nicotinic receptor activation. Future studies will aim to describe how these neuronal NG subpopulations regulate nicotine intake. The existence of "bottom-up" regulation of nicotine intake by circulating hormones and the NG may prove useful for the development of novel addiction therapies for two reasons: first, direct electrical stimulation of the vagus nerve has already been validated as a treatment for other neurological disorders; and second hormone levels & vagal activity can be altered by non-invasive means. Funding: R37DA020686.

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Poster

P764. Nicotine: Cognitive and Behavioral Effects, and Interventions

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Title: Dynamic activity of interpeduncular nucleus GABAergic neurons controls expression of nicotine withdrawal.

Authors: *P. KLENOWSKI, R. ZHAO-SHEA, T. G. FREELS, S. MOLAS, A. R. TAPPER; Deparment of Neurobiology, Brudnick Neuropsychiatric Res. Inst., Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: A critical brain area implicated in nicotine dependence is the interpeduncular nucleus (IPN) located in the ventral midbrain and consisting primarily of GABAergic neurons. Previous studies indicate that IPN GABAergic neurons contribute to expression of somatic symptoms of nicotine withdrawal, however, whether IPN neurons are dynamically regulated during withdrawal in-vivo and how this may contribute to *both* somatic and affective withdrawal behavior is unknown. To bridge this gap in knowledge, we expressed GCaMP in IPN GABAergic neurons and used in-vivo fiber photometry to record changes in fluorescence, as a proxy for neuronal activity, in male mice during nicotine withdrawal. Mecamylamine-precipitated withdrawal significantly increased activity of IPN GABAergic neurons in nicotine-dependent, but not nicotine-naïve mice. Analysis of GCaMP signals time-locked with somatic symptoms including grooming and scratching revealed reduced IPN GABAergic activity during these behaviors, specifically in mice undergoing withdrawal. In the elevated plus maze, used to measure anxiety-like behavior, an affective withdrawal symptom, IPN GABAergic neuron activity was increased during open-arm versus closed-arm exploration in nicotine withdrawn, but not non-withdrawn mice. Optogenetic silencing IPN GABAergic neurons during withdrawal significantly reduced withdrawal-induced increases in somatic behavior and increased open-arm exploration. Together, our data indicate that IPN GABAergic neurons are dynamically regulated during nicotine withdrawal, leading to increased anxiety-like symptoms and somatic behavior, which inherently decrease IPN GABAergic neuron activity as a de-arousal mechanism. These results provide a neuronal basis underlying the role of the IPN in the expression of somatic and affective behaviors of nicotine withdrawal.

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Adolescent nicotine hystory does not worsen schizophrenia-like symptoms evoked ky a phencyclidine-induced mice model

Authors: *A. DUTRA-TAVARES, *K. SEMEÃO, *J. MAIA, *L. COUTO, *A. MANHAES, *Y. ABREU-VILLAÇA;
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Abstract: The first symptoms of schizophrenia (SCHZ) are usually observed during adolescence, a developmental period during which first exposure to psychoactive drugs also occurs. These epidemiological findings point to adolescence as critical for nicotine addiction and SCHZ comorbidity. However it is not clear whether exposure to nicotine during this period has a detrimental impact on the development of SCHZ symptoms since there is a lack of studies that investigate the interactions between these conditions during this period of development. To elucidate the impact of a short course of nicotine exposure across the spectrum of SCHZ-like symptoms, we used a phencyclidine-induced adolescent mice model of SCHZ (2.5mg/Kg, s.c., daily, postnatal day (PN) 38-PN52; 10mg/Kg on PN53), combined with an established model of nicotine minipump infusions (24mg/Kg/day, PN37-44) (PCP-NIC). Additional groups include CT (saline minipumps with injections), PCP (saline minipumps with PCP injections) and NIC (nicotine minipumps with saline injections). Behavioral assessment began 4 days after the end of nicotine exposure (PN48) using the following tests: open field to assess the hyperlocomotion phenotype; novel object recognition, a declarative memory task; three-chamber sociability, to verify social interaction and prepulse inhibition, a measure of sensorimotor gating. In open field, a progressive increase in locomotion was observed (rANOVA: Day × Phencyclidine × Nicotine - $F_{2,204} = 2.9$, $p = 0.056$). This increase was identified in PCP group from day 1 to day 2 ($p = 0.039$) and from day 1 to day 3 ($p = 0.015$). Nicotine history reduced the magnitude of phencyclidine-evoked hyperlocomotion and impeded the development of locomotor sensitization. Phencyclidine-treated male mice (PCP and PCP-NIC) (uANOVA: Phencyclidine - $F_{1,53} = 6.0$, $p = 0.017$) presented a smaller preference for the new object when compared to non-treated ones (CT and NIC). Phencyclidine treatment (Phencyclidine x Nicotine - $F_{1,90} = 6.1$, $p = 0.015$) increased the latency for the first entry into the social side (PCP > CT, $p = 0.003$; PCP > NIC, $p = 0.002$, FPLSD), while nicotine history mitigated this effect (PCP > PCP-NIC, $p = 0.001$, FPLSD). Deficient PPI response was revealed in phencyclidine-treated mice (PCP and PCP-NIC) when compared to non-treated ones (CT and NIC) to the higher Pp level (80 dB) (uANOVA: Phencyclidine - $F_{1,102} = 8.2$, $p = 0.005$). In conclusion, our results show for the first time that nicotine history, restricted to a short period during adolescence, does not worsen SCHZ-like symptoms evoked by a phencyclidine-induced mice model.

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Poster

P769. Attentional Networks I

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Program #/Poster #: P769.01

Topic: H.01. Attention

Support: NIH/NINDS R01NS023945
NIH/NINDS RF123945-28

Title: Connectome of the basal forebrain cholinergic system in rat

Authors: *L. ZABORSZKY[1], P. GOMBKOTO[2], *C. CHAVEZ[1], P. VARSANYI[3];
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Abstract: Cholinergic neurons of the basal forebrain (BF) project to the entire cortex. Although this system was described initially as part of the diffuse cortical projection system, recent studies suggest that cholinergic projection to the cortex is not diffuse, but organized into segregated or overlapping pools of projection neurons. The extent of overlap between BF populations depends on the degree of connectivity between cortical targets of these projection populations (Zaborszky et al., 2015). The cortical target-specific groups of cholinergic neurons receive specific combination inputs (Gielow and Zaborszky, 2017). In order to analyze connectional data from different animals, we developed a pipeline for spatial registration of vectorial and image data. In more than 70 rat brains, that received pairwise conventional retrograde (FB and FG) or virus tracer injections in cortex, cholinergic neurons in the BF were mapped with the Neurolucida^{R} system. After mapping fluorescently labeled cells from 200 µm series, sections were restained with Nissl and images of sections were aligned to the existing maps. We implemented a Postgres schema to store vectorial cell data, delineations and images. This solution provided with a complete set of functions for analyzing cell densities, determining spatial relationships, and manipulating delineations. We implemented all the scripts for data visualization around the QGIS framework. This framework provides with very fast and smooth visualization of high-resolution images as well as vectorial data. We created a reference brain from a full series of 50 micron sections of a single brain, in which all cholinergic cells were mapped irrespective of their targets and then sections were stained for Nissl. These sections were imaged with 3 micron/pixel resolution and aligned in 3D. The software (Java, ImageJ) is able to slice this high resolution 3D stack of images in any plane to match sections from the experimental brains. The spatial registration of experimental sections to the reference brain is carried out using mixed rigid body, affine and B-Spline based elastic transformations. For each reference cell within its environment, we will be able to assess the probability of projection to each cytoarchitectonically defined cortical target ("context vector"). By assigning this context vector to each reference cell, we will use unsupervised methods such as K-means and hierarchical clustering to classify BF cells according to their projection probability to cortical areas. This connectome model, that captures the organizational principles of the basalo-cortical network, will facilitate the understanding the function of this network.

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Poster

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Topic: H.01. Attention

Title: Network Configurations Underlying External Versus Internal Attention

Authors: *P. LI[1], Y. WANG[2], N. B. TURK-BROWNE[3,4], B. HUTCHINSON[1];
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Abstract: Attention is critical for nearly every cognitive operation, with a fundamental distinction between attending to sensory (external) versus self-generated (internal) information. This distinction has manifested in a debate about the relationship between selective visuospatial attention and episodic remembering, and whether these processes share a common neural substrate. Exploring the neural bases of visuospatial attention and episodic remembering is difficult because they rely on coordinated activity distributed across the entire human brain. However, recent studies have shown that whole-brain functional connectivity can reliably capture attentional states, raising the possibility that similar techniques might reveal differences in large-scale brain networks across external and internal attention. In the current study, participants (N = 24) performed tasks that required attending to information that was either sensory (external) or mnemonic (internal), with the experimental conditions otherwise matched in terms of visual content and task difficulty. We then leveraged a data-driven technique known as full correlation matrix analysis (FCMA) to examine (i) whether whole-brain connectivity patterns differ systematically across external and internal attention and (ii) which connectivity patterns across brain regions characterize such differences. For the first goal, FCMA showed that patterns of background connectivity could be used to reliably decode external versus internal attention (77% accuracy). For the second goal, this approach revealed 16 regions of interest falling within the default mode network (DMN), task positive network (TPN) and retrosplenial cortex (RSC) whose connectivity configurations characterized the two attentional states. Specifically, connectivity within TPN and within DMN was significantly greater during external and internal attention, respectively, while RSC regions coupled flexibly with TPN/DMN depending on the task. Complementary representational similarity analyses suggested that RSC further differentiated external from internal attention based on its task-evoked pattern of activity. Together, these results suggest that the network configuration of DMN, TPN, and RSC indicate how attention is being directed outwards or inwards.

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Poster

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Topic: H.01. Attention

Support: DFG Grant AL2408/1-1

Title: High-amplitude co-fluctuations drive connectivity of intrinsic neural oscillations and underlie auditory attentional control

Authors: *M. ALAVASH[1], M. WÖSTMANN[2], J. OBLESER[2];
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Abstract: Recent advances in network neuroscience suggest that human resting state functional connectivity is driven by bursts of high-amplitude co-fluctuations of hemodynamic responses measured using fMRI (Faskowitz et al., 2020). We here build on these new insights and ask (1) whether connectivity of intrinsic neural oscillations manifests high-amplitude co-fluctuations as such, and (2) whether and how these connectivity events unfold during the deployment of auditory selective attention? We reanalyzed two recently published EEG data sets of resting state (N = 154; Alavash, Tune, Obleser, 2021) and an auditory attention task (N = 33; Wöstmann, Alavash, Obleser, 2019), respectively. During the task, an auditory spatial cue was presented to the participants asking them to attend to one of two concurrent tone streams and judge the pitch difference (increase/decrease) in the target stream. We source-localized EEG, and following leakage correction, measured time-resolved power-envelope correlations across the entire cortex within alpha and beta frequency ranges. Specifically, per time point (50-ms resolution) we calculated the product of power-envelopes across all node pairs. Next, to capture co-fluctuations around the mean, timeseries of products were z-scored. Finally, per time point we calculated the standard deviation of z-scored products across the entire cortex. Accordingly, we obtained a timeseries of standard deviations per individual during rest or the auditory task. Connectivity events were defined as time points during which the standard deviation exceeded its 95th percentile. In line with recent fMRI work, alpha and beta connectivity derived from high-amplitude co-fluctuations showed higher similarity with static connectivity as compared to low-amplitude co-fluctuations (paired permutation test; alpha: $t = 9.1$, $p < 0.01$; beta: $t = 6.8$, $p < 0.01$). Similar results were found during the auditory task (alpha: $t = 15.6$, $p < 0.01$; beta: $t= 20.8$, $p < 0.01$). In addition, cortical maps of the alpha and beta connectivity events overlapped with posterior and frontoparietal connections, respectively. Importantly, during the auditory attention task, beta connectivity events occurred often during processing of the spatial cue, while alpha connectivity events occurred during processing of the tone streams. Our results suggest that high-amplitude power-envelope co-fluctuations drive connectivity of alpha and beta oscillations. Critically, these connectivity events appear to underlie ongoing deployment of auditory selective attention in a functionally distinct manner, that is, anticipation of stimuli versus selective processing of them.
1

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Poster

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Topic: H.01. Attention

Support: NIH Grant MH108591
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Title: A brain-based universal measure of attention

Authors: *K. YOO[1], M. D. ROSENBERG[3], Y. KWON[1], Q. LIN[1], E. W. AVERY[1], D. SCHEINOST[1], R. T. CONSTABLE[2], M. M. CHUN[1];
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Abstract: Attention has a ubiquitous role in perception and cognition [1]. Attentiveness explains behavioral performance fluctuations both within and across individuals [2], and attention deficits are common in mental illness and symptomatic of brain damage [3]. Despite this central importance, there is no singular way to measure a person's overall attentional functioning across tasks. The fact that there are so many different attention tasks suggests that attention is not a unitary construct but rather multifaceted [1]. Therefore, it is important to understand what is common and what is unique among the different attention tasks and to predict them with minimal testing.
To develop a universal measure that integrates a common component of attention, we analyzed original data from 92 participants performing three different attention-demanding tasks - gradual-onset continuous performance task (gradCPT) [4], multiple object tracking (MOT), and visual short-term memory (VSTM) - during fMRI. We first constructed a suite of whole-brain network models that significantly predict a profile of multiple attentional components (sustained attention, divided attention and tracking, and working memory capacity) from task- or rest-based connectomes of novel individuals. We leveraged the network models to probe brain systems that support common and separable factors of attention functions across individuals. Multiple brain regions across the salience, subcortical, and frontoparietal networks drove accurate predictions, supporting a general attention factor across tasks, which is distinguishable from task-specific ones.
Furthermore, connectome-to-connectome transformation modeling [5], a novel approach for generating an individual's task-related connectomes from their resting-state connectome alone, substantially improved the predictive power of resting-state fMRI for attention function.
Finally, we built a new universal attention measure by combining the connectome transformation and general attention factor models. The universal attention model showed superior generalization to various attention measures across four independent datasets (total $N = 495$), including two local datasets [6, 7] and two open databases (ADHD-200 consortium [8] and Human Connectome Project [9]), suggesting the broad utility of our model for both research and clinical applications in diverse settings.
References
[1] Chun et al., 2011.
[2] Weissman et al., 2006.
[3] Biederman et al., 1991.
[4] Esterman et al., 2013.
[5] Yoo et al., 2020.
[6] Rosenberg et al., 2016.
[7] Rosenberg et al., 2018.
[8] Consortium, 2012.
[9] Van Essen et al., 2013.

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Poster

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Topic: H.01. Attention

Support: National Science Foundation 2043740

Title: Tracking the dynamics of neural synchrony with time-resolved inter-subject correlation

Authors: *T. CHAMBERLAIN[1], A. L. CORRIVEAU[3], H. SONG[1], M. D. ROSENBERG[2];
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Abstract: Recent work has demonstrated the utility of decomposing functional connectivity into its time-resolved parts to study the contribution of moment-to-moment activity fluctuations (Esfahlani et al., 2020). Here, we extend this work to ask if the same method of "temporally unravelling" Pearson correlation can be used to calculate a TR-by-TR estimate of intersubject correlation (ISC). Compared to traditional dynamic ISC approaches, this method would be less computationally intensive, eliminate the need for extra parameters such as window size, and provide a more fine-grained estimate of changes in ISC over time.

We analyzed data from 575 6-21-year-olds from the Healthy Brain Network dataset. Functional MRI data were collected as participants watched a 3-min and a 10-min film clip (Clip 1, Clip 2). To track moment-to-moment changes in neural synchrony across participants, we computed a novel form of dynamic ISC, time-resolved ISC (trISC). Specifically, we performed element-wise multiplication of each z-scored time series in a given node with that of the group average, resulting in a trISC time course for each participant, node, and movie clip.

Validating trISC as a measure of changes in stimulus-driven brain activity, we observed significantly higher trISC for participants watching the same movie than different movies in 98% of nodes in the 268-node atlas. Of the nodes where this difference was greatest, there were significantly more nodes in high-level visual regions than expected by chance.

We next asked whether participants showed greater trISC doing more engaging movie moments as demonstrated in recent work relating sliding-window dynamic ISC to narrative engagement (Song et al., 2020). Because we did not have an in-scanner measure of participants' attention to the movies, we collected engagement ratings in an independent online sample (n = 20). To validate these ratings, we used eye-tracking data collected as a subset of participants in the HBN sample watched Clip 1 and 3 min of Clip 2 during EEG. Changes in gaze standard deviation were negatively correlated with the independent engagement ratings for both clips, indicating greater gaze synchrony during more engaging movie moments. Finally, we found that trISC scaled with engagement across individuals, such that participants showed greater neural synchrony during more engaging moments in 12 nodes for Clip 1 and 32 nodes for Clip 2. In contrast, replicating past work, lower neural synchrony during engaging moments was only observed in 3 and 1 nodes, respectively. Ultimately this study offers proof of concept for a novel form of dynamic ISC which allows time-resolved tracking of neural synchrony across individuals.

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Poster

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Topic: H.01. Attention

Support: NIMH Grant MH117991

Title: Neural Mechanisms of Attentional Control Modulates Task Performance in Deep Neural Networks

Authors: *S. DAS[1], G. R. MANGUN[1], M. DING[2];
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Abstract: Feature-based attention modulates neural activity in the sensory cortex to enhance the processing of task-relevant stimuli and suppress task-irrelevant stimuli. The feature similarity gain model of attention proposes that feature-based attention modulates neural activity according to the neuron's tuning property. We tested the idea in a deep neural network (DNN) model of the ventral visual pathway. Transfer learning was applied to fine-tune VGG16 pretrained separately on two different datasets (ImageNet and VGGFace) to enable the DNN to classify images from 4 object categories: (1) male and female faces in the face categories, and (2) natural and manmade scenes in the scene categories. The images used in the test set though belonging to these 4 categories, were neither part of nor belonged to any category in the pretraining datasets. The task for the network was to detect the presence of a certain object category. Performance of 91% was achieved. When tested on compound or merged images (images from two different categories were superimposed), however, the network's performance fell to chance level. Attention mechanisms were then introduced to enhance performance. Tuning curves were estimated for artificial neurons. Both multiplicative and additive modulations were applied according to the neuron's response preference. Attention increased network performance by 15% ± 10% across specific categories. The network responded to attention only when the category belonged to its repertoire, i.e., the network pretrained on ImageNet only responded to the scene categories. Similarly, the task performance of the network pretrained on VGGFace only improved when tested on the face categories. Thus, by using images and labels which are not a part of the database on which the model is pretrained, we explore how attention is generalizable to modulate the performance of a deep neural network based on its pretraining or prior expertise. These results demonstrate that DNNs (1) provide a fruitful testing bed for attention mechanisms and (2) the attention mechanisms are heavily dependent upon the pretraining of the network model, (3) may yield predictions that can be further tested in experimental studies.

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Poster

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Program #/Poster #: P769.07

Topic: H.01. Attention

Support: NIH Grant MH117991

Title: Frontoparietal Control of Willed Attention

Authors: *Q. YANG[1], S. MEYYAPPAN[1], J. J. BENGSON[2], G. R. MANGUN[3], M. DING[1];
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Abstract: Cueing paradigms are commonly used to study the neural mechanisms of visual spatial attention control. In these paradigms, each trial starts with an external cue, which instructs the subject to pay covert attention to a spatial location in order to process an impending stimulus. Neuroimaging studies have consistently shown that the dorsal attention network (DAN) is activated following the cue. Recent work has introduced a new form of cueing which asks the subject to spontaneously decide which spatial location to attend (willed attention). We examined the neural substrate of willed attention control by analyzing fMRI data recorded at two institutions (UF and UC Davis) using the same willed attention paradigm. In addition to instructional cues, a choice cue was included, which prompted the subject to choose the side of the visual field to attend. Applying the general linear model we found that both instructional cues and choice cues activated the DAN. Choice cues additionally activated frontoparietal regions including the dorsal anterior cingulate cortex (dACC), anterior insula (AI), dorsal lateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL). An MVPA analysis showed that for neural activity evoked by choice cues, decoding accuracy in these frontoparietal regions was significantly above chance level, whereas for instructional cues, decoding accuracy was at chance level. These results, consistent across the two datasets, suggest that willed visual spatial attention is controlled by three major brain networks: the salience network (dACC and AI), the central executive network (DLPFC and IPL), and the DAN.

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Poster

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Program #/Poster #: P769.08

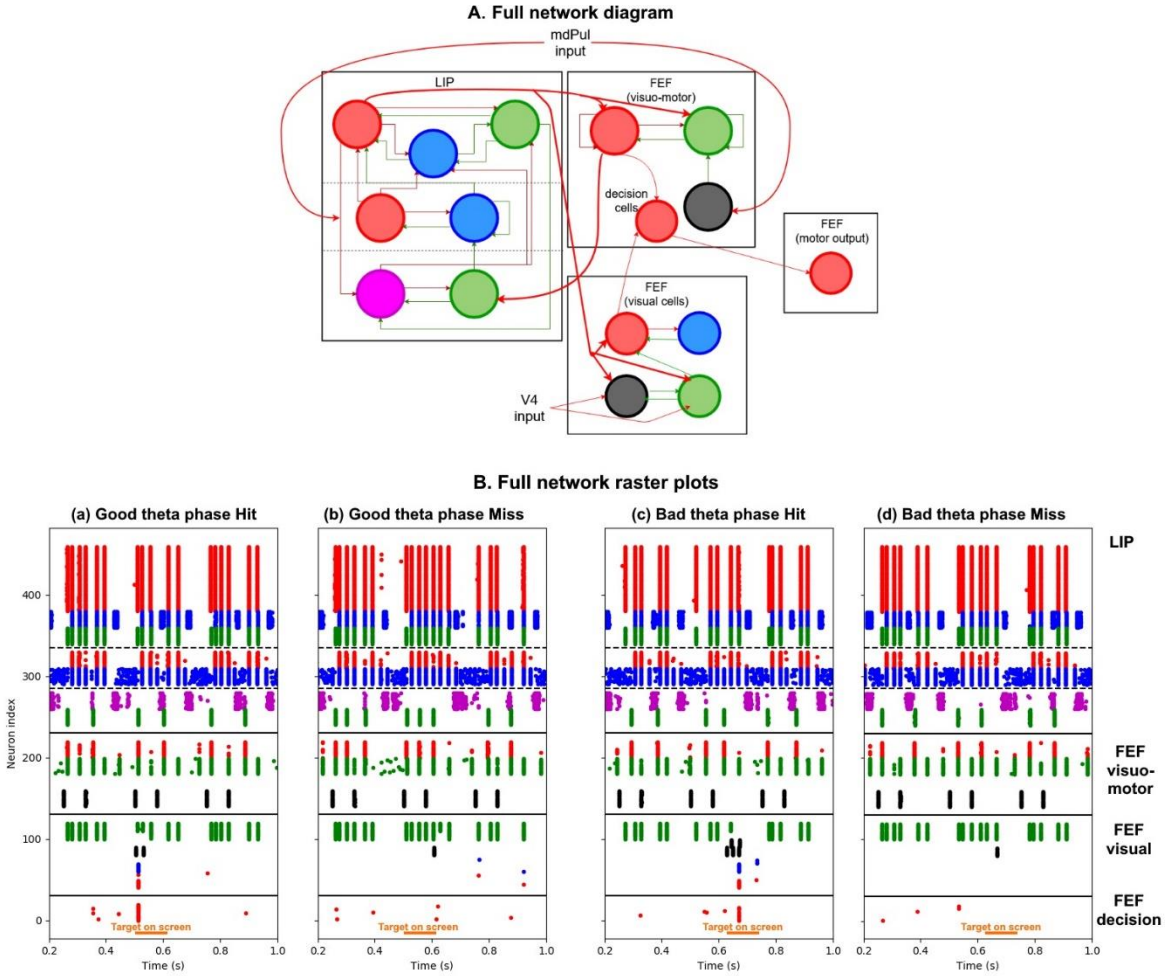
Topic: H.01. Attention

Support: NIH Grant P50-MH109429

Title: Interacting rhythms enhance sensitivity of target detection in a fronto-parietal computational model of visual attention

Authors: A. AUSSEL[1], I. C. FIEBELKORN[3], S. KASTNER[3], *N. KOPELL[2], B. R. PITTMAN-POLLETTA[1];
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Abstract: Even during sustained attention, the enhanced processing of attended stimuli waxes and wanes rhythmically. Humans and non-human primates performing a sustained visual attention task exhibit periods of enhanced and relatively diminished visual processing and target detection. These periods of enhanced and diminished visual processing alternate in both time (at 4 or 8 Hz, depending on the prior appearance of a statistically informative cue) and space (between cued and uncued locations). These alternating attentional states occur alongside alternating dynamical states, in which a spatial attention network including lateral intraparietal cortex (LIP), the frontal eye field (FEF), and the mediodorsal pulvinar exhibits different patterns of rhythmic activity and functional connectivity at α;, β;, and γ; frequencies - rhythms associated with visual processing, working memory, and motor suppression. To assess whether and how these multiple interacting rhythms contribute to periodicity in attention, we constructed a biophysically-detailed computational model of this attention network consisting of multiple functional modules. Our model reproduced the rhythmic dynamics and behavioral consequences of observed attentional states, and suggested a novel dynamical mechanism for the switch from a 4 to 8 Hz rhythm in hit rates after cue appearance. *In silico* manipulations demonstrated that the frequencies and mechanisms of experimentally observed rhythms optimize sensitivity in visual target detection while maintaining functional flexibility. The model illuminates how multiple functional modules, each exhibiting oscillatory dynamics arising from distinct mechanisms, both compete and collaborate to allocate attentional resources in a variety of conditions.



Disclosures: A. Aussel: None. **I.C. Fiebelkorn:** None. **S. Kastner:** None. **N. Kopell:** None. **B.R. Pittman-Polletta:** None.

Poster

P769. Attentional Networks I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P769.09

Topic: H.01. Attention

Support: NSERC Discovery
Brain Repair Centre Knowledge Translation
Nova Scotia Health Research Foundation Catalyst
Mitacs Accelerate
Mitacs Globalink

Title: Assessing the efficacy of the brain's networks of attention: Evolution of the Attention Network Tests, a database of their findings and a more engaging version

Authors: *R. M. KLEIN[1], S. ARORA[1], R. ALMEIDA[2], C. R. MCCORMICK[1], N. D. MCDONALD[1]; [1]Dalhousie Univ., Halifax, NS, Canada; [2]Univ. Federal Fluminense, Rio de Janeiro, Brazil

Abstract: Developments in attention research have produced a number of methodologies for assessment. One such tool, the Attention Network Test (ANT), measures the efficacy of three networks of attention (alerting, orienting and executive control) as described ~30 years ago by Posner & Petersen. The ANT (developed 20 years ago) and its many variants will be featured in this presentation. We have developed an open-access website repository called the ANT Database (http://attentionnetwork.ca/) which allows users to retrieve the findings from the roughly 900 studies that, to date, have used any version of the ANT to answer any question. We will exemplify the use of this resource by describing how it has been used to generate a number of quantitative meta-analyses on such topics as development, ADHD, cross-cultural differences, bilingual differences, depression, anxiety, autism spectrum disorder, and how it provided the basis for a review of lifestyle influences on attention. We will discuss the particular benefits of some of the different ANT variants, with an emphasis on the AttentionTrip (first described at the 2013 meeting of the SFN), a game-like task that increases engagement and is now accessible to participants on a portable iPad. Since its development we have validated its use with younger adults, adults with autism, and child participants. More recent experiments have aimed at exploring its applicability with older adults, and how to generate more robust executive network scores that are similar to the original ANT. For situations that might encourage, and for participants who might experience, boredom, the demonstrated engagement advantage of AttentionTrip might make it the ANT of choice.

Disclosures: R.M. Klein: None. **S. Arora:** None. **R. Almeida:** None. **C.R. McCormick:** None. **N.D. McDonald:** None.

Poster

P769. Attentional Networks I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P769.10

Topic: H.03. Decision Making

Support: Human Frontiers Research Grant to JG, RGP0018/2016

Title: The neural coordination of attention and decisions

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Abstract: To make adaptive decisions in natural environments, we must not only commit to an action but must also determine which information to gather to best guide those actions. Because the amount of information available in natural environments far exceeds our processing capacity, we must select which information to rely on for guiding our actions. However, most studies of selective attention have highly constrained situations where participants are instructed where to attend. This approach is not suitable for probing natural attentional control, and an open question is how the brain determines attentional priority of task-relevant information. Our hypothesis is that priority is defined by the information gains that a sensory discrimination is expected to bring. Our approach rests on the premise that attention should optimally conform to Bayesian rules of inference under uncertainty. According to Bayesian logic, to update posterior beliefs, prior beliefs and new information are combined in proportion of their reliability. Thus, the priority of a stimulus should increase with its predictive validity (%V) and prior uncertainty. We used a novel task that combines probabilistic inference with an attention manipulation. Participants inferred a hidden state (a jar containing upright and inverted letters), after seeing two letters -that could differ in their %V- sequentially drawn from the jar. To manipulate attention, we flashed the 2nd letter in the periphery, and we measured perceptual sensitivity. Consistent with a Bayesian strategy, participants prioritize second letters with high %V over low %V, and this bias is enhanced by prior uncertainty. Uncertainty and predictive validity also influenced the decision weight in the final jar decision. The influences of %V and uncertainty on attention can be dissociated from other factors, including reward expectation, pupil size and the decision weight in the final jar decision. We will use this task in combination with fMRI to determine how %V and uncertainty are integrated within the executive network. We expect that the frontal eye field and intraparietal sulcus -areas computing attentional priority- will encode attentional biases based on %V, and this bias will be modulated by areas encoding decision uncertainty. Overall, our results suggest that expected information gains modulate top-down attentional control, and provide empirical evidence about the coordination of attention and decisions.

Disclosures: F.J. Domínguez-Zamora: None. **J.J. Geng:** None. **J.P. Gottlieb:** None.

Poster

P769. Attentional Networks I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P769.11

Topic: H.01. Attention

Support: ERC-CoG-2014-646696

Title: 18-months stability of neural auditory-attentional filters and listening behaviour in a large longitudinal sample

Authors: *S. TUNE[1,2], M. ALAVASH[1,2], J. OBLESER[1,2];
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Abstract: Successful listening is thought to depend on forms of neural filter strategies that separate relevant from irrelevant information. In a recent EEG study (Tune et al., in press), using a challenging spatial-attention listening task, we probed how two prominent auditory filtering strategies relate to listening success; namely the lateralization of auditory alpha power versus the alignment of slow auditory cortical responses to speech input ('speech tracking'). In a large longitudinal cohort of healthy aging adults, at T1 (N = 155, 38-80 yrs, median = 61 yrs), stronger speech tracking (estimated as reconstruction accuracy of speech envelopes) at the state-(within-participant)-level and at the trait-(between-participants)-level predicted better behavioral performance while alpha lateralization did not. These findings provide compelling evidence for speech tracking as a neural marker of individual, trial-specific listening success.
Yet, the reliability of both trait-level auditory filter strength and the link of auditory filter state to single-trial listening behavior is currently unknown. Here, we address these questions in a subsample who underwent measurements again after ~1.5 years (T2; N = 100, median = 63 yrs, 42-82 yrs).
First, we asked whether trait-level strength of speech tracking or alpha lateralization at T1 would be predictive of its respective strengths at T2 while accounting for potentially modulating influences of age or hearing acuity. Unexpectedly, the individual average strength of each neural filter was largely uncorrelated from T1 to T2, that is, neither one poses a reliable neural trait measure (tracking: $\beta = .12$, SE = .10, p =.23; alpha: $\beta = .13$, SE = .10, p =.20).
Next, we scrutinized the previously observed beneficial effect of stronger state-level speech tracking on trial-wise behavior within the T2 sample. Here, lending credibility to the functional relevance of speech tracking as neural measure of attentional state, we replicated the effect of speech tracking state on accuracy in both its size and direction (OR = 1.09, SE = .03, p =.013). The stability of this singe-trial brain-behavior relationship provides important support for the role of speech tracking as individualized neural marker of listening success.
In sum, our results underscore the functional importance of state-level neural variability for behavior while calling into question the robustness of trait-level characterization of neural-attentional filters.

Disclosures: S. Tune: None. **M. Alavash:** None. **J. Obleser:** None.

Poster

P830. Episodic and Episodic-Like Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P830.01

Topic: H.07. Long-Term Memory

Support: Spanish Government grant BES-2017-079829
ICREA Academia, PID2019-111199GB-I00

Title: Post-encoding hippocampal theta phase-coupled high frequency activity reinstatement to support episodic memory formation in humans

Authors: *L. SAINT AMOUR DI CHANAZ[1,2], X. WU[1,2], K. LEHONGRE[3], C. ADAM[4], V. NAVARRO[4], V. LAMBRECQ[4], M. CARREÑO MARTINEZ[5], E. CONDE[5], P. ROLDAN[5], A. VALERO CABRE[6], A. PÉREZ-BELLIDO[1], L. FUENTEMILLA[1,7,2,8];
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Abstract: Computational models and animal studies suggest that ongoing hippocampal theta rhythm coordinates high frequency activity (HFA) to support memory encoding and retrieval. Here, we show evidence of similar theta phase coding regime in humans during offline periods immediately following episodic encoding. We analyzed hippocampal activity from intracranial electroencephalography (iEEG) recordings from epilepsy patients who encoded unique picture sequences depicting life-like episodes followed by a 2sec offline period. Memory for these episodes were tested immediately after the encoding task and after 24hrs. We found that hippocampal patterns of HFA (30-12Hz) elicited during picture encoding were reinstated at the offset period and the degree of HFA reinstatement predicted memory recollection for the episode in the delayed test (i.e., at 24hrs). We also found that hippocampal HFA coupled specific theta (6-9Hz) phase states during picture encoding and at the offset period. Critically, episodic offset hippocampal HFA coupled to opposed theta phase states as a function of whether episodes would be later recollected or forgotten in the delayed memory test. Our findings provide important evidence of the hippocampal mechanisms that support memory formation during offset periods immediately following episodic encoding.

Disclosures: L. Saint Amour di Chanaz: None. **X. Wu:** None. **K. Lehongre:** None. **C. Adam:** None. **V. Navarro:** None. **V. Lambrecq:** None. **M. Carreño Martinez:** None. **E. Conde:** None. **P. Roldan:** None. **A. Valero Cabre:** None. **A. Pérez-Bellido:** None. **L. Fuentemilla:** None.

Poster

P830. Episodic and Episodic-Like Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P830.02

Topic: H.07. Long-Term Memory

Support: NIH Grant NS076856

Title: Partially overlapping spatial environments trigger reinstatement in the human hippocampus and schema-like representations in the prefrontal cortex

Authors: *L. ZHENG[1], Z. GAO[2], A. MCAVAN[1], E. ISHAM[1], A. D. EKSTROM[1];
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Abstract: When asked to think about a city that we have visited, we typically retrieve not only places directly related to finding our goal within that city but also retrieve other locations within this city incidentally, a phenomenon termed "holistic" retrieval. Yet, the neural mechanisms underlying such holistic retrieval in spatial memory remains unsolved, particularly for multiple spatial environments that share common elements. Here, we asked 27 human participants to learn three partially overlapping virtual reality environments and retrieve the details of each environment while undergoing high-resolution functional magnetic resonance imaging (fMRI). The novel functional sequences we employed permitted imaging of the hippocampal subfields but also coverage of the whole brain, including the prefrontal cortex, allowing us to test hypotheses about both hippocampal and cortical contributions to spatial memory. Using multivariate pattern analysis, we found that the unique landmarks of an environment were reinstated "incidentally" in the hippocampus, even when they were not presented in the retrieval probe. This finding therefore provides empirical evidence for "holistic retrieval" of spatial memory. In addition, for stores that were shared between cities, we found evidence for pattern separation (representational orthogonalization) in hippocampal subfield CA23/DG and "repulsion" in CA1: differentiation beyond orthogonalization. This finding therefore suggests a possible neural mechanism for how common elements across different environments might be accessed. Furthermore, we found evidence for representation of the common spatial layout across the three environments in medial prefrontal cortex, suggestive of "schema" like representations that may contribute to learning of the spatial structure across the three environments. Finally, we also found evidence for unique environmental codes within hippocampal subfields, consistent with our past work identifying specific neural codes for spatial environments within the hippocampus. Taken together, our findings therefore provide a novel framework for how unique and common elements of multiple spatial environments are accessed computationally within the human brain and implicate specific roles for hippocampus and prefrontal cortex in such processes.

Disclosures: L. Zheng: None. **Z. Gao:** None. **A. McAvan:** None. **E. Isham:** None. **A.D. Ekstrom:** None.

Poster

P830. Episodic and Episodic-Like Memory I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P830.03

Topic: H.07. Long-Term Memory

Support: NIH U01NS103792
NIH U01NS117839
Brain Canada program

Title: Neurons detect cognitive boundaries to structure episodic memories in humans

Authors: *J. ZHENG[1], A. G. P. SCHJETNAN[2], M. YEBRA[3], B. GOMES[3], C. P. MOSHER[4], S. K. KALIA[5], T. A. VALIANTE[6], A. N. MAMELAK[7], G. KREIMAN[8], U. RUTISHAUSER[4];
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Abstract: While experience is continuous, memories are organized as discrete episodes ("events"). Cognitive boundaries are thought to segment experience and structure memory, but how this process is implemented remains unclear. To address this question, we investigated the neuronal mechanisms underlying the identification of cognitive boundaries in humans under semi-realistic continuous experience (i.e., video clips). We recorded single neuron activity (in total 985 neurons) from 20 drug-resistant epilepsy patients while subjects encoded and retrieved their memory of video clips embedded with different cognitive boundaries (soft boundaries: episodic transitions between related events; hard boundaries: episodic transitions between unrelated events from different movies). Behaviorally, both soft and hard boundaries enhanced recognition of video clip content that followed a boundary, whereas hard boundaries impaired memory of the temporal order between events. Single neurons in the medial temporal lobe signaled the presence of boundaries (either only hard boundaries n = 36, or both soft and hard boundaries, n = 42) with increased firing rates. The firing rate and spike phase (i.e., spike timing relative to the theta phase of local field potentials) of these boundary-responsive neurons during encoding predicted subjects' memory strength as assessed by scene recognition and temporal order discrimination accuracy, respectively. Moreover, boundary-induced neural state changes during encoding correlated with improved scene recognition memory and were anti-correlated with temporal order memory, suggesting a plausible neural mechanism for shaping episodic memories. Lastly, successful recognition correlated with the reinstatement of the neural state presented shortly after a boundary during retrieval. These findings reveal a neuronal substrate for detecting cognitive boundaries that transform experience into mnemonic episodes and structure mental time travel during retrieval.

Disclosures: J. Zheng: None. **A. G. P. Schjetnan:** None. **M. Yebra:** None. **C.P. Mosher:** None. **S.K. Kalia:** None. **T.A. Valiante:** None. **A.N. Mamelak:** None. **G. Kreiman:** None. **U. Rutishauser:** None.

Poster

P830. Episodic and Episodic-Like Memory I

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Program #/Poster #: P830.04

Topic: H.07. Long-Term Memory

Support: NIHM Grant R03MH116872

NIH T32 HL007901 (RB)

Title: The relationship between MTL functional brain activity at encoding and subsequent memory depends on post-encoding sleep quality during a daytime nap

Authors: *R. BOTTARY[1,2], P. THAKRAL[1], M. RITCHEY[1], E. KENSINGER[1];
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Abstract: Introduction: Brain state changes following emotional memory encoding can serve as "mnemonic filters", increasing the contingency of memory outcomes on encoding-related functional brain activity in medial temporal lobe (MTL) structures (Ritchey et al., 2017). Memory traces are replayed in the MTL during non-rapid eye movement (NREM) sleep, in turn strengthening communication between MTL and cortical structures during memory retrieval. However, it is unknown whether NREM sleep moderates the association between MTL activity during encoding and emotional memory retrieval success. The present study aimed to address this question.
Methods: 37 healthy, young adults successfully completed two fMRI scans separated by a nap opportunity. Pre-nap, participants viewed negative, neutral and positive images paired with sound clips and verbal labels. Participants' memory for these multisensory stimuli was tested post-nap. Encoding parameter estimates (stimulus > fixation) from two MTL structures (amygdala and hippocampus) were entered into a Memory (subsequently remembered, subsequently forgotten) x Valence (negative, neutral, positive) x Hemisphere (left, right) ANOVAS. Separate ANCOVAs covaried total sleep time (TST) and NREM sleep percentage (NREM%).
Results: No significant Memory main effect or interactions between Memory, Valence and Hemisphere were observed in the hippocampus or amygdala (all Fs < .60). In the hippocampus, Memory (remembered > forgotten) was significantly modulated by TST ($F[1,34] = 4.92$, $p = .033$) and NREM% ($F[1,34] = 6.01$, $p = .02$). We further observed a trending Valence x Memory x NREM% interaction ($F[2,68] = 2.82$, $p = .085$). In the amygdala, we observed a significant Memory x Hemisphere x TST interaction ($F[1,34] = 12.35$, $p = .001$), driven by greater right hemispheric activity for subsequently remembered items. We further observed marginal Memory x NREM% ($F[1,34] = 3.43$, $p = .073$) and Valence x Memory x Hemisphere x NREM% ($F[2,68] = 2.70$, $p = .077$) interactions, driven by subsequent memory activity for negative stimuli and the right hemisphere.
Conclusions: Our findings suggest that the relation between MTL activity during memory encoding and post-nap memory depends upon the quality of sleep in the nap. Sleep effects appear strongest for negative memory retrieval.

Disclosures: R. Bottary: None. **P. Thakral:** None. **M. Ritchey:** None. **E. Kensinger:** None.

Poster

P830. Episodic and Episodic-Like Memory I

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Program #/Poster #: P830.05

Topic: H.07. Long-Term Memory

Support: NIA Grant 2RF1AG039103

Title: Effects of Age on Item and Source Subsequent Memory Effects Identified with fMRI

Authors: *E. S. LIU[1], J. D. KOEN[2], J. T. MATTSON[3], M. D. RUGG[1];
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Abstract: Effects of Age on Item and Source Subsequent Memory Effects identified with fMRI
E. Song Liu, Joshua D. Koen, Julia T. Mattson, Michael D. Rugg
Age-related decline in episodic memory performance is attributed in part to ineffective encoding. In the present study, we examined the effects of age on the neural correlates of the encoding of item and source memories using an experimental procedure that minimized the potentially confounding effects of memory strength. We combined the data from two independent but closely similar experiments (total Ns = 45 younger and 52 older adults). The participants underwent fMRI while performing a study task requiring one of two judgments ('bigger or smaller than a shoebox' or 'found indoors or outdoors') on a series of images of common objects. On a subsequent surprise memory test administered outside of the scanner participants were required make an 'old/new' recognition judgment on each test object and, for any object judged old, to then judge the task it was associated with at study. Of importance, both judgments were made on a 5-point confidence scale, and only highly confident judgments were used to define, for the purposes of the fMRI analyses, correct source (CS; source plus item correct) and correct item (CI; source incorrect, item correct) judgments. A third class of events – item misses (IM) – was also included in the analyses. A 2 (experiment) x 2 (age group) x 3 (subsequent memory judgment) ANOVA on the fMRI data acquired at study was conducted to identify ROIs that were then subjected to further analysis. We identified 8 clusters where BOLD activity was greater for remembered than less well remembered or forgotten study items, and 7 clusters that demonstrated the reverse pattern. In general, age differences were subtle: subsequent memory effects (SMEs) tended to show a 'strongly' graded pattern (CS > CI > IM) in young, and 'weakly' graded pattern (CS > IM) in older adults. Notably, in bilateral hippocampus, subsequent memory effects (SMEs) did not differ according to age and were uniquely associated with successful source rather than item memory (CS > CI = IM). Moreover, the magnitude of hippocampal SMEs robustly predicted source memory performance in the older ($r = 0.422$, $p = 0.002$) adults. No such relationship was evident, however, in the young group ($r = 0.050$, $p = 0.743$). These findings suggest that, after controlling for item memory strength, age differences in SMEs are subtle, when they are evident at all, and do not extend to the hippocampus. Additionally, variation in hippocampal activity appears to play a more important role in mediating source memory performance in older than in young adults.

Disclosures: E.S. Liu: None. **J.D. Koen:** None. **J.T. Mattson:** None. **M.D. Rugg:** None.

Poster

P830. Episodic and Episodic-Like Memory I

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Program #/Poster #: P830.06

Topic: H.07. Long-Term Memory

Support: NIH Grant MH065635
The Dana Foundation

Title: Latent infantile memories influence new learning experiences in adulthood

Authors: *B. BESSIÈRES[1], L. SILENZI[1,2], C. M. ALBERINI[1];
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Abstract: Early life experiences are known to shape the development of the brain, resulting in lifelong consequences on adult cognitive functions and behavior. Paradoxically, the memories formed in infancy appear to be rapidly forgotten and the mechanistic bases by which they can influence adult learning remain to be identified. Using rodent models, we previously demonstrated that the apparently forgotten infantile memories are not actually lost. In fact, at later ages, and up to adulthood, they can be reinstated by certain reminders, implying that infant memories are stored long term in latent forms. Here we show that infant episodic learning influences adult behavior by forming stable memory traces or schemas, i.e., frameworks of acquired knowledge that affects the processing of new information. Mice exposed to contextual fear conditioning (CFC) in infancy can reinstate the memory in adulthood if they are presented with a low intensity footshock in the same context in which they received the CFC training; a protocol (known as saving) that by itself is unable to elicit any detectable memory. We also found that only infantile, but not adult CFC, facilitates a new CFC learning received in a distinct context in adulthood, indicating that during a developmental critical period, learning builds long lasting memory representations that later affect the processing of new information. By using state-of-the-art genetic tools to map and silence the cell networks activated by learning in infancy, we also found that the reactivation of the cell ensembles active during infantile learning is necessary for the return of memories in adulthood, as well as for facilitating a similar novel adult learning. These results led us to conclude that infantile learning builds long-lasting memory schemas that influence new learning experiences in adulthood.

Disclosures: B. Bessières: None. **L. Silenzi:** None. **C.M. Alberini:** None.

Poster

P830. Episodic and Episodic-Like Memory I

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Program #/Poster #: P830.07

Topic: H.07. Long-Term Memory

Support: Deutsche Forschungsgemeinschaft (SA-2146/6-1)

Title: A selective disengagement of CA3 for the retrieval of very remote memories: a fundamental principle of memory consolidation

Authors: *E. ATUCHA[1], C. FUERST[1], M. SAUVAGE[1,2];
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Abstract: The CA3 hippocampal subfield has been suggested to contribute to memory retrieval by supporting pattern completion, the completion of full memory representations based on detailed features

of these representations. However, detailed features degrade as memory ages raising the possibility that pattern completion/CA3 might not contribute to a decisive manner to the retrieval of very remote memories (20, 40 years-old memories in humans comparable to 6 month and 1 year-old memories in mice based on life expectancy). We have recently established that, unlike CA1 that is engaged in fear memory retrieval independently of the age of the memory (up to 1 year-old memories in mice), CA3's contribution is limited to the recall of recent and early remote memories (i.e. up 1 months old memories). In addition, we showed that parahippocampal areas (MEC, LEC, PER, POR) were optimally recruited upon the retrieval of the most remote memories as reported for the prefrontal cortex, also tightly connected to the hippocampus, in studies focusing on early remote memory retrieval (Lux et al, Elife, 2016; Atucha et al, Bioarchiv 2021). Here, we tested if the disengagement of CA3 overtime is a fundamental principle of memory consolidation by investigating if CA3 is also disengaged for the retrieval of memories devoid of fearful content. Very little is known about early remote and very remote memory retrieval of neutral events due to the difficulty of retaining neutral memories over delays greater than 1 month in rodents. Hence, we first optimized an object-in-place paradigm to allow for memory traces to persist up to 6 months after memory encoding and imaged activity during memory retrieval in CA1 and CA3, parahipppocampal areas and prefrontal cortex (ACC, IL, PL) with high resolution by detecting the RNA of the immediate early gene Arc. As observed with fear memories, we found that the contribution of CA3 was limited to the retrieval of recent (1 day, 1 week) and early remote (1 month) memories while CA1 was engaged independently of the age of the memory and received a maximal support from parahippocampal areas for the most remote memories (6 months-old). In addition, this latter activation matched that observed in the ACC, suggesting a comparable kinetic of recruitment of cortical areas connected to the hippocampus that play a role in memory. Altogether, our results bring further support to a new concept of memory consolidation according to which distinct MTL subnetworks support memory retrieval as memories age and underline the necessity for further investigations aiming at dissociating the qualitative contribution of the parahippocampal areas and ACC to memory retrieval overtime.

Disclosures: E. Atucha: None. **C. Fuerst:** None. **M. Sauvage:** None.

Poster

P830. Episodic and Episodic-Like Memory I

Location: Virtual Only

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Program #/Poster #: P830.08

Topic: H.07. Long-Term Memory

Support: NIH Grant MH104384

Title: Optogenetic stimulation of the basolateral amygdala after spatial Barnes maze training modulates recent versus remote memory in rats

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Abstract: How recent versus remote memories are consolidated and recalled is an extensively debated topic within the field of learning and memory, but it is well known that the basolateral amygdala (BLA) modulates many types of memories consolidated across multiple memory systems. Systems consolidation asserts that, over time, memories undergo neural reorganization becoming less dependent on the hippocampus and more dependent on neocortical networks, such as the mPFC. Recent work indicates that contextual fear memory traces for recent and remote retrieval are laid down at the time of training but in separate brain regions that are then responsible for the recall of those memories depending on the length of time since the original learning. This raises the possibility that the BLA modulates the consolidation of each trace in a dissociable manner. Although some prior work has examined roles for the BLA in recent vs. remote memory consolidation, such work used footshock-based training paradigms, which are confounded by the BLA being a potential storage site for these memories. Thus, it is not known how the BLA modulates a single non footshock-based memory expressed at different timepoints following learning. To address this question, male and female Sprague-Dawley rats received bilateral intra-BLA microinjections of an AAV with a CaMKIIα promoter to express the opsin ChR2(E123A), a depolarizing cation channel, and implantation of optical fibers aimed at the BLA. Rats then underwent 4 consecutive training trials on a spatial version of the Barnes maze, in which they had to use extramaze cues to find the escape port. Immediately following training, rats received 15 minutes of bursts of 40 Hz (473 nm, 5 ms pulse width, given for 2 seconds every 10 seconds) optical stimulation of BLA cell bodies. Retention tests occurred 2- and 30-days after training. Following testing, rats were euthanized, and histology was performed to verify virus and optical fiber placement. Initial results found no effect of such stimulation on retention at the 2-day (recent) timepoint. However, the results indicate decreased latency to locate the escape port and increased duration spent in the target quadrant of the maze at the 30-day (remote) timepoint, suggesting enhanced retention at the remote timepoint compared to control animals. Ongoing experiments are examining whether inhibiting the BLA immediately after training affects recent and remote retention. Nonetheless, these initial results suggest that the BLA is capable of dissociably modulating the consolidation of memories later expressed at recent vs. remote timepoints.

Disclosures: B. Glickman: None. **R.T. LaLumiere:** None.

Poster

P891. Cognitive Natural Aging: Neural Mechanisms II

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Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P891.01

Topic: H.12. Aging and Development

Support: NIH Grant R01AG050523 to T.A.P.

Title: Individual differences in Glutamate/Glutamine (Glx), but not GABA, predict behavioral performance in older and younger adults

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Abstract: Healthy aging is associated with changes in the neurochemical profile of the brain. Previous studies have demonstrated age-related reductions in both gamma-aminobutyric acid (GABA; the primary inhibitory neurotransmitter of the human brain), and glutamate (the most abundant metabolite and primary excitatory neurotransmitter). However, regional differences in metabolite changes and their impact on behavioral performance are not yet fully understood. In 58 young adults (aged 18 to 29 years) and 79 older adults (aged 65+), we used 3 Tesla Magnetic Resonance Spectroscopy (MRS) to quantify GABA and Glx (a composite measure of glutamate and glutamine) concentrations in three visual cortex voxels, two auditory cortex voxels, and two sensorimotor cortex voxels. Out of the scanner, participants completed an extensive behavioral battery, on which factor analysis was performed to extract summary measures quantifying performance in visual, auditory, tactile, and motor domains. We used these scores to investigate relationships between regional GABA and Glx concentrations and behavioral performance. Young adults demonstrated significantly higher GABA and Glx concentrations in multiple brain regions than older adults. In both young and older adults, both GABA and Glx concentrations correlated more strongly across hemispheres (e.g., left and right auditory cortex) than across different regions within hemisphere (e.g., left auditory and motor cortex). Finally, across the full participant sample and in each age group separately, regional Glx concentrations explained significant variability in associated factors underlying behavioral performance. Visual Glx concentrations best predicted higher-level visual performance, auditory Glx concentrations best predicted higher-level auditory performance, and sensorimotor Glx best predicted fine motor performance. This pattern was not observed for GABA concentrations. These findings demonstrate age-related alterations in multiple neurotransmitter systems across multiple brain regions and link regional Glx concentrations with associated behavioral performance.

Disclosures: M. Simmonite: None. **T.A. Polk:** None.

Poster

P891. Cognitive Natural Aging: Neural Mechanisms II

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Topic: H.12. Aging and Development

Support: NCT01472744

Title: Data-driven MRI analysis reveals fitness-related functional change in Default Mode Network following exercise intervention, which is associated with cognitive performance

Authors: *K. MCDONALD[1], T. MORRIS[1], S. ANTERAPER[2], M. VOSS[3], S. WHITFIELD-GABRIELI[1], K. ERICKSON[4], E. MCAULEY[5], A. KRAMER[1];
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Abstract: As the U.S. population grows older, more effective and predictive methods are needed to maintain and improve cognitive and brain health in later life. Previous research has indicated that cardiorespiratory fitness is structurally and functionally neuroprotective in healthy older adults, and may

delay the onset of neurodegenerative diseases such as Alzheimer's and vascular dementias. However, many questions remain with regard to the role of fitness on cognitive and brain health. Data were collected in the "Fit and Active Seniors Trial" from 2015-2018. One purpose of this study was to investigate whether baseline fitness was associated with change in functional brain connectivity during a six-month exercise intervention and to determine whether the magnitude of change in connectivity was related to post-intervention cognitive performance. Low active older adults (n=139) enrolled in and completed a 6-month exercise intervention and underwent neuropsychological testing, functional neuroimaging, and cardiorespiratory fitness testing before and after the intervention. Participants (60-80 years, 71.9% female) were randomized into one of four groups: Dance (n=40), Walk (n=28), Walk + nutritional supplement (n=31), or active control (i.e., stretch and tone; n=40). A data-driven multi-voxel pattern analysis was performed on resting-state functional MRI scans to determine whole-brain patterns of connectivity. The correlation between pre-intervention fitness in all groups ($\bar{x}$ = 19.72, $\sigma = \pm 4.55$) and connectivity change was significant in the precentral gyrus (voxel threshold $p < 0.001$, cluster threshold $p<0.05$, corrected for family-wise error), which was associated with the Somatosensory Network. Using the precentral gyrus as a seed, post-hoc analyses revealed that the connectivity pattern was derived from increased correlations in the Dorsal Attention Network and increased anti-correlations in the Default Mode Network (DMN). Increased anti-correlations between the precentral gyrus seed and the DMN were associated with improved post-intervention performance on fluid reasoning (p=0.02) and perceptual speed (p=0.03) tasks. The findings suggest that in a sample of low-active older adults, those with higher fitness at baseline were more likely to experience increased functional connectivity as a result of participating in less sedentary activity for six months, and the characterizations of the connectivity change was associated with components of cognition. These findings emphasize the need for older adults to maintain a physically active lifestyle that enhances cognitive and brain health.

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Poster

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Program #/Poster #: P891.03

Topic: H.12. Aging and Development

Support: National Institute on Aging Grant R01AG062590

Title: Segregation of functional brain networks confer network resilience and mediate relationships between network resilience and cognition

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Abstract: Functional brain networks must balance between segregation and integration to maintain the adaptive cognitive processing required for normal cognitive function. Associative functional brain networks, in particular, tend to be highly segregated from other brain networks, reflecting their

specialized roles in cognition. However, segregation of associative brain networks declines in late aging, which is typically viewed as a compensatory mechanism, and is associated with disruptions in cognitive abilities. In many complex systems, segregation of function between subcomponents within systems can enhance resilience of system function against perturbations, but it is currently unknown whether segregation similarly facilitates resilience within functional brain networks. Here we use a subset of the Human Connectome Project - Aging dataset (n=324, ages 60-90) to investigate the relationships between network resilience, functional segregation and cognition in aging individuals. We first reproduced earlier results, finding that the degree of whole brain segregation, quantified with the previously established segregation index, was correlated with cognitive performance in elderly subjects. Next, we simulated targeted attacks on functional brain networks, as a proxy for their resilience, and show that segregation in many functional networks underlies resilience against such attacks. Finally, we found that segregation in associative brain networks mediates an association between network resilience and cognition. Together these findings indicate segregation as a general network mechanism brain networks use to facilitate cognitive abilities, confer network resilience, and mediate relationships between network resilience and cognition.

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Poster

P891. Cognitive Natural Aging: Neural Mechanisms II

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Program #/Poster #: P891.04

Topic: H.12. Aging and Development

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P30AG019610

Title: Higher-order resting state network change after 3 months of cognitive training in healthy older adults

Authors: *C. HARDCASTLE[1], J. N. KRAFT[1], H. K. HAUSMAN[1], A. O'SHEA[1], A. ALBIZU[1], N. D. EVANGELISTA[1], E. BOUTZOUKAS[1], E. J. VAN ETTEN[2], P. K. BHARADWAJ[2], H. SONG[2], S. G. SMITH[2], E. PORGES[1], S. DEKOSKY[1], G. A. HISHAW[2], S. WU[1], M. MARSISKE[1], R. COHEN[1], G. E. ALEXANDER[2], A. J. WOODS[1];
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Abstract: Cognitive training shows promise in reducing dementia risk and mitigating cognitive decline in older adults, yet the functional neural correlates have not been explored. Resting state networks (RSN) are anatomically distinct brain areas that function together over time. The connectivity of the frontoparietal control network (FPCN), cingulo-opercular network (CON), dorsal attention network (DAN), and default mode network (DMN) are involved in inter-network modulation, executive functioning, attention, and

cognitive status in aging. Previous research suggests these RSNs may be associated with cognitive training. By identifying underlying brain networks associated with cognitive interventions, researchers could improve efficacy of cognitive training. This study examined RSN changes associated with 3 months of cognitive training in a sample of healthy older adults.58 healthy older adults (M age = 71.2, SD = 4.7) were recruited as part of a larger clinical trial through the University of Florida and the University of Arizona. Participants were randomized into a cognitive training (CT; n=30) or education control (ET; n=28) group. CT group underwent 40 hours of cognitive training on 4 attention/speed of processing and 4 working memory tasks over a span of 12-weeks. The ET group watched 40-minute educational videos. Participants in CT and ET groups received either sham or active transcranial direct current stimulation, although this was not a variable of interest. Participants underwent resting-state functional magnetic resonance imaging at pre- and post-training time points. Functional images were processed and average connectivity of FPCN, CON, DMN, and DAN were extracted through use of the CONN Toolbox v18b via SPM 12. Group by time interactions were assessed through mixed repeated measures ANCOVA controlling for tDCS group, mood, age, sex, education, and scanner.There were no statistically significant group by time interactions for FPCN, CON, DMN, or DAN. However, FPCN group by time interaction had a small-medium effect size [$F(1,50) = 2.77$, $p=.102$, partial $\eta^2=.053$] and pairwise comparisons revealed increased FPCN connectivity in the CT group after training ($p=.027$).Our results suggest that 3 months of cognitive training may result in higher connectivity of the FPCN in a sample of healthy older adults, although power analysis suggests a larger sample size is needed. This implies the FPCN, which has a role in modulating between network connectivity, may be a neural target to strengthen cognitive training response. Future research should assess functional brain changes after cognitive training in a larger group and at more time points.

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Poster

P891. Cognitive Natural Aging: Neural Mechanisms II

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Topic: H.12. Aging and Development

Support: NIH Grant AG068149

Title: Age-related neural dedifferentiation for scenes and faces: evidence from ERPs

Authors: *R. E. PICHOT, D. HENRECKSON, M. FOLEY, J. D. KOEN;
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Abstract: There is a growing body of work showing that age-related neural dedifferentiation - reductions in the selectivity and precision of neural representations - contributes to cognitive aging. This research has

primarily used fMRI to examine age-related reductions in neural selectivity for different categories of visual stimuli. Unlike fMRI, the temporal resolution of EEG permits examination of whether neural dedifferentiation results from an age-related reduction in 'maximal' levels of neural selectivity, a delay in the time the maximal neural selectivity, or both. The present research examined age-related neural dedifferentiation by examining scene-sensitive (P200) and face-sensitive (N170) ERP components. A total of 44 young and 44 older adults viewed images of scenes, objects, and faces in the context of a 1-back task. The scene-selective P200 and face-selective N170 components were measured from first presentation scene and face trials, respectively, contrasted with objects. Relative to young adults, the P200 in older adults was reduced in peak amplitude and delayed in peak latency. A similar pattern was observed for the N170 but only over right hemisphere electrodes. We also tested a prediction from a computational model proposing that age-related neural dedifferentiation results from age increases in "neural noise" (i.e., the aperiodic signal). However, our findings did not clearly support the prediction of this model. There was no clear relationship between the aperiodic signal and the P200 and N170 components. These findings provide novel evidence that neural dedifferentiation results from both reductions in the amplitude of and delays in the selectivity of neural activity, and motivate future research to identify the mechanism giving rise to this phenomenon.

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Poster

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Support: Priority Program, SPP 1772 from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), Grant VO 1432/19-1
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Title: Frontoparietal brain activation during dual-task walking is associated with cardiovascular and motor coordinative fitness

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Abstract: Walking while performing an additional task is an integral part of our daily life. With increasing age, this dual-tasking (DT) performance typically declines. Cardiovascular and motor coordinative fitness have been shown to be positively associated with DT performance. Whether brain activation patterns while DT differ with respect to the physical fitness level, however, has not been investigated so far. Here, we applied fNIRS to investigate the neural correlates during DT walking in healthy older adults and its association with cardiovascular and motor coordinative fitness. Data of 41 older adults were analyzed (age: 68.79 ± 3.79, 22 females). Participants completed a baseline task (standing) and three tasks (treadmill walking at 1 m/s, Stroop task, Serial 3's task) under single and DT conditions (Walking + Stroop, Walking + Serial 3's). Task order was mixed with 5 trials per task, 30 s per

trial. Behavioral outcome measures were gait (step time variability) and cognitive performance (Balance Integration Score [BIS_{cog}]). Brain activity was measured using fNIRS over prefrontal and parietal regions. Neurophysiological outcome measures were oxygenated (OxyHb) and deoxygenated hemoglobin (DeoxyHb). Cardiovascular fitness ($VO2_{peak}$) was assessed by use of a graded exercise test (Spiroergometry) and motor coordinative fitness by use of three different motor tests to assess manual dexterity, balance and movement speed (composite score). Four linear models were applied to investigate the effects of Task (DT Stroop, DT Serial 3's), Region (DLPFC, VLPFC, IPL, SPL (for OxyHb, DeoxyHb only)), and Cardiovascular or Motor Coordinative Fitness on OxyHb, DeoxyHb, Step Time Variability (gait), and BIS_{cog} (cognition). First results indicate that both Cardiovascular Fitness ($p < .001$, $\eta^2 = .05$) and Motor Coordinative Fitness ($p = .016$, $\eta^2 = .02$) were positively associated with overall OxyHb and negatively with overall DeoxyHb ($p < .001$, $\eta^2 = .04$ and $p < .001$, $\eta^2 = .01$) during DT. These effects were neither task nor region-specific (no interactions). Partly in line with that, both Cardiovascular Fitness and Motor Coordinative Fitness were positively related to BIS_{cog} ($p = .031$, $\eta^2 = .01$ and $p = .006$, $\eta^2 = .02$), but not Step Time Variability ($p = .788$, $\eta^2 < .01$ and $p = .090$, $\eta^2 < .01$). We could confirm that a higher physical fitness was accompanied by higher brain activation and higher cognitive performance during DT. Results indicate improved brain health and DT performance in physically fit participants.

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Poster

P891. Cognitive Natural Aging: Neural Mechanisms II

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Title: Neural evidence for age-related deficits in the representation of state spaces

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Abstract: Current theories of decision-making distinguish between model-free (MF) decision strategies which rely on action/outcome associations and model-based (MB) decision strategies, which rely on a complete representation of the task structure (Daw et al., 2011). These decision strategies are located on the extremes of an efficiency/flexibility trade-off (Bolenz et al., 2019; Eppinger et al., 2021). The MF strategy requires little cognitive effort but is inflexible if the environment changes. The MB strategy requires much more cognitive effort but is highly flexible as it relies on a model of the task structure that can be used to adapt to changes in the environment.While younger adults flexibly engage in a

combination of MF and MB decision-making, older adults have been shown to rely on MF decision-making which has been attributed to deficit in the representation of the decision-making environment, necessary to engage in the MB strategy (Eppinger et al., 2013; Eppinger et al., 2017). To understand the neural mechanisms that underly this age-related shift, we used a combination of computational modeling and EEG to examine older adults' performance and neural activity under high compared to low demands on the representation of the task structure. We had younger and older adults complete a modified two-stage Markov decision task under two transition probability conditions. In the 80%–20% condition, due to the large difference between the common and rare transitions, the internal structure of the task should be simpler to represent, and thus the upcoming state should be easier to predict than in the 60%–40% condition. We used computational modeling, and single-trial EEG analyses to establish neural markers of age-related changes in MB decision-making across both conditions. In line with our behavioral results, we found neural evidence (P300 component) that younger, but not older adults had a better task representation in the 80%-20% condition. Further, single trial analyses revealed that participants' neural activity (P300) covaried with the degree to which they updated their cognitive map of the state space of the task (state value prediction errors). Consistent with the diminished state space hypothesis of human aging, our findings suggest that deficits in goal-directed, MB behavior in older adults result from impairments in the representation of state spaces of cognitive tasks.Based on previous work in younger adults (Momennejad et al., 2017) we are currently investigating whether older adults may also engage in intermediate strategies. In a follow-up study, we test this possibility and examine the neural mechanism supporting successor representation using EEG.

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Poster

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Title: The functional neural correlates of the Useful Field of View (UFOV) task in older adults

Authors: *J. N. KRAFT[1], A. ALBIZU[1], A. O'SHEA[2], H. K. HAUSMAN[2], C. HARDCASTLE[2], N. D. EVANGELISTA[2], E. M. BOUTZOUKAS[2], E. VAN ETTEN[6], P. K. BHARADWAJ[6], H. SONG[6], S. G. SMITH[6], S. DEKOSKY[3], G. A. HISHAW[7], S. WU[4], M. MARSISKE[2], R. COHEN[2], G. E. ALEXANDER[6], E. C. PORGES[2], A. J. WOODS[5];
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Abstract: Declines in processing speed occur in aging, and are critical markers of cognition. Studies suggest that Useful Field of View (UFOV) training may ameliorate cognitive decline, with interventions demonstrating up to a 29% reduction of Alzheimer's disease risk. Despite its efficacy, little is known about the neural correlates of this paradigm. The current study investigated the functional neural correlates of the UFOV task by assessing blood oxygen level dependent (BOLD) activation patterns in older adults.

233 healthy older adults completed the UFOV task while undergoing task-based functional MRI. During the *stimulus* portion of this task, the participant must identify a target in the center of the screen and the location of a peripheral target. During the *probe* portion, the participant performs a forced choice response, deciding if the object in the center and the location of the peripheral target are identical to the *stimulus* screen. First level contrasts modeled hemodynamic response within participants. Group level analyses assessed the unique BOLD response associated with the *stimulus* and *probe* components of the task and shared patterns of activation Age, education, sex and scanner were included as covariates in all second-level models. Significant clusters were corrected at a false discovery rate (FDR) of $p<0.05$. The above models were rerun with task performance included to assess the differential impact of accuracy on BOLD activation.

Widespread whole brain activation was evidenced in the *stimulus>probe* contrast [$t(228)=16.00$; 95,175 voxels]. Conversely, the *probe>stimulus* contrast was associated with unique activation patterns within the inferior temporal gyrus, middle frontal gyrus, and parahippocampal gyrus [$t(228)=7.30$; 6,634 voxels]. In the *stimulus+probe>rest* conjunction analysis, we observe activation patterns within the precentral gyrus, occipital pole, insula, and middle frontal gyrus [$t(460)=13.92$; 32,724 voxels]. Evaluating the impact of accuracy, we observe similar whole brain activation patterns in the *stimulus>probe with accuracy* contrast [$t(227)=6.21$; 38,981 voxels]. Interestingly, no significant clusters survive FDR corrections in the *probe>stimulus with accuracy* contrast. Analyzing the *stimulus+probe> rest with accuracy* contrast, we see activation patterns more focally centered in the frontal and parietal lobes [$t(459)=6.28$, 11,862]. To date, this is the largest study assessing BOLD activation during UFOV task completion. Understanding the neural underpinnings of the UFOV could provide insight into potential avenues for intervention optimization, further increasing the efficacy of UFOV interventions.

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Poster

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Title: Preclinical Alzheimer Disease Pathology Partially Mediates the Relationship Between Cortical Thickness and Cognitive Control

Authors: *N. S. MCKAY[1], A. DINCER[1], V. MEHROTRA[2], A. J. ASCHENBRENNER[1], D. BALOTA[1], R. C. HORNBECK[1], J. C. MORRIS[1], T. L. S. BENZINGER[1], B. A. GORDON[1];
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Abstract: Previous research has shown that with age and disease, the integrity of grey matter structures decline. One such measure of grey matter integrity is cortical thickness, where lower values represent thinning of the cortical surface. Given that cognitive performance tends to decline with age, we were interested in investigating whether performance on attention-based tasks was related to cortical thickness measured using magnetic resonance imaging (MRI) in an unimpaired older adult cohort. Further, although often unmeasured in studies of cognitive aging, many older adults will present with Alzheimer Disease (AD) pathologies such as beta-amyloid (Aβ) deposition, despite being asymptomatic. Therefore, we were also interested in quantifying how much of the behavior-structure relationship seen in older adult cohorts is driven by preclinical AD. 511 cognitively unimpaired (CDR™=0) older adults (Age: *M*=68.2, *SE*=0.38) enrolled in studies at the Knight Alzheimer Disease Research Center, were included in these analyses. All participants completed an MRI and several cognitive measures (Stroop, Simon, and CVOE); a subset of individuals (*n*=396) also underwent Aβ-positron emission tomography (PET). A spatial cortical map highlighting regions where cortical thickness and cognition were related was created and this map was entered into subsequent analyses as our MRI variable. We used an established attentional control composite as our behavioral measure of interest. Linear models were conducted to elucidate the relationship between cortical thickness and cognition, and a mediation analysis was performed to examine whether Aβ deposition impacted this relationship. Using vertex-wise general linear models, we found that reduced cortical thickness in temporal, medial- and lateral-parietal, and dorsolateral prefrontal cortex, predicted worse performance on an attention task composite. Interestingly, mediation analysis showed that levels of Aβ partially account for the observed relationship between cortical thickness and attentional control. These results demonstrate that behavioral variability seen in older adult populations reflects corresponding changes in brain anatomy, specifically cortical thickness. Furthermore, our results support the hypothesis that preclinical AD, as measured by Aβ deposition, is partially driving what would otherwise be considered general aging in a cognitively normal older adult population.

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Poster

P917. Single-Cell Techniques II

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Title: Next generation lineage tracing of brain development by single-cell and spatial transcriptomics

Authors: *M. RATZ, L. VON BERLIN, J. FRISÉN;
Karolinska Inst., Stockholm, Sweden

Abstract: The mammalian brain contains a large number of cells that develop from a thin sheet of neuroepithelial progenitor cells. High throughput single cell technologies have been used to define the molecular diversity of hundreds of cell types in the nervous system. However, the lineage relationships between mature brain cells and progenitor cells are not well understood, because transcriptomic studies do not allow insights into lineage relationships and classical fate-mapping techniques are not scalable. Here we show *in vivo* barcoding of early progenitor cells that enables simultaneous profiling of cell phenotypes and lineages in the mouse brain using single cell and spatial transcriptomics. We reconstructed more than 2,000 clones to uncover the existence of fate-restricted progenitor cells in the mouse hippocampal neuroepithelium and show that microglia and perivascular macrophages are derived from primitive myeloid precursors that massively expand to generate widely dispersed progeny. By coupling spatial transcriptomics with lineage tracing, we obtained clonal and regional maps that revealed the differential expression of molecular signals sensed by clonally related cells to adapt to their microenvironment. Finally, we uncovered shared single cell gene expression programs of clonally related cells that might be associated with distinct response behaviors of brain cells originating from the same progenitor cell.

Disclosures: M. Ratz: None. **L. von Berlin:** None. **J. Frisén:** F. Consulting Fees (e.g., advisory boards); Consultant to 10X Genomics.

Poster

P917. Single-Cell Techniques II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P917.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Huntingtons disease (HD) human embryonic stem cells (hESCs) with mono-allelic HTT exon 12 genomic barcoding show applicable pharmacological responses, retain relevant neuronal differentiation capacity and demonstrate allele selectivity screening potential.

Authors: *M. R. BROWN[1], B. ATANASOVSKA[2], G. SERVANT[2], M. G. VROUWE[2], A.-M. ZUURMOND[2], L. J. ANTON[1], E. F. SOUSA[1], E. THATCHER[1], M. IOVINO[1], D. F. FISCHER[1], P.

MITCHELL[1], G. MCALLISTER[3], I. MUNOZ-SANJUAN[3], T. F. VOGT[3], R. Z. CHEN[3];
[1]Charles River Labs., Saffron Walden, United Kingdom; [2]Charles River Labs., Leiden, Netherlands;
[3]CHDI Management/CHDI Fndn., New York, NY

Abstract: Selectively targeting mutant (m)*HTT* mRNA remains an important therapeutic objective for HD. Phenotypic screening efforts focusing on m*HTT* mRNA as target require a robust and high-throughput method to identify novel small molecule inhibitors, but an existing allele-selective assay read-out is lacking. Here we aim to validate a cellular assay developed for screening modulators of endogenous m*HTT* mRNA in an allele-specific manner. This tool encompasses a hESC line that harbors one barcoded *HTT* allele (either wt or m*HTT*) and employs ViewRNA technology to quantify both barcoded and non-barcoded *HTT* mRNA expression levels. An HD hESC line (22/56 CAG repeats) was engineered using CRISPR/Cas9 gene editing of the CAG repeat with introduction of silent mutations throughout one of the *HTT* exon 12 alleles to generate a mono-allelic barcode. After homology directed substitution of one allele, clones were isolated and characterized for on-target integration, mono-allelic linkage and HTT protein expression. We show that these *HTT*-barcoded hESCs could demonstrate an applicable pharmacological response with an allele-specific quantification method, and further that these cells retain disease-relevant differentiation potential. We demonstrated non allele-selective *HTT* mRNA lowering in *HTT*-barcoded hESCs treated with Branaplam, a compound targeting an RNA splicing mechanism, using ViewRNA quantification. By characterization of neuronal fate marker expression using branched DNA and immunocytochemistry methods, we have confirmed that wt *HTT* barcoded hESCs retain the capacity for successful differentiation towards a disease-relevant neuronal phenotype. *HTT*-barcoded striatal-like neurons were then investigated to confirm that the multiplexed ViewRNA assay method remained applicable after differentiation, and assessed for differentiation dependent sub-cellular *HTT* transcript localization. These *HTT*-barcoded striatal neurons can be similarly interrogated by ViewRNA assay and represent a tool allowing high throughput investigation of allele-specific *HTT* mRNA pharmacological modulation potential in a disease relevant cell type.

Disclosures: M.R. Brown: None. **B. Atanasovska:** None. **G. Servant:** None. **M.G. Vrouwe:** None. **A. Zuurmond:** None. **L.J. Anton:** None. **E.F. Sousa:** None. **E. Thatcher:** None. **M. Iovino:** None. **D.F. Fischer:** None. **P. Mitchell:** None. **G. McAllister:** None. **I. Munoz-Sanjuan:** None. **T.F. Vogt:** None. **R.Z. Chen:** None.

Poster

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Program #/Poster #: P917.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

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Sanford Burnham Prebys Medical Discovery Institute funds

Title: Single-nucleus RNA-sequencing reveals cell-type-specific RNA isoform diversity in the human brain

Authors: *C. LIU[1,2], C. PALMER[2,1], W. J. ROMANOW[1], J. CHUN[1];
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Abstract: Single-cell sequencing technologies have expanded our ability to investigate transcriptomes at a cellular level. Single-nucleus RNA-sequencing (snRNA-seq) can identify cell-type-specific alterations in gene expression, however, this approach does not provide information about how RNA isoform expression may vary among different cell types or physiological conditions. Long-read transcriptomic solutions, such as Pacific Biosciences' Iso-seq approach, produce reads up to 10kb in length which can resolve full-length isoforms. Utilizing long-read (Pacific Biosciences) as well as short-read (Illumina) sequencing technologies, we conducted snRNA-seq on 29 human Down Syndrome (DS) and non-DS control prefrontal cortex samples. Combining these approaches allowed us to identify cell types and attribute isoforms identified in long reads to individual cells. We detected vast RNA isoform diversity within specific cell types and numerous novel sequences that varied across cell types. Isoforms containing novel features such as intra-exonic junctions (IEJs) - previously associated with somatic gene recombination - novel exons, and partial intronic retention were identified. These results underscore the presence of diverse and varied RNA isoforms contributing to cellular functions in the human brain.

Disclosures: C. Liu: None. **C. Palmer:** None. **W.J. Romanow:** None. **J. Chun:** None.

Poster

P917. Single-Cell Techniques II

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Program #/Poster #: P917.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: This work was funded by the Allen Institute for Brain Science

Title: Qcr: a snakemake pipeline for quality control assessment of single cell or nucleus rna sequencing data

Authors: *S. SOMASUNDARAM, N. JORSTAD, K. SMITH, J. GOLDY, J. GUZMAN, T. PHAM, A. TORKELSON, N. GUILFORD, A. YANNY, E. LEIN, R. D. HODGE, T. BAKKEN, J. A. MILLER;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Over the past decade single cell and nucleus RNA sequencing (sc/sn RNA-seq) technologies have been instrumental for identifying and characterizing gene expression profiles of cell types in multiple organ systems in many species. Application of snRNA-seq in human brain has provided new insights into cell type function, connectivity and susceptibility to disease. Droplet-based methods such as 10x Chromium 3' v3 sequencing can capture tens of thousands of data points per experiment. While the majority of these represent individual nuclei, some include two or more nuclei, are missing nuclei

entirely, or contain damaged or otherwise low-quality nuclei. Therefore snRNA-seq data needs to be filtered to infer the true nuclei prior to clustering to identify distinct and accurate cell type populations without losing biologically relevant cell types. Previous studies have used either manual selection or one of several published computational algorithms that employ different strategies to identify low quality nuclei. However, manual selection is only feasible with a small number of donors and few flexible and intuitive pipelines exist got large batch processing.
Here we present Quality Control on snRNA-seq (QCR), which is a Snakemake pipeline for robust and reproducible quality assessment and filtering of sc/sn RNA-seq data. QCR incorporates several steps for flagging and a thorough filtering of low-quality cells. This comprehensive pipeline takes a Seurat object of a single sample or integrated samples as input, performs a series of steps for flagging and filtering nuclei as potential low quality data points for exclusion, and outputs these results along with a report containing UMAPS, bar plots and scatter plots for visual and quantitative verification of results. Quality metrics are calculated both for nuclei and for "metacells" (small group of cells from Louvain clustering in Seurat) to mark poor quality cells. Furthermore, each step of QCR is implemented as a separate module, making the pipeline adaptable to different experimental protocols.
We have run QCR on a publicly accessible set of nuclei collected from the neocortex of 78 human donors during neurosurgical resections for tumors and intractable epilepsy and show that it excludes predominantly low-quality data points while retaining predominantly high-quality nuclei.

Disclosures: S. Somasundaram: None. **N. Jorstad:** None. **K. Smith:** None. **J. Goldy:** None. **J. Guzman:** None. **T. Pham:** None. **A. Torkelson:** None. **N. Guilford:** None. **A. Yanny:** None. **E. Lein:** None. **R.D. Hodge:** None. **T. Bakken:** None. **J.A. Miller:** None.

Poster

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Program #/Poster #: P917.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 1RF1MH123220-01, 102-01-037-20: "A Community Framework for Data-driven Brain Transcriptomic Cell Type Definition, Ontology, and Nomenclature"

Title: Cell Type Explorer: an interactive multimodal atlas of primary motor cortex

Authors: *R. E. A. SANCHEZ[1], T. MOLLENKOPF[1], B. STAATS[1], B. AEVERMANN[2], R. DALLEY[1], R. GALA[1], N. W. GOUWENS[1], N. L. JORSTAD[1], H. KIR[3], B. R. LONG[1], A. MUKORA[1], D. OSUMI-SUTHERLAND[3], P. RAY[1], R. SCHEUERMANN[2,4], S. SOMASUNDARAM[1], S. TAN[3], B. TASIC[1], C. L. THOMPSON[1], C. VAN VELTHOVEN[1], A. YADAV[1], Y. ZHANG[2], H. ZENG[1], M. J. HAWRYLYCZ[1], E. LEIN[1], J. A. MILLER[1];
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Abstract: Defining and characterizing cell types in the brain is a critical problem in modern neuroscience. The BRAIN Initiative Cell Census Network (BICCN) has generated and reported on a multimodal atlas of cell types in mammalian primary motor cortex consisting of large-scale, integrated datasets describing single-cell transcriptomes, chromatin accessibility, DNA methylomes, spatially resolved single-cell transcriptomes, morphology, electrophysiological properties, neuronal connectivity and novel transgenic mouse lines and viral tools. Using the single cell transcriptomic data as a framework, a taxonomy of cell types with a hierarchical organization that is conserved across mouse, marmoset, and human has been defined. The Cell Type Explorer is an interactive web-based tool that allows users to browse data comprising the BICCN primary motor cortex atlas at each level of the taxonomy. This tool contains individual Cell Type Cards that cover transcriptomically-defined cell types in the primary motor cortex, as well as biologically driven, lower-resolution groupings of these types ("subclasses" and "classes") that are highly consistent across modalities and match historically defined types. Each Cell Type Card provides text summaries and data visualizations across multiple modalities and describes key characteristics of a given cell class, subclass, or type, including specific marker gene combinations. Cell Type Cards and their underlying taxonomies are associated via a data-driven ontology, allowing for text-based search and comparison of cell type properties across the motor cortex. Each Card also provides links to archives containing both raw and processed data files, relevant manuscripts, and other resources for analysis and visualization from the Allen Institute and collaborating BICCN laboratories. The Cell Type Explorer represents a rich new resource for the neuroscience community that can serve as a complement to studying cell types from manuscripts and traditional data viewers.

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Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P924.01

Topic: I.03. Anatomical Methods

Support: Knut and Alice Wallenberg Foundation

Title: Widening the 3D view: processing and presentation pipeline of brain volume imaging data

Authors: E. HUSÉN[1], *J. MULDER[1], D. TABAR[2], M. UHLÉN[1], T. HÖKFELT[1], C. ADORI[1]; [1]Neurosci., Karolinska Inst., Solna, Sweden; [2]Atomontage, Wilmington, DE

Abstract: OBJECTIVE AND RATIONALE Traditional immunohistology and immunofluorescence-based analysis of brain tissue is performed on thin sections. Volume immunostaining- and clearing methods (e.g. iDISCO, Scale, CLARITY), in combination with three-dimensional (3D) image acquisition

by light sheet microscopy, generate a more comprehensive tissue overview. This becomes vital in case of complex tissues, such as the brain. The main challenges in the field of volume imaging are related to quality of staining and lipid clearing, image acquisition, 3D data-processing, analysis, visualization, and data sharing. In the recent years, the number of neuroscience publications using volume imaging approaches has increased. In most of these publications, 3D data are provided as movie files to highlight and illustrate biological concepts or findings. For educational purposes, we earlier generated volume imaging of various human tissues, which are publicly accessible as videos on the webpage of the Human Protein Atlas; for instance, imaging of human Alzheimer's disease-affected brain tissue (https://youtu.be/RqKRSU3fJKY), or human locus coeruleus (https://www.youtube.com/watch?v=GK_FUs6KiIw) and substantia nigra tissues (https://youtu.be/8J150NZa14k). We used this project to establish an optimised workflow for future volume imaging projects. The video format however limits the size of the shared data and does not allow interactive presentation. METHODS AND RESULTS We have worked with tissue samples of the human brainstem nucleus locus coeruleus and optimized iDISCO volume immunostaining protocol and image acquisition strategy for human brain tissue. Furthermore, we developed image processing and cell segmentation workflows using ImageJ. In collaboration with Atomontage, we explored possibilities to share our 3D data using a novel volumetric 3D content-sharing platform. This 3D platform maintains data in its pure voxel form, preserving the integrity of data. The platform is cloud based, allowing more flexible data processing, and generating an efficient sharing of volume data in real time. We explored and visualized various aspects of the locus coeruleus connectivity in the Atomontage platform, such as the complex circuitry and spatial relation of tyrosine hydroxylase expressing neurons. CONCLUSION Voxelized data that is rendered in the cloud allows in-depth analysis, provides a more interactive way for users to investigate 3D data, as well as presents an alternative for sharing movie files. Using voxel rendering will not deform the datasets, and image quantification routines can be built within the cloud environment.

Disclosures: E. Husén: None. **J. Mulder:** None. **D. Tabar:** A. Employment/Salary (full or part-time):; Atomontage. **M. Uhlén:** None. **T. Hökfelt:** None. **C. Adori:** None.

Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P924.02

Topic: I.03. Anatomical Methods

Support: Pilot Project of Quebec Bioimaging Network
NSERC Discovery Grant

Title: Antigenicity is preserved in mice brains fixed with three different solutions used in human gross anatomy laboratories

Authors: *E.-M. FRIGON[1], M. DADAR[2], D. BOIRE[3], J. MARANZANO[4];
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[3]Univ. du Quebec a Trois-Rivieres, Trois-Rivieres, QC, Canada; [4]Univ. du Quebec a Trois-Rivieres, Trois-Rivières, QC, Canada

Abstract: Brain banks are the main source of brain tissue available to researchers. However, a much larger number of specimens could be obtained from gross anatomy labs at a lower cost. These specimens are fixed with different types of embalming solutions appropriate for dissections, but we ignore if they also preserve brain tissue antigenicity. Since the fixation periods of human bodies are long (2-7 months), we applied different fixative solutions on mice brains. The goal was to assess and compare the tissue quality and antigenicity of the main cell populations in mice brains fixed by perfusion with three solutions used for human body preservation. We used six C57BL/6J mice (3 males, 3 females) perfused with: 4% paraformaldehyde (PAF, N=2), saturated salt solution (SSS, N=2) and alcohol solution (AS, N=2). The brains were extracted, cryoprotected, frozen and cut into 40µm sections for histological analysis. The macroscopic and microscopic quality of the tissue were compared. The antigenicity was assessed by immunohistochemistry of five antigens: myelin proteolipid protein (PLP), myelin basic protein (MBP), neuronal nuclei (NeuN), glial fibrillary acidic protein (GFAP) (astrocytes) and ionized calcium binding adaptor molecule1 (Iba1) (microglia). Antigenicity was qualitatively compared and NeuN was quantitatively assessed using an automatic algorithm based on a multi-level filtering approach. The tissue fixed with SSS and AS showed a poorer macroscopic quality than the PAF fixed tissue according to three variables: texture, ease of manipulation and ease of mounting. The SSS and AS slices had a viscous texture, were difficult to manipulate (fragile and adherent) and difficult to mount (not completely displayed on the slide without tears). Microscopically, we assessed quality using two variables: presence of blood vessels and cutting/manipulation artifacts. Both were present in SSS and AS and absent in PAF fixed tissue, reflecting a better quality of the latter. However, all five antigens were present and correctly observable in every specimen, regardless of the fixative solution. Quantitative comparison of NeuN across the three types of fixed tissues showed similar counts (normalized to surface area): 446 (PAF), 434 (SSS) and 478 (AS) in layers 2-3 of the secondary motor cortex. Although these solutions are designed to preserve specimens for dissections, they preserved tissue antigenicity for several brain cell populations and do not alter the number of neurons. Fixation with the PAF-based solution produced sections that were easier to manipulate, with less artefacts. Histological analysis may be applied on human brains from gross anatomy labs and brain banks.

Disclosures: E. Frigon: None. **M. Dadar:** None. **D. Boire:** None. **J. Maranzano:** None.

Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P924.03

Topic: I.03. Anatomical Methods

Title: Revising the Nissl stain: reducing hazards and expanding access

Authors: *K. R. URSTADT;
Cognitive Sci., Occidental Col., Los Angeles, CA

Abstract: The Nissl stain is a widely-used standard for delineating the neuroanatomical boundaries and locations of brain regions under brightfield microscopy. However, the accessibility of this classic stain to younger audiences or classrooms with lower budgets has been hindered A) by its potential hazards, B) subsequent expenses required to protect trainees from those hazards, and/or C) expenses from procuring such reagents from a scientific supplier versus local drug stores. In particular, flammable, toxic, irritant, and/or carcinogenic chemicals are typically used in this staining process in regular lab settings. Here, lower hazard and less costly alternative reagents are proposed to replace some or all of those hazardous components. The primary goals were to replace 1) Xylene or chloroform as a defatting/delipidation agent, 2) Acidified 100% ethanol as a differentiating agent, and 3) Permount or DPX as a coverslipping medium. For defatting and differentiation purposes, the following reagents were assessed: 100% ethanol, 91% isopropanol, 0.2% and 10% Triton X-100, 2% dish soap (~0.2-0.6% SDS), and acidic (pH 5.5) water. For coverslipping, polyvinyl alcohol, Karo (corn syrup), medium chain triglyceride oil, and mineral oil were assessed. Stains with these lower hazard reagents were compared against slices from the same brains that underwent traditional Nissl staining, and quantification was performed with colorimetric and overall intensity measurements in ImageJ. Results suggest that A) ethanol, isopropanol, 0.2% Triton, and 10% Triton are effective defatting agents, B) ethanol, isopropanol, 0.2% Triton, and potentially 10% Triton are effective differentiating agents, and C) mineral oil is the most effective non-hazardous coverslipping medium tested. By revealing alternative reagents for performing the Nissl stain, this classic neuroanatomical tool will be more accessible to a wider audience of students and trainees.

Disclosures: K.R. Urstadt: None.

Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P924.04

Topic: I.03. Anatomical Methods

Title: Diversifying the Nissl stain's utility as a fluorescent counterstain

Authors: *H. C. PONCE[1], K. R. URSTADT[2], P. A. VIEIRA[3];
[1]Psychology, California State University, Long Beach, Torrance, CA; [2]Dept. of Cognitive Sci., Occidental Col., Los Angeles, CA; [3]Psychology, CSU Dominguez Hills, Carson, CA

Abstract: The Nissl stain is a standard histological method used to identify neural structures and locations within the brain. A lesser-known fact is that this stain can also be used as a red fluorescent counterstain when diluted substantially. However, this method is not always accessible to young scientists or classrooms with tighter budgets due to 1) potential hazards, 2) expenses to provide sufficient protection from said hazards, and/or 3) costs from procuring said reagents from scientific suppliers versus convenience stores. Additionally, the use of certain nonpolar/nonaqueous chemicals in regular Nissl staining makes this stain less compatible with other fluorescent reporters commonly used in neuroscience. Thus, it was imperative to find safer and more fluorophore-compatible alternatives to xylene and chloroform (defatting agents), acidified ethanol (differentiating agent), and Permount and DPX (coverslipping media). Thus, the following reagents were assessed for defatting and differentiation

efficacy: 100% ethanol, 91% isopropanol, 2% dish soap (~0.2-0.6% SDS), 0.2% and 10% Triton X-100, and acidic (pH 5.5) water. For coverslipping, mineral oil was assessed. After applying protocols substituting these reagents and using cresyl violet to stain rat brain sections, those sections were compared against a color-inverted version of Nissl stains from the rat brain atlas. Subjective rankings were performed, assessing similarity of staining intensity, Nissl body contrast from background, and gray vs white matter differentiation. Results suggest that ethanol, isopropanol, and potentially 0.2% Triton and 10% Triton are effective defatting agents, while ethanol, isopropanol, 0.2% Triton, 10% Triton, and acidic water are effective differentiating agents. Interestingly, acidic water may be a gentler differentiating agent compared to others. Although it is non-drying, mineral oil is a comparable coverslipping medium to DPX or Permount. These results show that various lower-hazard reagents can be used to perform Nissl staining, and are likely more compatible with fluorophores commonly used in neuroscience, thus enabling a wider audience of students, trainees, and researchers to use this classic stain.

Disclosures: H.C. Ponce: None. **K.R. Urstadt:** None. **P.A. Vieira:** None.

Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

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Program #/Poster #: P924.05

Topic: I.03. Anatomical Methods

Support: Pilot Project of Quebec Bioimaging Network
NSERC Discovery Grant

Title: Performance of an automated multi-level filtering approach to count immunolabeled neurons in the mouse brain

Authors: *M. DADAR[1], E.-M. FRIGON[2], D. BOIRE[3], J. MARANZANO[4];
[1]Laval Univ., Quebec, QC, Canada; [2]Anatomie, Univ. Du Quebec A Trois-Rivieres, Trois-Rivieres, QC, Canada; [3]Anatomie, UQTR, Trois-Rivieres, QC, Canada; [4]Univ. du Quebec a Trois-Rivieres, Trois-Rivieres, QC, Canada

Abstract: Histopathology is the Gold Standard assessment to determine the biological substrate of changes taking place in an organ. Quantification of neurons performed either fully manually or assisted by microscopic softwares is a time-consuming task. Our goal was to develop a MATLAB open-source software to quantify neurons in a consistent fashion, comparable to counts performed by an expert rater. The brain of a C57BL/6J mouse perfused with 4% paraformaldehyde was extracted, cryoprotected, frozen and cut into 40µm sections. Neurons were immunolabeled with a NeuN antibody. The sections were photographed (20x magnification) using a DSU Spinning Disk confocal microscope (Olympus BX51W1) coupled to Neurolucida software (MBF Bioscience). The secondary motor cortex (layers 2-3) was chosen as the region of interest (ROI) in left (L) and right (R) hemispheres for this analysis. The automated method counts cells through the following steps: 1-Conversion to grayscale; 2-Multi-level morphological top and bottom hat filtering (disk-shaped structuring element with radius values of 100, 50, 20, and 10 voxels, respectively); 3-Conversion of the filtered image to a binary image using a histogram based

threshold; 4-Separating connected components; 5-Removing components smaller than a minimum acceptable cell size threshold (180 voxels); 6- Splitting components larger than a maximum acceptable cell size threshold (1800 voxels) by repeatedly removing edges from the binary mask and morphologically opening the image; 7-Labeling each separate component as a cell. An expert rater counted the neurons in the ROIs using Neurolucida software (jp2 format) and Display software (minc format). The expert counted 433 (L) and 381 (R) cells on Neurolucida and 446 (L) and 387 (R) cells on Display (within overlapping areas), with 402 and 360 cells co-localizing in the two counts: i.e. 90-93% agreement across softwares. In a second read using Display, the expert counted 489 (L) cells, with 459 cells co-localizing with the first read: i.e. 93% agreement. The automated method counted 504 (L) and 541 (R) cells, compared with expert counts (using Display) of 485 (L) and 461 (R). 430 (L) and 403 (R) cells were detected by both: i.e. 89% and 87% agreement. Our results show that the variability across softwares is similar to intra-rater variability. The automated neuronal counts generated by our new algorithm had an excellent agreement with expert rater counts (similar to intra-rater agreement) and can be used to analyze entire brain surfaces for multiple specimens, a task that would be too time consuming to perform manually.

Disclosures: M. Dadar: None. **E. Frigon:** None. **D. Boire:** None. **J. Maranzano:** None.

Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

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Program #/Poster #: P924.06

Topic: I.03. Anatomical Methods

Support: European Research Council – FRONTHAL - 742595

Title: Morphofunctional mapping of the anterior part of the human thalamus

Authors: *A. SALMA[1,2], C. DÁVID[1,3], L. ACSÁDY[1];
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Abstract: The connectivity between the anterior part of the human thalamus (ATh) and the frontal cortex is crucial for complex cognitive processes. The ATh is also a major target for deep brain neurosurgery in various neurological disorders such as epilepsy, Parkinson's disease or essential tremor. Functionally relevant nuclear segmentation is essential for understanding both healthy and pathological processes of the brain, however, a comprehensive division of the human ATh, based on morphological and biological properties, is still lacking. Our aim in this study was to create a reliable nuclear segmentation of the ATh based on thalamic cell types and afferents using functional neurochemical markers.
We used series of coronal thalamic sections from postmortem brains and performed immunocytochemistry for vesicular glutamate transporter types 1 and 2 (vGluT 1, 2), parvalbumin, calretinin and calbindin. The combination of the selected markers clearly outlined the major nuclear divisions of the human ATh. We also performed quantitative analysis of the density distribution of $vGluT2^{+}$ subcortical afferents to validate our nuclear segmentation. Albeit, the exact position, proportion

and afferentation of particular nuclei differed from the accepted schemes. We found major deviations in the relative position of the two major motor thalamic nuclei receiving cerebellar and basal ganglia afferents and excitatory afferents in the human rostral mediodorsal nucleus was also unexpected. We found that inter-individual variation in nuclear positions is more prevalent than in rodent models. The quantitative analysis of the subcortical afferents showed characteristic intra- and inter-nuclear differences that became the basis for our segmentation.
Our process of using a combination of several neurochemical markers yields a relevant and functionally informative nuclear segmentation which provides a novel understanding of the functions of the thalamic nuclei. Our results indicate nucleus-specific, complex combinations of afferent systems which display both evolutionary conserved and highly derived human features. Further findings, in particular the understanding of inter-individual variation, will provide a uniquely useful perspective for neurosurgical procedures.
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Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

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Program #/Poster #: P924.07

Topic: I.03. Anatomical Methods

Support: Amici Lovanienses Foundation
Michael J. Fox Foundation

Title: Deep phenotype profiling of iPSC-derived neurons with CODEX® multiplexed-imaging

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Abstract: Human-induced pluripotent stem cell (hiPSC) models have been hailed as a breakthrough for understanding disease and developing new therapeutics. The major advantage of iPSC-derived neurons is, that they carry the genetic background of the donor, and such models could be more predictive for clinical translation. However, these cell models are time-consuming and expensive. It is therefore essential to develop highly multiplexed assays to maximize the readout from these models. Here, we employed a new ultra-high multiplexed immunofluorescence imaging technology CO-Detection by indEXing (CODEX) based on based on the principle of cyclic detection of oligo-conjugated antibodies. We differentiated human iPSCs into mixed neuronal cultures on glass coverslips. We tested and optimized over 30 human antibodies to phenotype these neuronal cultures for neuronal subtypes of cortical, dopaminergic, and medium-spiny neurons, glia including microglia, astrocytes, and oligodendrocytes, and pre- and postsynaptic markers. We show that CODEX can be applied to iPSC culture conditions and developed protocols for the neurons to sustain multiple wash-stain cycles. CODEX is a powerful technique to complement single-cell technologies for in-depth phenotype analysis.

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Poster

P924. Staining, Immunohistochemistry, Fluorescence Microscopy

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Title: Brain-wide cellular resolution snapshots of neuronal activity with Npas4 and cFos

Authors: *D. G. WHEELER[1,2], C. LO[1], A. MURRY[1], N. GUANZON[1], A. A. KEISER[3,4], M. PETERS[3], M. A. WOOD[4,3], R. AZEVEDO[1,3,4], S. GANDHI[1,3,4];
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Abstract: Recent advances in optical clearing and light sheet imaging have opened an exciting new avenue for brain-wide, cellular resolution immunostaining at the forefront of a dimensional shift from 2D to 3D histology. Providing access to the intricate anatomy of the whole intact brain, new tissue clearing methods can provide neuroscientists with unbiased and complete pictures of brain anatomy and function. With our optimized iDISCO-based clearing methods and our Mesoscale Imaging System for the ZEISS Lightsheet Z.1 microscope, we can image entire mouse brains in ~25 min. Further, our machine learning-enabled 3TK software identifies individual cells throughout the brain and aligns them to the Allen Reference Atlas to produce a regionalized read-out of cellular patterns across 100's of brain areas. We have applied this technology to generate cellular resolution maps of neuronal activity by measuring the immediate-early gene (IEG) products Npas4 and cFos. Expression of cFos is driven by Ca^{2+}-signaling downstream of neuronal activity and is commonly used to mark active neurons. However, cFos expression is also driven by cAMP elevations and signaling pathways engaged by neurotrophins or other paracrine factors. In contrast, Npas4 expression is neuron-specific and tightly tuned to Ca^{2+}-dependent signaling pathways. Using our Npas4 recombinant rabbit monoclonal antibody and a commercial cFos antibody, we developed whole-brain co-staining procedures and performed experiments on mice kept in the dark and exposed to light for various periods of time. After 24 hours in the dark, we found a large number of cFos(+) neurons, yet these same neurons did not express Npas4, suggesting that factors other than neuronal activity *per se* drove cFos expression at baseline. After light exposure, the lower baseline expression of Npas4 supported a much larger fold-change increase in expression than with cFos, where the elevated baseline of cFos(+) cells masked the precise identification of the stimulus-related 'trace'. The fidelity of the Npas4 response allowed our statistical anatomics tools to identify a large number of brain regions, some expected and some not, that had elevated neuronal activity after light exposure. Similarly, in Contextual Fear Conditioning experiments, home cage mice expressed much less Npas4 than cFos,

allowing for more precise monitoring of changes in neuronal activity after context exposure and shock. Our pipeline for brain-wide monitoring of cFos and Npas4 expression allows for high-fidelity monitoring of neuronal activity with Npas4 and also allows for mapping responses to GPCRs or trophic factors by measuring cFos(+)/Npas4(-) neurons.

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Poster

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Topic: I.04. Physiological Methods

Support: NIH SPARC U01 NS113873

Title: Sex difference in colorectum innervated mechanosensitive afferents distribution characterized by GCaMP recording in DRGs (SPARC)

Authors: *T. GUO, J. LIU, L. CHEN, Z. BIAN, G. ZHENG, B. FENG;
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Abstract: *Background*: Significant sex difference is present in the clinical symptoms of visceral pain associated with irritable bowel syndrome (IBS): female patients report more intense pain sensation. The gastrointestinal (GI) motility properties also differ in sex with male showing shorter transient time and faster gastric empty. Consistent with the clinic observations, female rats showed a more sensitive and cycle-dependent visceral motor response to colorectal distension. However, very little is known regarding the potential sex differences in the GI neurophysiology. In this study, we implement a high-throughput optical recording approach to detect sensory afferents innervating distal colon and rectum (colorectum) in mice of both sexes. We further assessed the changes of sensory innervation in hypersensitized mice induced by zymosan treatment. *Methods*: Mice carrying GCaMP6f gene were crossbred with VGLUT2-Cre mice. Colorectum with pelvic nerve, lumbar splanchnic nerve, and T12 to S1 dorsal root ganglia (DRGs) from the offspring were dissected out in continuity. DRG neurons in response to colorectal distension and/or shear flow were functionally categorized into 4 classes: muscular-mucosal, mucosal, high- and low-threshold muscular afferents. To induce visceral hypersensitivity, zymosan (30mg/mL, 0.2 mL) was transanally administrated for 3 consecutive days. *Results*: More than 2400 colorectal afferents were recorded from saline- and zymosan-treated mice of both sexes. Within the male group, colorectum has higher proportion of thoracolumbar (TL) innervation (T12, T13, L1, L2) than lumbosacral (LS) innervation (L5, L6, S1). In male mice, zymosan treatment resulted in significant increase in the

proportion of TL innervation and the number of mucosal neurons per mouse in all four TL DRGs. In contrast, female mice showed comparable innervation properties between saline- and zymosan-treated groups. *Conclusion*: Our results have revealed a sex difference in sensory innervation of the colorectum and zymosan induced a significant increase in mucosal populations in the TL pathway in male mice. This current study draws further research on the potential innervation differences between sexes, which could play critical roles in the sex difference in visceral pain and other GI-related symptoms.

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Topic: I.03. Anatomical Methods

Title: Precise Spatial Multiplexing for Neuronal Cell Profiling in Mouse Brain Fresh Frozen Tissue with ChipCytometry

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Abstract: Understanding the spatial distribution of key neuronal cell populations is critical in advancing our understanding of disease to inform the development of novel therapeutics. Here we present the analysis of fresh frozen (FF) tissue samples from mouse brain using a novel precise spatial multiplexing technology called ChipCytometry, which combines iterative rounds of targeted fluorescent staining with high dynamic range imaging to facilitate quantitative phenotyping with single-cell resolution. Standard FCS files are generated from multichannel OME-TIFF images, enabling identification of cellular phenotypes via flow cytometry-like hierarchical gating. In this study, a 13-plex assay was used to identify and quantify relevant cellular phenotypes and subtypes for neurobiology and neuro-oncology applications. The results show precise expression levels for each marker in the assay in each individual cell in the sample, while maintaining spatial information about each cell. Spatial analysis of the samples reveals neuronal cell heterogeneity including clusters of microglia and cholinergic neurons in a region rich with glutamatergic neuronal cells, demonstrating the utility of the ChipCytometry platform for the in-depth cellular profiling of mouse FF tissue samples.

Disclosures: A.J. Northcutt: A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker Company. **A. Pandita:** A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker Company. **C. Winkeler:** A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker Company. **M. Tyler:** A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker Company. **T. Campbell:** A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker Company. **K. Gamber:** A. Employment/Salary (full or part-time):; Canopy Biosciences, A Bruker

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Poster

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Title: A comparison of tissue clearing techniques for high-resolution imaging of the cortical vasculature

Authors: *M. MATOSSIAN, A. BORTEL, D. THOMMANA, V. M. MOCANU, A. SHMUEL; McGill, Montreal, QC, Canada

Abstract: Introduction To gain a clear understanding of the mechanisms underlying Blood Oxygenation Level-Dependent functional magnetic resonance imaging in the brain, we need to quantify the structural organization and density of blood vessels. The goal of our current project is to compare and optimize methods of in-vivo labeling of the vasculature and tissue clearing for obtaining high-resolution images of vessels in the neocortex. We compare the aqueous solution-based tissue clearing method 'Clear, Unobstructed Brain/body Imaging Cocktails" (CUBIC) to the organic solvent-based clearing method 'three-dimensional imaging of solvent-cleared organs' (3DISCO) and its variant, iDISCO+. Methods We cut 3 mm thick coronal slabs of the mouse brain. We intracardially inject wheat germ agglutinin Alexa Fluor before perfusion. Next, we incubate our samples into a series of solutions to achieve transparency. Finally, we image our samples using the Opera Phenix microscope, a spinning disk confocal that allows screening multiple samples in one imaging session with the use of multi-well plates. Results Organic solvents clear the brain significantly faster than CUBIC-related solutions. Using the two DISCO methods, it takes 3 ± 1 days to have optically transparent mouse brain slabs. With CUBIC, it takes 32 ± 10 days. CUBIC introduces variations in clearing duration as a function of tissue thickness and animal age. Clearing a 3 mm thick slab takes 8 ± 3 more days relative to a 2 mm thick slab for a mouse of a same age. The clearing duration increases with increasing age of the mouse. Based on our Opera Phenix images, we can obtain homogenous vasculature labelling throughout the cortex. Finally, we noticed, qualitatively, that iDISCO+ provides greater signal to noise ratio compared to the two other methods.

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Poster

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Title: A red fluorescent protein-based calcium indicator to study rapid calcium dynamics in the endoplasmic reticulum

Authors: *K. BERGLUND[1], X. DENG[2], M. A. STERN[1], X.-Q. YAO[2], B. DONG[2], D. OUEDRAOGO[2], M. A. GHANE[2], Y. ZHUO[2], C. MCBEAN[2], Z. Z. WEI[1], S. GOZEM[2], S. P. YU[1], L. WEI[1], N. FANG[2], A. M. MABB[2], G. GADDA[2], D. HAMELBERG[2], R. E. GROSS[1], J. J. YANG[2];
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Abstract: Calcium indicator proteins are versatile and indispensable tools for cell type-specific and subcellular imaging in the biomedical field, especially in neuroscience. Here we report a novel calcium indicator, R-CatchER, engineered from a red fluorescent protein that targets the endoplasmic reticulum (ER). Unlike conventional calcium indicator proteins, R-CatchER does not utilize the EF-hand motif as a calcium sensing mechanism. Instead, a single calcium binding site was engineered within the scaffold of RFP near the chromophore through point mutations and molecular dynamics simulation. *In vitro* characterization of the recombinant protein confirmed one-to-one binding stoichiometry and showed that the new indicator had affinity and kinetics suitable to study rapid calcium dynamics in the ER. When transiently expressed in primary cortical neurons in culture, R-CatchER showed proper targeting in neuronal ER. We quantified ER calcium responses to electrical stimulation as well as activation of metabotropic glutamate receptors in different compartments of neurons. R-CatchER was sensitive to reveal an ER calcium transient to a single electrical stimulus and its red-shifted spectrum allowed for simultaneous monitoring of cytosolic calcium through commonly used calcium-dependent green/yellow fluorescent proteins, such as jGCaMP7s and XCaMP-Y. We further developed a recombinant adeno-associated viral vector to express R-CatchER and XCaMP-Y in the same neurons *in vivo*. Two-photon imaging in the mouse motor cortex revealed fluctuations of ER calcium in awake animals during locomotion. Thus, R-CatchER provides unique opportunities to study ER calcium dynamics quantitatively in neurons while leaving green/yellow spectra for different imaging purposes.

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Poster

P928. Optical Methodology: Calcium Indicators and Related Methodologies

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Topic: I.04. Physiological Methods

Support: BrainMatrix NFR

Title: An updated suite of viral vectors for in-vivo calcium imaging using local and retro-orbital injections

Authors: *S. GRØDEM, I. NYMOEN, G. H. VATNE, V. BJÖRNSDOTTIR, K. LENSJØ, M. FYHN;
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Abstract: Calcium imaging using genetically encoded Ca2+ indicators (GECIs) is a widely adopted method to measure neural activity in modern neuroscience. Here, we explore the use of systemically administered viral vectors for brain-wide expression of GECIs, and adapt novel GECIs to optimize signal-to-noise. We show that systemic injections of PHP.eB AAVs to express GECIs is a highly promising technique for imaging neural activity and circumvent the need for transgenic GECI expressing mouse lines. We also establish the use of novel soma-targeted GECIs that outperform current Ca2+ indicators using both systemic and local virus injections.

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Poster

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Title: Electroporation as a noninvasive method for loading neurons with calcium indicators in the gastropod mollusk Berghia stephanieae

Authors: J. W. BROWN, E. S. HILL, W. N. FROST;
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Abstract: With central nervous systems comprising on the order of 10,000 large, often identifiable neurons, gastropod mollusks represent attractive systems for large-scale activity imaging, in which the

correlations between brain and behavior can be readily interrogated and manipulated at the level of individual neurons and complete neural circuits. Although absorbance voltage-sensitive dyes (VSDs) have proven profitable in imaging simultaneous activity in dozens to hundreds of gastropod neurons over extended periods of time and can be loaded through simple bath application, these indicators are not ideal for smaller-diameter neurons due to their low signal-to-noise ratios. Other activity indicators, including certain fluorescent VSDs and AM ester calcium dyes, generate more intense signals in smaller neurons but may require surgical intervention for loading, including the de-sheathing of ganglia or pressure injection of dye into the neuropil. Here, we present two variations of a noninvasive dye-loading protocol, involving electroporation of the charged calcium indicator Cal-520 potassium (Cal-520-K; AATBioquest) directly through the tissue sheath overlying the isolated CNS of the aeolid nudibranch *Berghia stephanieae*, the subject of an NIH BRAIN Initiative project. In one iteration of our method, *Berghia* neurons are individually electroporated by placing a 1-µm-tipped electrode loaded with 5-55 mM Cal-520-K against the overlying ganglionic sheath and generating a high-frequency pulse train (50 Hz/7 s trains with 5 ms/-25 V pulses) using a pulse stimulator. We have furthermore had preliminary success bulk-loading Cal-520-K into over a dozen neurons simultaneously: after briefly proteasing the brain, it is placed into a customized chamber between two Ag/AgCl electrodes, immersed in a 5 mM solution of Cal-520-K, and electroporated (1-2 Hz, 5-7 s trains with 50-100 ms/15-30 V biphasic pulses). Following a recovery period of 45-90 minutes, preparations loaded via both methods are imaged using widefield fluorescence microscopy. This approach has been used to record spontaneous action potential activity from neuronal somata as small as 10 µm in diameter. Additional experiments involving simultaneous calcium imaging and sharp-electrode intracellular recordings of neurons in the abdominal ganglion of *Aplysia californica* individually electroporated with Cal-520-K have moreover demonstrated a one-to-one correspondence between calcium transients and action potentials in tonically firing neurons driven at rates up to ~9 Hz. Higher firing rates result in fusion of the calcium signal into a smooth parabola useful for detecting bursts of activity.

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Poster

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Title: Inferring single-trial neural population dynamics from calcium imaging with sub-frame temporal resolution via deep learning

Authors: *F. ZHU[1], H. GRIER[3], R. TANDON[6], C. CAI[7], A. GIOVANNUCCI[7,8,9], M. T. KAUFMAN[4,5], C. PANDARINATH[6,2];
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Abstract: In many brain areas, neural populations act as a coordinated network whose state is tied to behavior on a moment-by-moment basis and millisecond timescale. Two-photon (2p) calcium imaging is a powerful tool to probe network-scale computation, as it can measure the activity of individual neurons, sample from multiple layers simultaneously, and sample from identified cell types. However, estimating network states and dynamics from 2p measurements has proven challenging. Here we present the Recurrent Autoencoder for Discovering Imaged Calcium Latents (RADICaL), a deep learning method to precisely infer network dynamics from 2p measurements. RADICaL builds on AutoLFADS - a state-of-the-art method for modeling neural dynamics from spiking activity - for application to deconvolved calcium signals, whose statistics and temporal dynamics are quite distinct from electrophysiologically-recorded spikes. In particular, we developed a novel network training strategy, selective backpropagation through time (SBTT), which allows recovery of network dynamics with substantially higher temporal precision than previously possible. SBTT enables training neural networks at sub-frame temporal resolution by accurately accounting for the differences in the sampling times of individual neurons caused by 2p laser scanning. In synthetic tests, RADICaL inferred network states with higher fidelity than current state-of-the-art methods, particularly for high-frequency components (e.g., a 2-5x increase in accuracy for 15 Hz signals with 33 Hz frame rate). When applied to 2p recordings from motor and somatosensory cortical areas in mice performing a water grab task, RADICaL de-noised individual neurons' responses on single trials and produced estimates of neural population states that closely corresponded to single-trial variations in reach kinematics. The de-noised representations led to substantially higher performance in decoding the mice's paw position and velocity on a moment-by-moment basis (~1.5-2x improvement). Taken together, these results demonstrate that RADICaL infers network states from 2p imaging data with unprecedented accuracy and temporal resolution, which is valuable for understanding how population activity is linked to ongoing behavior on a moment-by-moment basis.

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Poster

P928. Optical Methodology: Calcium Indicators and Related Methodologies

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Title: Identify the sampling rate contribution to the Ca^{2+} temporal dynamics detected by fiber photometry

Authors: Y. JIANG, S. GHIASVAND, B. ZHANG, *X. YU;
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Abstract: In contrast to the conventional optical imaging methods, fiber photometry enables the detection of Ca^{2+} transients in a similar temporal scale of local field potential (LFP) spikes, providing a powerful surrogate of in vivo electrophysiological recordings with simultaneous functional MRI. A critical issue has been raised when comparing the slow calcium responses acquired at the sub-second sampling rate by optical imaging methods with the fast Ca^{2+} transients with fiber photometry over 1kHz. **Methods:** we recorded the fiber photometry-based Ca^{2+} transients at different sampling rates with simultaneous LFP. **Results: Fig. 1A** shows representative calcium traces at 39 and 5k Hz and simultaneous LFP spikes upon stimulation. The averaged calcium transients demonstrated comparable amplitudes in trials with different sampling rates but with increased variation at the lower sampling rate (**Fig. 1B)**. Importantly, the contrast-to-noise ratio (CNR) showed the lowest values in the trial with a 39 Hz sampling rate (**Fig 1D**), of which a monophasic slow response was represented across the 3 stimulation-on period (**Fig 1C**). **Conclusion**: This work offers a thorough analysis of sampling rate contribution to different temporal dynamics of Ca^{2+} transients detected by fiber photometry. The monophasic slow Ca^{2+} response acquired at 39Hz raises a critical issue when interpreting the slow dynamics of recorded Ca^{2+} events from individual neurons or neuronal ensembles detected by conventional optical imaging methods with a 20-40 frame rate.

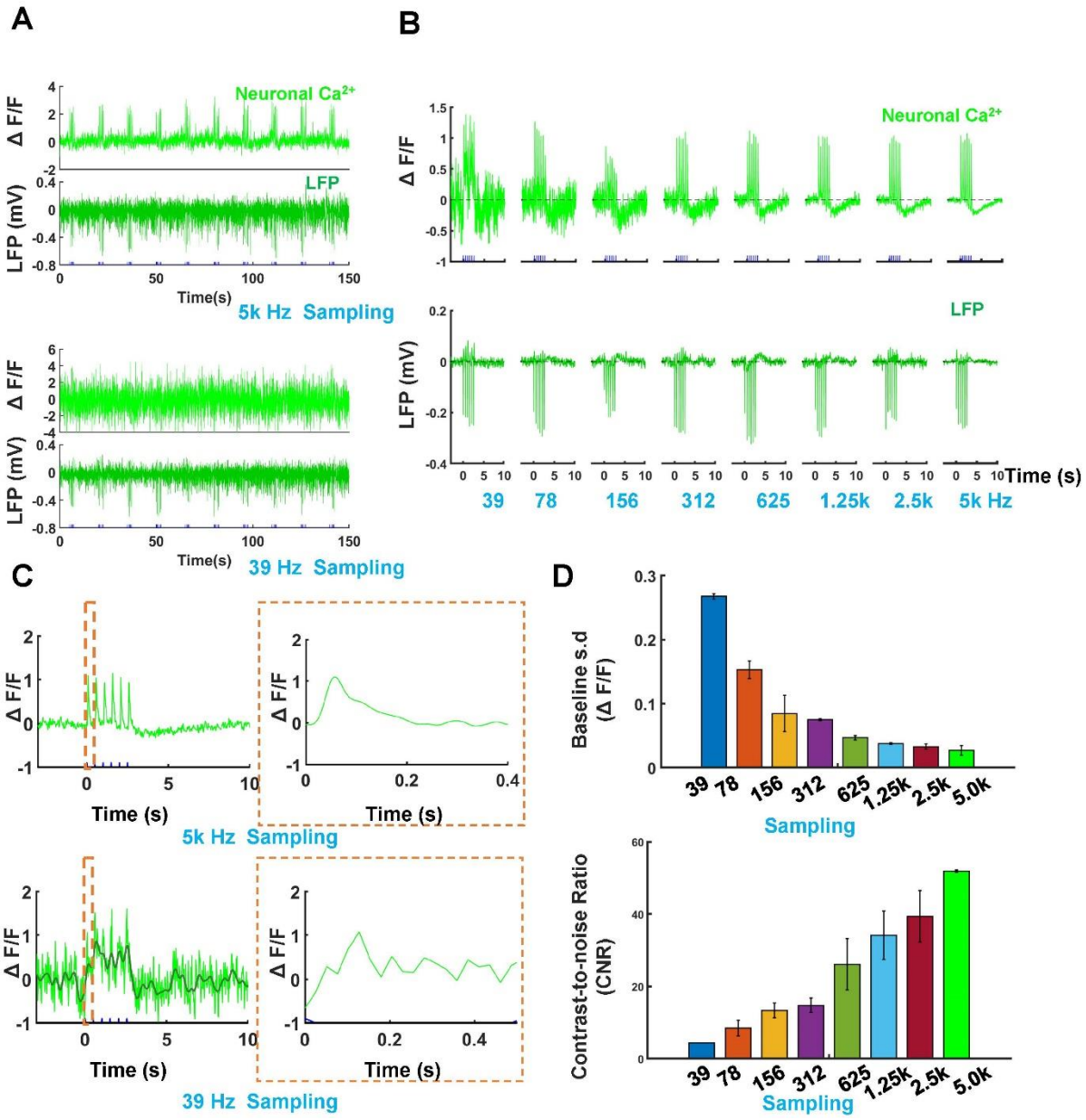


Figure 1. Characterizations of fiber photometry of neuronal Ca^{2+} responses acquired at different sampling rates. (A) The representative time course of neuronal Ca^{2+} signal acquired at 5000 and 39 Hz with simultaneous LFP. (B) Temporal features of one epoch sensory response at different sampling rates. (C) A zoomed-in view onto the initial seconds, exhibiting different neuronal Ca^{2+} transients. The dark green curve overlaid on the 39 Hz sampling (2 Hz low pass filter). (D) The baseline noise variation and the CNR as the function of the sampling rates (mean ± SEM, n = 2).

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Poster

P928. Optical Methodology: Calcium Indicators and Related Methodologies

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Title: Custom-address serial holography for the measurement of spike correlations between neurons in mouse visual cortex

Authors: *W. AKEMANN[1], S. WOLF[2], V. VILLETTE[2], C. VENTALON[2], J.-F. LÉGER[2], S. DIEUDONNÉ[2], L. BOURDIEU[2];
[1]IBENS, École Normale Supérieure, Paris, France; [2]IBENS, Ecole Normale Supérieure, Paris, France

Abstract: Custom-address serial holography (CASH) is a new method for optical recording of indicator-reported neuronal activity in 3D cortical volumes at high speed *in-vivo*. Our current implementation allows random address sampling of 20 cells at 1 kHz up to 200 cells at 0.1 kHz in head-fixed behaving mice across a cortical space of 500 x 500 x 500 mm^3 size. Using fast acousto-optic spatial light modulation, every single laser pulse of a 40 kHz regenerative amplifier is individually patterned to serially address a selection of target cells with a square 5x5 spot excitation volume covering the cell body and, for the prevention of recording artefacts, the surrounding space in anticipation of the cell displacements during animal behavior. The recorded activity is corrected for neuropil signaling component by weighted subtraction of a neuropil reference signal obtained by interleaved sampling of neuropil activity close to each cell. We performed 3D-CASH recordings of GCaMP6f expressing neurons in layer 2/3 and 5 of mouse primary visual cortex in response to moving contrast gratings and applied MLspike and blind sparse deconvolution to estimate spike events. Pairwise correlation was higher between neuron pairs in the same layer versus neuron pairs in different layers. Principal component analysis of the correlation matrix revealed a principal component assigning weights of opposite sign to neurons in layer 2/3 versus layer 5. Furthermore, closest follower spikes occurred with higher probability in a neuron of the same layer than neurons located in a different layer with a mean latency of 17±60 ms. Following the temporal periodicity of the stimulus, the spike rate of the response features a phasic component (R_1) together with a non-phasic component (R_0). Measured R_1/R_0 values are broadly distributed with weak bimodality resembling the transition between pure non-phasic response of neurons with complex receptive field to phasic response of neurons with simple receptive field. Our data validate 3D-CASH as a method for assessing neuronal activity in small 3D-distributed cortical circuits at high sampling rate.

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Poster

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Program #/Poster #: P928.07

Topic: I.04. Physiological Methods

Support: NIH BRAIN grants R01 1NS113278
NIH Grant R01 MH111438
NIH NINDS grant R35 NS097265
NIH instrument grant S10MH124733

Title: Development of a Photonic crystal fiber (PCF)-based fiber photometry for multi-channel cellular-specific recording

Authors: *Y. JIANG[1], M. FROSZ[2], X. YU[1];
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Max Planck Inst. for the Sci. of Light, Erlangen, Germany

Abstract: Given its MR compatibility and fast sampling of Ca^{2+} transients in millisecond scale, fiber photometry presents a powerful surrogate of *in vivo* electrophysiology when combining with fMRI to decipher the neuro-glio-vascular (NGV) coupling events. However, it remains challenging to distinguish NGV signaling at deep brain regions using fiber photometry. Here we proposed to develop a photonic crystal fiber (PCF) array-based multi-channel recording system, enabling the detection of cell-specific neuronal signals (e.g. GCaMP-based Ca^{2+} or GluSnFR-based Glutamate) from local NGV circuit. The PCF array has interleaved solid and hollow cores, allowing the optical signal transmission with little interference from adjacent ones using a light path designed in-house (**Fig 1A**). Each solid core has a diameter of 8-10 microns, matching the size of the neuronal soma, and the total PCF array tip covers cellular ensembles in a 250x250 μm^2 area. Here, we recorded the cellular specific neuronal signal using an sCMOS camera with ~1K sampling rate. In this work, we showed the multi-channel recording of the glutamate signals in the infragranular layer of the cortex. As shown in **Fig 1B**, the evoked Glu spikes can be detected from multiple solid cores through 36 channels upon forepaw electrical stimulation. In particular, we are detecting the different temporal dynamics of the evoked Glu signals from individual cores (e.g. Fig 1B, core 1, 7, 35), indicating the cellular-specific recording capability of the PCF-based imaging device. In summary, different from conventional fiber bundles, the PCF array enables multi-channel ultrafast cellular recording significantly reduces cross-talk, providing a unique recording device to measure distinct signaling events in the local NGV circut.

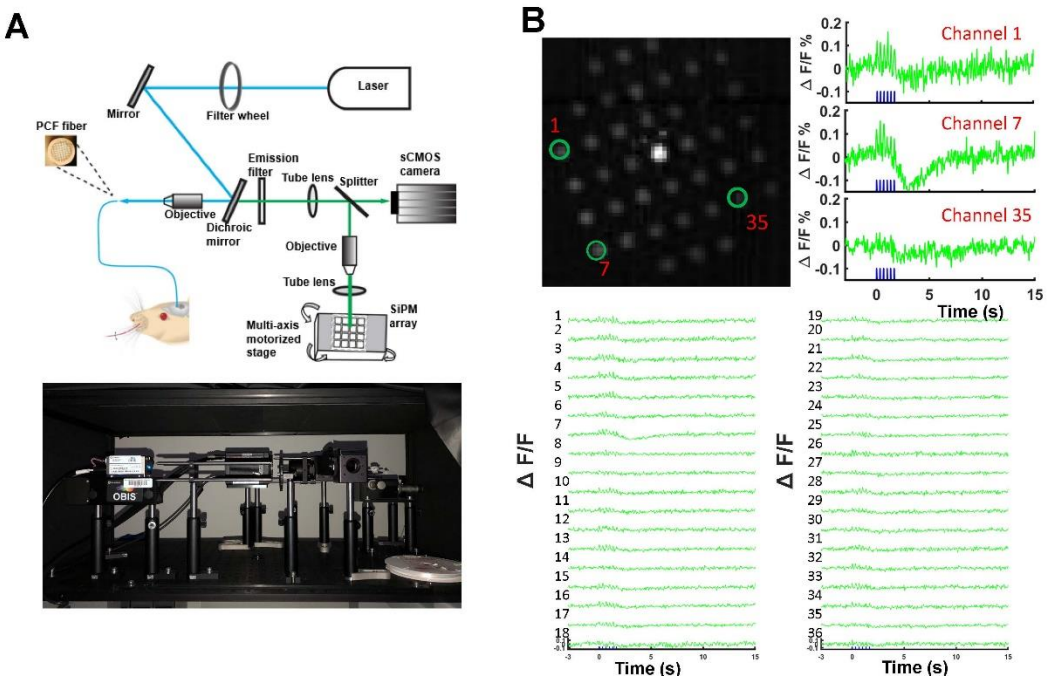


Figure 1. Multi-channel recording of Glu signal with PCF array. (**A**) The PCF-based imaging scheme and setup with 36 channels for in vivo parallel imaging. (**B**) The evoked Glu spikes from three channels (1, 7, 35) were represented to show the different temporal dynamics upon electrical stimulation of the forepaw (3 Hz, 2 s, 2mA).

Disclosures: Y. Jiang: None. **M. Frosz:** None. **X. Yu:** None.

Poster

P928. Optical Methodology: Calcium Indicators and Related Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P928.08

Topic: I.04. Physiological Methods

Title: Dual color imaging in freely-behaving rodents using a head-mountable one photon miniscope.

Authors: *G. RIZZI, S. GULATI, K. ZITELLI, A. STAMATAKIS;
Inscopix, Palo Alto, CA

Abstract: We have developed a miniscope platform nVueTM that enables dual color imaging in freely-behaving rodents, thus greatly expanding the current range of in vivo imaging applications. The nVue system enables numerous applications, including simultaneous imaging of Ca2+ activity in two distinct populations of cells, imaging Ca2+ activity with static markers that can identify neurons based on projection, activity, or genetics, and imaging Ca2+ activity alongside blood flow. To enable dual color imaging, we have integrated two separate LEDs into the miniscope to image green and red indicators

without crosstalk. To correct for chromatic shifts in green and red focal planes, we have also developed novel GRIN lenses that minimize axial chromatic aberrations. Furthermore, we use electronic focusing capabilities of our miniscope to automatically correct for any residual color aberration. We have also developed an analysis algorithm that enables detection of colocalized red and green cells. We have performed a rigorous characterization of the miniscope performance on the benchtop and in vivo. To validate several features of this miniscope, we imaged medial prefrontal cortical neurons expressing GCaMP in addition to the contralaterally-projecting neurons labeled with TdTom using a novel retrograde transport agent (rAAV2-retro-CAG-tdTomato). Using this preparation, we have validated that we are able to 1) correct for chromatic aberrations in vivo to merge the red and green channels and, 2) register the co-localized neurons as a subset of projection-specific neurons.

Disclosures: G. Rizzi: A. Employment/Salary (full or part-time):; Inscopix. **S. Gulati:** A. Employment/Salary (full or part-time):; Inscopix. **K. Zitelli:** A. Employment/Salary (full or part-time):; Inscopix. **A. Stamatakis:** A. Employment/Salary (full or part-time):; Inscopix.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.01

Topic: I.04. Physiological Methods

Title: High throughput screening using QPatch II and Qube 384 systems: electrophysiological evaluation of primary neurons, glial cells and hiPSC-derived motor neurons

Authors: *B. BADONE, K. BODDUM, K. R. ROSHOLM;
Sophion Biosci. A/S, Ballerup, Denmark

Abstract: The QPatch II and Qube 384 are two automated patch-clamp (APC) systems useful for evaluating the electrophysiological properties of different cell models, with the possibility to perform high throughput compound screening for drug discovery. These systems provide high fidelity recordings which in combination with accurate, low volume applications, make them ideal for studying both voltage- and ligand- gated ion channels. With a rapidly increasing number of ion channels identified as potential therapeutic targets in neurological diseases, there is an urgency of finding valid neuronal cell models. Among these, primary brain cells and human induced pluripotent stem cells (hiPSCs)-derived neurons are promising physiological models for evaluating ion channels properties and potential drugs. Here we used our APC systems for studying both voltage-gated (Na_V, K_V) and ligand-gated ($GABA_A$) ion channels by comparing two different brain models: *i)* primary neurons and astrocytes dissociated from mouse and rat brains, respectively; and *ii)* hiPSC-derived motor neurons. Patch-clamp recordings require healthy membranes for high resistance sealing; however, different isolation methods may alter the membrane composition and change intracellular characteristics. Here we demonstrate that the electrophysiological properties of both brain cell models are maintained during APC recordings, confirming that both QPatch II and Qube 384 are powerful platforms for investigating brain cell models.

Disclosures: B. Badone: None. **K. Boddum:** None. **K.R. Rosholm:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.02

Topic: I.04. Physiological Methods

Title: The effect of inter-trial on the quantification of intracortical facilitation in the primary motor cortex

Authors: K. J. NORDA[1], R. BOSS[1], M. PREMYANOV[1], D. MORRIS[1], D. AYLENDER[1], Z. A. RILEY[2], ***B. POSTON**[1];
[1]Univ. of Nevada Las Vegas, Las Vegas, NV; [2]Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Intracortical facilitation (ICF) is a common paired-pulse transcranial magnetic stimulation (TMS) measurement used to quantify interneuron activity in the primary motor cortex (M1). Due to the prevalence of the technique, most of the stimulation parameters to optimize quantification of ICF have been established. However, the underappreciated methodological issue of the time between MEP trials (inter-trial interval; ITI) has been rarely reported, unstandardized, and different ITIs have never been directly compared in a paired-pulse TMS study. This is important because a previous single-pulse TMS study found MEP amplitude reductions during the course of TMS trial blocks for short ITIs of 5 seconds and below, but not for a long ITI of 10 seconds (Julkunen et al. 2012). Similar overall effects of short and long ITIs were reported by (Moller et al. 2009) during the measurement of single-pulse recruitment curves. The purpose was to determine the influence of different ITIs on the measurement of ICF at rest. Sixteen young men and women completed a single experimental session. Surface EMG was recorded from the first dorsal interosseous (FDI) muscle of the right hand in response to TMS of the left M1. Each experiment involved: 1) resting motor threshold (RMT) quantification; 2) identification of the TMS intensity required to elicit a 1 mV MEP with a 10 second ITI; and 3) 4 separate ICF trial blocks presented in randomized order with each block utilizing one of 4 different ITIs (4, 6, 8, and 10 seconds). Each ICF trial block involved 52 trials (26 single-pulse MEP trials and 26 condition-test trials). ICF was always evoked using a 10 millisecond interstimulus interval, a conditioning stimulus intensity of 90% of RMT, and a 1 mV test stimulus intensity. The primary outcome was the amount of ICF (% facilitation). One-way ANOVAs indicated no significant differences in test MEP amplitudes ($P = 0.992$), conditioned MEP amplitudes ($P = 0.94$), and therefore ICF between the 4 ITIs ($P = 0.477$). The findings of this methodological study indicate that ITIs between 4-10 seconds provide nearly identical ICF values. Based on these results, it is recommended that an ITI of 4 seconds be utilized for quantification of ICF to optimize participant and investigator comfort as well as the time efficiency of TMS experiments.

Disclosures: K.J. Norda: None. **R. Boss:** None. **M. Premyanov:** None. **D. Morris:** None. **D. Aylender:** None. **Z.A. Riley:** None. **B. Poston:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.03

Topic: I.04. Physiological Methods

Support: NIH NINDS T32 - NS 7292-33
Smith Foundation Odyssey Award
Brandeis Innovation SPROUT grant

Title: Adaptamaze adaptable and automated rodent behavior maze system

Authors: *J. OLSON[1], C. A. LEPPLA[1], J. H. BLADON[1], S. P. JADHAV[2];
[2]Psychology, [1]Brandeis Univ., Waltham, MA

Abstract: Mazes are a fundamental and widespread tool in behavior and systems neuroscience research due to rodents' natural proclivity to navigate towards rewards. Beginning in the early 20th century (Small, 1901), navigation experiments have uncovered landmark discoveries in learning & memory (Tolman et al., 1946) and its neural substrates (O'Keefe & Dostrovsky, 1971; Olton & Samuelson, 1976). Today, unique mazes are designed to test specific questions in these fields (Ainge et al., 2007; Böhm & Lee, 2020; Knierim et al., 2000; Nitz, 2006; Olson et al., 2017; Porter et al., 2018; Steiner & Redish, 2014; Tanila et al., 2018; Wilson et al., 2015), and standard maze designs are pervasive and underlie foundational tasks in learning and memory, decision-making, and even anxiety (e.g. Barnes, 1979; Frank et al., 2000; Handley & Mithani, 1984; Morris et al., 1982; O'Keefe & Dostrovsky, 1971; Olton & Samuelson, 1976). Facilitated by advances in neural data recording capabilities and machine learning analytical techniques, increasingly complex behavioral paradigms that include multiple environments are desired to investigate contextual memory and representations, spatial remapping, and adaptive decision making.

Unfortunately, current maze designs often limit potential experimental configurations. For simple or standardized designs, each maze is frequently one static piece with limited flexibility for configuration. This approach requires separate mazes to be made, stored, and positioned for any multi-environment recording. The demand on space and their inflexibility limits potential experiments. Alternatively, trainee scientists will spend months learning engineering skills to design and build complex, automated mazes to address a specific question. Despite the time invested, these mazes are rarely capable of flexible changes into novel maze configurations, and so the same cost in design and manufacturing recurs for each experiment.

To alleviate these issues, we developed an automated modular maze system to create flexible and scalable maze environments. The maze can be formed into multiple configurations in minutes. Reward wells integrated into the track pieces enable automated lick detection and reward delivery. Automated barriers can be placed between any track components, allowing additional environmental manipulations during a behavioral session. This maze system enables novel behavioral and neurophysiology experiments without the time and monetary costs that come with custom behavioral track design and with greater reproducibility and repeatability, potentially leading to greater advances in rodent behavior and neurophysiology knowledge.

Disclosures: J. Olson: None. **C.A. Leppla:** None. **J.H. Bladon:** None. **S.P. Jadhav:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.04

Topic: I.04. Physiological Methods

Support: NIH Grant R01 NS117405
NIH Grant R01 NS088674

Title: An improved system for simultaneous transcranial magnetic stimulation and single-unit recordings in non-human primates

Authors: *R. KOTHARE, S. M. GOETZ, R. HAMDAN, B. WANG, W. M. GRILL, A. V. PETERCHEV, M. A. SOMMER;
Duke Univ., Durham, NC

Abstract: Transcranial magnetic stimulation (TMS) is an FDA-cleared, non-invasive form of neuromodulation. While its effects in the human brain have been assessed at the macroscopic level (e.g. EMG, EEG, fMRI), there is a lack of understanding of finer-scale responses on the neuronal circuit level, and this limits the rational design of therapeutic TMS protocols. We aim to quantify the neuronal effects of TMS through single-unit recordings in the target region of stimulation in awake macaques. One of the main challenges of simultaneous recording during TMS is the presence of large, electromagnetically induced artifacts that hinder the isolation of small neuronal signals. We previously developed an electrophysiology system capable of resolving action potentials shortly after TMS pulses (Mueller et al. 2014). To improve on that system, which required manual tuning of artifact cancellation and used components that are now obsolete, we developed an updated, three-stage amplifier system that is more robust, automatic, and offers short recovery times after a pulse. To reduce capacitive coupling between the TMS coil and the recording system, we adapted a method from Li et al. (2017) involving the application of a grounded conductive coating to the coil. We also developed a low-inductance input connection that mitigates the inductive TMS artifact in the electronics, decreases leakage current into the brain, and reduces variability of the artifact across experiments better than the previous input connection. Additionally, we assessed the performance of three electrode materials - tungsten, platinum-tungsten, and platinum-iridium - with our system. Lastly, we developed post-processing methods to isolate better action potentials from the recorded signal. Overall, we present a new system capable of resolving neural signals within ~1-2 ms after the TMS pulse and reproducible for use in other laboratories.

Disclosures: R. Kothare: None. **S.M. Goetz:** None. **R. Hamdan:** None. **B. Wang:** None. **W.M. Grill:** None. **A.V. Peterchev:** Other; Rogue Research, Tal Medical/Neurex, Magstim, MagVenture, Neuronetics, BTL Industries, Advise Connect Inspire. **M.A. Sommer:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.05

Topic: I.04. Physiological Methods

Title: High throughput electrophysiological screen of large molecules: evaluating snake neurotoxins and the neutralization potential of recombinant antibodies

Authors: *K. BODDUM[1], L. LEDSGAARD[2], M. BUSK[1], D. BELL[1], A. H. LAUSTSEN[2];
[1]Sophion Biosci., Ballerup, Denmark; [2]Dept. of Biotech. and Biotherapeutics, Tech. Univ. of Denmark, Kongens Lyngby, Denmark

Abstract: Currently, more than 90% of approved drugs are small molecules, but large molecules (> 1.000 Da, also known as biologics) are rapidly rising in prominence and importance in drug discovery and already constitute the lion's share of top 10 selling drugs worldwide.
Large molecules have gained attention due to their mode of action, often achieving greater target specificity and potency than small molecule drugs. This, however, comes at a cost: often, they are expensive and scarce and can have unwanted polyreactivity ("stickiness"). In addition, they are more sensitive to their environment, as their three-dimensional structure is key to their function and relies on other, weaker interactions than covalent bonds. Two automated patch-clamp (APC) systems, QPatch II and Qube 384, have long been used in advancing drug discovery on ion channels, developing much-needed novel treatments, including large molecules targeting ion channels. Using APC, we have evaluated two groups of α-neurotoxins (7-8 kDa) and IgG antibodies (150-170 kDa).
Method
Snakebite is a highly neglected tropical disease, causing 100,000 yearly deaths and around 400,000 amputations. Each snake species has a unique venom, consisting of several dozen different toxins. One of the most medically relevant groups of snake toxins is α-neurotoxins, targeting the nicotinic acetylcholine receptor (nAChR). Evaluating the potential of recombinant monoclonal antibodies (mAbs) in the IgG format to neutralize α-cobratoxin (an α-neurotoxin from *Naja kaouthia*) and thereby prevent the inhibition of the nAChR response, planar whole-cell patch-clamp experiments were carried out on QPatch II, briefly: The human-derived Rhabdomyosarcoma RD cell line, endogenously expressing the muscle-type nAChR was patched, and the inhibitory effect of α-cobratoxin was evaluated, followed by a study of the concentration-dependent neutralizing effect of seven different IgGs. Next, the Qube 384 was employed for combinatory screening of both neutralizing potential and toxin cross-reactivity. In total, six different α-neurotoxins from four different elapid snake species were tested against 15 different IgGs.
Conclusion
The study demonstrated the potential of a range of IgGs to neutralize α-neurotoxins from several snake species. This is a critically important step toward enabling the design of novel, broadly-neutralizing recombinant antivenoms against snakebite envenoming. This work highlights the potential and advantages of using high-throughput electrophysiology systems to evaluate the functional activity of two large molecules, in this case, protein-based toxins and antibodies.

Disclosures: K. Boddum: A. Employment/Salary (full or part-time):; Sophion Bioscience. **L. Ledsgaard:** None. **M. Busk:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **D. Bell:** A. Employment/Salary (full or part-time):; Sophion Bioscience, Sophion A/S. **A.H. Laustsen:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.06

Topic: I.04. Physiological Methods

Support: NIH Grant R01NS102727
NIH Grant R01DA029639

Title: Towards the perfect pipette: manufacture and reuse of high gigaseal, low noise electrodes for patch clamp electrophysiology

Authors: *M. C. YIP[1], C. R. LANDRY[2], M. M. GONZALEZ[1], C. R. FOREST[1];
[1]Woodruff Sch. of Mechanical Engin., [2]Wallace H. Coulter Sch. of Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA

Abstract: Reuse of intracellular patch clamp electrodes was thought to be impossible due to accumulation of cellular debris in and around the tip of the electrode during patch clamp processes. However, in recent years, this fundamental limit of patch clamping has been overcome by trailblazing studies using detergents and oxidizers to remove cellular debris from the one micrometer diameter electrode aperture enabling immediate reuse in both single pipette and planar patch configurations. The innovation of cleaning a pipette has enhanced patch clamp automation such as the PatcherBot, an artificial intelligence-guided robot capable of performing 10-12 patch recordings per hour in cultured cells slices without human intervention. We have previously demonstrated that this technique can successfully clean and reuse a pipette over 100 times, and while such advances are noteworthy, all patch clamp experiments are limited by the original quality of the pipette and the need to constantly manufacture replacements. Improvements toward making the perfect pipette have been documented including the use of quartz electrodes for significantly low-noise recordings and the nano-machined tips of pipettes using focused ion beam (FIB) milling for high-resistance (>3 GΩ) junctions (or gigaseals) with the cell membrane. While fabricating these pipettes are laborious and time-consuming, the technology of cleaning pipettes enables greater efficacy and utilization out of each pipette. Here, we present an extension of the method for cleaning pipettes that enables re-uses towards perfect pipettes with no measurable change in yield or recording quality. Specifically, we will demonstrate cleaning of low-noise quartz pipettes and high gigaseal FIB-milled pipettes and show time-based scalability of pipette reuse by storing and reusing pipettes overnight (patch with the same pipette 10-12 hours later). This technology development will raise the high-quality recording capabilities of patch clamp electrophysiology, enabling repeatable high throughput experiments across neuroscience that can be readily adapted to fields ranging from *in vitro* phenotypic screening to single ion channel pharmacological screening.

Disclosures: M.C. Yip: F. Consulting Fees (e.g., advisory boards); Neuromatic Devices. **C.R. Landry:** None. **M.M. Gonzalez:** None. **C.R. Forest:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.07

Topic: I.04. Physiological Methods

Support: NIH Grant MH123711
NIH Grant NS102727

Title: Morpho-electric classification of single neurons in intact brain organoids

Authors: *C. R. LANDRY[1], W. NUI[3], Z. WEN[3], C. R. FOREST[2];
[1]Wallace H. Coulter Dept. of Biomed. Engin., [2]George W. Woodruff Sch. of Mechanical Engin., Georgia Inst. of Technol., Atlanta, GA; [3]Dept. of Psychiatry and Behavioral Sci., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Human brain organoids have been shown to contain a diverse range of cell types representative of the developing human brain. Understanding the diversity of these cell types in terms of structure, function, and genetics is critical for understanding human neurodevelopment. However, current cell type classification methods in brain organoids rely on RNA-seq and immunohistochemistry, in part because of the technical challenges and low throughput associated with patch clamp electrophysiology. Using fully automated and semi-automated methods developed in our laboratory to perform patch clamp recordings in large, intact human brain organoids, we are working to fills the gaps in cell type classification in human brain organoids. To this end, we have developed a pipeline to collect electrophysiological and morphological data from single brain organoid neurons without disrupting the fine neuronal structure or local synaptic network. To demonstrate the utility of this approach, we will show **1)** semi-automated patch clamp recordings of deep neurons from mature human brain organoids (i.e., 120 days in vitro), **2)** morphological reconstruction of deep neurons using biocytin-based labeling, **3)** and whole-mount imaging of intact brain organoids using CUBIC tissue clearing. Using this initial dataset from dozens of mature, intact human brain organoids, we will propose approaches for integrating morphological and electrophysiological cell types into current cell type models for human brain organoids.

Disclosures: C.R. Landry: None. **W. Nui:** None. **Z. Wen:** None. **C.R. Forest:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.08

Topic: I.04. Physiological Methods

Support: NIH Grant 1-U01-MH106027-01
NIH Grant R01NS102727
NIH Grant R01 EY023173
NSF Grant EHR 0965945
NSF Grant CISE 1110947
NIH Grant R01DA029639

Title: Fully automated fluorescence-guided patch clamp for cell type-specific electrophysiology in adult mouse cortex

Authors: *M. M. GONZALEZ[1], A. M. GOETTEMOELLER[2], M. J. M. ROWAN[2], C. R. FOREST[1];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Emory Univ., Atlanta, GA

Abstract: Recently, single-neuron RNA sequencing has allowed for the identification of an incredible diversity of neuronal cell types in the cortex. Characterizing the distinct electrophysiology of these cell types is an important step toward understanding the physiological properties across all cortical regions. Patch clamp electrophysiology enables the recording of single-cell behavior with unrivalled spatiotemporal resolution. While patch clamp can yield high fidelity electrophysiology data, the process is often challenging and time-consuming. Even with the development of automated patch clamp systems, many of these approaches cannot independently select and patch cells based on cell type. To enable targeted electrophysiological profiling of neurons in the cortex, we developed a fully automated, fluorescence-guided patch clamp electrophysiology rig which targets distinct cell types in ex vivo acute slices. By employing newly developed deep learning-based image processing methods and cleaning the patch pipettes for immediate reuse, the automated patch clamp robot could identify and patch 20 labeled GABAergic interneurons expressing green fluorescent protein from a single mouse, achieving quality of recording equivalent to a patch-clamp expert. The process reduces the time to patch and can be scaled to target other cell types by injecting multiple AAVs, using transgenic mice, and using additional filter cubes to filter different spectra. This advancement in automated patch clamp will enable a more efficient and robust characterization of neuronal behavior by programmatically targeting different cell types within the same slice while reducing the amount of time necessary to acquire high fidelity data.

Disclosures: M.M. Gonzalez: None. **A.M. Goettemoeller:** None. **M.J.M. Rowan:** None. **C.R. Forest:** None.

Poster

P937. Electrophysiology Methods: Cellular

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:00 AM - 11:00 AM

Program #/Poster #: P937.09

Topic: H.08. Learning and Memory

Support: Supported by the Simons Foundation

Title: How much error is in your spiking data? Quantifying errors in spike sorting with ground truth.

Authors: *L. M. F. KLAVER, E. AKBAR, R. C. BULLINS, K. C. ARNDT, E. T. GILBERT, D. F. ENGLISH;
Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Mammalian brains encode information in the spiking activity of populations of neurons. To study population coding in behaving animals, spikes from ensembles of hundreds of neurons can be recorded with extracellular electrodes and assigned to their source neurons using spike sorting.
For decades, one problem has reduced the rigor and reproducibility of spike sorted data: it has been impossible to meaningfully quantify sorting accuracy because of insufficient empirically validated data, termed ‘ground truth’. Ground truth data for spike sorting consist of extracellular recordings in which a subset of neurons are also recorded with a second, unambiguous technique, such as a glass electrode.

Ground truth data are essential for quantifying spike sorting performance and developing automatic spike sorters to replace manual methods which are time-consuming and error prone. Such automatic sorters are urgently needed, as novel technologies will soon enable the recording of so many neurons that manual curation will no longer be possible.
We have generated a ground truth dataset in awake, behaving mice recorded from the hippocampus. Using SpikeInterface, we investigated performance and error sources of spike sorters on our data. Sources of error include different neuronal activity and signal artifacts; locomotion, electromyographic artifacts, local field potential oscillations, population synchrony, waveform changes during bursting, and electrode drift. We found that the contribution of these individual errors to overall error rates depend upon interactions between brain area, cell type, state, and upon choice of sorting algorithm and its parameters. These results will provide the neuroscience community with quantitative guidelines for spike sorting, and will aid in algorithm development. The resources presented will improve the rigor and reproducibility of all spike sorted data.

Disclosures: L.M.F. Klaver: None. **E. Akbar:** None. **R.C. Bullins:** None. **K.C. Arndt:** None. **E.T. Gilbert:** None. **D.F. English:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.01

Topic: A.05. Axon and Dendrite Development

Support: NIH R35 NS097340
NSF IOS-1853719

Title: Tace/ADAM17 dependent proteolytic processing of the Fra/Dcc receptor is required for commissural axon guidance

Authors: *Y. ZANG, K. CHAUDHARI, G. BASHAW;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Accurate axon targeting is a critical early step during the assembly of the neuronal network. This process requires signaling cascades that are coordinated across the growth cone plasma membrane by transmembrane axon guidance receptors. In particular, the conserved Frazzled (Fra)/Deleted in Colorectal Cancer (Dcc) receptor promotes axon growth and attraction in response to its ligand netrin. Fra can also function independently of Netrin in *Drosophila* commissural neurons to promote axon midline crossing. In this context, Fra undergoes gamma-secretase dependent cleavage to generate an intracellular domain that translocates to the nucleus to activate the transcription of Commissureless, a positive regulator of midline crossing. However, what signal activates the gamma-secretase cleavage of Fra and whether it is conserved for Dcc is currently unknown. Here we show that the Alzheimer's disease-associated ADAM family metalloprotease Tace/ADAM17 cleaves the extracellular domains of Fra and Dcc, and this step is required for Fra's transcriptional activity. Tace/ADAM17 is expressed in the developing *Drosophila* nerve cord and mouse spinal cord, and removal of *tace* in *Drosophila*

commissural neurons enhances *fra*-dependent axon projection deficits. In *Drosophila* ipsilateral neurons and in mouse dorsal spinal cord commissural explants, Tace/ADAM17 overexpression abrogates netrin-dependent axon growth and attraction. Our findings reveal a conserved role for Tace/ADAM17 in the Fra/Dcc signaling pathway during early development of the central nervous system. Further, as axon guidance receptors also function outside of the nervous system and play diverse roles in development and disease, the pathway defined here linking ADAM metalloprotease and gamma-secretase-dependent receptor cleavage to the nuclear import and transcriptional activity of an axon guidance receptor is likely be broadly important.

Disclosures: Y. Zang: None. **K. Chaudhari:** None. **G. Bashaw:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.02

Topic: A.05. Axon and Dendrite Development

Support: Wings for Life
Italian Ministry of Foreign Affairs and International Cooperation

Title: Physical stimulation of axon outgrowth and neural maturation via magnetic forces

Authors: A. FALCONIERI[1], S. DE VINCENTIIS[1], J. LOPANE[1], S. FIGOLI[1], S. GHIGNOLI[1], M. BAGGIANI[1], D. CONVERTINO[3], M. MAINARDI[4], V. CAPPELLO[3], M. ONORATI[1], L. MARCHETTI[3,2], M. COSTA[4], ***V. RAFFA**[1];
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Abstract: Neurons are mechanosensitive cells that respond to direct application of force [1]. Recently, our team developed a method based on magnetic nanobeads to magnetize axons and pulling them through a precise and controllable magnetic field vector [2]. Pulled axons of hippocampal neurons were found to increase in length and branching and addition of new mass was confirmed [3]. Here, we focused on the local response evoked by this stimulus. Our results suggest that the nanobeads localise in close proximity of axonal microtubules (MT) and the pulling force promotes their polymerization. As MTs modulate axonal transport dynamics, it was not surprising to find an alteration of the trafficking vesicles and their accumulation in the pulled axons. Considering that some of these vesicular components, like RNA granules and late endosomes, are involved not only in axonal transport but also in local translation [4], we analysed ribosomes in active translation, confirming their accumulation under the stimulus. Collectively, these results gave rise to the idea of the pulling force coordinating, through the modulation of MT dynamics, a cross-talk between axonal transport and local translation and that this complex dialogue could be the basis for addition of new mass. The analysis of local transcriptome supports this idea and some genes involved in regulation of cytoskeletal dynamics were found dysregulated. However, the larger number of differentially expressed genes were involved in synaptic formation/maturation. At the synaptic level, we found alteration of the ultrastructure, increase in the co-localization of pre- and post-synaptic

elements and increase of neuronal excitability under the stimulus. Interestingly, our results were confirmed in both developing hippocampal neurons and neural precursor cells, providing another line of evidence that mechanical stimuli may play a fundamental role in shaping endogenous mechanisms of neural development. 1. De Vincentiis, S., Falconieri, A., Scribano, V., Ghignoli, S., Raffa, V. Manipulation of axonal outgrowth via exogenous low forces.International Journal of Molecular Sciences, 2020, 21(21), pp. 1-27, 8009 2. Raffa V, Falcone F, De Vincentiis S et al. Piconewton Mechanical Forces Promote Neurite Growth. Biophysical journal 115(10), 2026-2033 (2018)3. De Vincentiis, S., Falconieri, A., Mainardi, M., ...Costa, M., Raffa, V. Extremely Low Forces Induce Extreme Axon Growth. Journal of Neuroscience, 2020, 40(26), pp. 4997-5007 4. Cioni, J-M. at al. Late Endosomes Act as mRNA Translation Platforms and Sustain Mitochondria in Axons. Cell. 2019 Jan 10; 176(1-2): 56-72.e15.

Disclosures: A. Falconieri: None. **S. De Vincentiis:** None. **J. Lopane:** None. **S. Figoli:** None. **S. Ghignoli:** None. **M. Baggiani:** None. **D. Convertino:** None. **M. Mainardi:** None. **V. Cappello:** None. **M. Onorati:** None. **L. Marchetti:** None. **M. Costa:** None. **V. Raffa:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.03

Topic: A.05. Axon and Dendrite Development

Support: BRFSG-2016-11
NIH R01 NS095908
NIH T32 MH020068
NIH T32 NS062443
NIH T32 GM077995
NIH T32 GM760139

Title: Nell2 and robo3 control axon guidance and neuronal migration in the developing spinal cord

Authors: *A. J. TULLOCH, Z. J. DELOUGHERY, J. ABOLAFIA, A. JAWORSKI;
Neurosci., Brown Univ., Providence, RI

Abstract: Guidance of migrating neurons and growing axons to their destinations is essential for proper nervous system wiring. The signaling pathways that control and cross-coordinate these steps in neural circuit development remain incompletely understood. In the embryonic spinal cord, the Robo3 receptor guides commissural axons across the floor plate at the ventral midline. Robo3 promotes midline crossing by executing three functions in parallel, as it inhibits repulsion from floor plate-derived Slit proteins, potentiates Netrin-1 attraction to the midline, and mediates NELL2 repulsion from the ventral horn. These varied signaling outputs of Robo3 synergize to steer commissural axons towards and across the floor plate with high fidelity, and they appear to be partially redundant. Consistent with this idea, inactivation of the repulsive Robo3 ligand NELL2 by itself does not appear to cause commissural axon guidance errors unless combined with loss of one *Robo3* allele, which partially impairs the two additional functions of Robo3. Here, we revisited the roles of NELL2 and Robo3 in commissural neuron wiring through detailed

phenotype analysis of knockout mice. We discovered that, early during spinal cord development, commissural pioneer axons aberrantly project into the ventral horn after loss of NELL2, even in the presence of both *Robo3* wild-type alleles. Further, we present evidence that NELL2 and Robo3 control neuronal cell body positioning in the ventral spinal cord. Finally, we show that Robo3 helps confine axons within the neural tube, as loss of Robo3 causes aberrant commissural axon growth into the body periphery. Together, these findings uncover novel functions for NELL2-Robo3 signaling in axon guidance and neuronal migration, thereby enhancing our understanding of mechanisms that control neural circuit assembly.

Disclosures: A.J. Tulloch: None. **Z.J. Deloughery:** None. **J. Abolafia:** None. **A. Jaworski:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.04

Topic: A.05. Axon and Dendrite Development

Support: UBACYT 0769

Title: Gdnf and epha3 ectodomain regulate retinal ganglion cell axon guidance.

Authors: *G. SPELZINI[1,2], M. MEDORI[1,2], J. RONDÓN MARTÍNEZ[1,2], M. ROBALDO[1,2], L. R. TERUEL[1,2], V. SANCHEZ[1,2], L. FIORE[1,2], G. E. SCICOLONE[1,2];
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Abstract: Previously we showed that tectal EphA3 stimulates axon growth of nasal retinal ganglion cells (RGC) toward the caudal tectum preventing them from branching in the rostral tectum. GDNF participates in the formation of topographic connections of motor neurons of the spinal cord with the muscles of the lower limbs, stimulating axon growth interacting with Eph/ephrin system. However its effect on RGC axon growth and guidance is not clear and there is no evidence about the combinatorial effects of EphA3 and GDNF. We demonstrated that GDNF and EphA3 stimulate RGC axon growth.Our purpose was to study the individual and combinatorial effects of EphA3 and GDNF on RGC axon guidance.We cultured chicken embryo nasal retinal explants and dissociated RGCs on poly-L-lysine/laminin and exposed them to control conditions, to EphA3 ectodomain (aggregated EphA3-Fc), to GDNF or to EphA3-Fc plus GDNF to evaluate their effects on axon guidance.To confirm that EphA3 has a positive effect on the axon guidance of nasal RGCs, we developed the technique of Stripe assay using retinal explants. Nasal RGCs axons preferentially grow on a substrate with EphA3 instead of a permissive substrate of laminin in the stripe assay. This axonal preference is not modified with the addition of GDNF.
In order to evaluate the participation of soluble gradients of GDNF and EphA3 on the axonal guidance of nasal RGCs, we developed a chemotaxis test using the Dunn's chamber. This consists of two concentric rings in one glass slide face. An annular bridge lower than the rest of the slide separates both wells. The

external well contains a chemoattractant while the internal well contains culture medium. A linear gradient of chemoattractant is formed by diffusion across the bridge between two wells.
The results showed that RGC axons change their directions of growth toward gradients of EphA3 and GDNF. Besides, EphA3-Fc and GDNF together present the highest effects in comparison to the effects produced by any of them alone.
This demonstrates that GDNF and EphA3 not only stimulate RGC axon growth but their gradients also have chemoattractant effects on nasal RGC axons, suggesting that both of them present synergistic effects.
Supported by UBACYT 0769.

Disclosures: G. Spelzini: None. **M. Medori:** None. **J. Rondón Martínez:** None. **M. Robaldo:** None. **L.R. Teruel:** None. **V. Sanchez:** None. **L. Fiore:** None. **G.E. Scicolone:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.05

Topic: A.05. Axon and Dendrite Development

Support: ETH Grant ETH–24 19–02

Title: A developmentally induced gene expression address space for axonal navigation

Authors: *S. KERSTJENS, G. MICHEL, R. J. DOUGLAS;
Inst. of Neuroinformatics, Zürich, Switzerland

Abstract: During brain development, billions of axons must navigate over multiple spatial scales in order to reach specific targets, and so form functional circuits. However, the genome has insufficient information capacity to encode all of these routes independently. Therefore, we are exploring mechanisms of development that could provide a compressive encoding of the global wiring task. One important aspect of our proposed mechanism is that development induces a global address space, analogous to a space of postal codes. Here we report experimental evidence for such an address space embedded in the gene expression patterns of mouse brain. We analysed expression data of 1240 genes in developing and adult mouse brains measured through *in situ* hybridization at 8 time points, and binned in 3D voxels of 80-200μm (larger voxels at later time points), by the Allen Institute for Brain Science. We found that gene expression covariance partitions the brain into a global spatial hierarchy of nested contiguous regions. The hierarchy is stable over at least the measured time points (accuracy of at least 80%, controlled baseline 67%), ranging from E11.5 to P56, and embedded reliably in the expression of any sufficiently large set of randomly chosen genes (accuracy of at least 80% with at least 50 genes). We explain mathematically, and confirm through simulation, that this global hierarchy can arise from two simple constraints on mitosis: That the mitotic daughter cells have, on average, a similar gene expression profile to their parent; and that, on average, they do not migrate too far from one another. With these features—hierarchical spatial structure, stability, and ease of induction—the hierarchy is consistent with a global address space for a global wiring mechanism.

Disclosures: S. Kerstjens: None. **G. Michel:** None. **R.J. Douglas:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.06

Topic: A.05. Axon and Dendrite Development

Support: Davidson Faculty Study and Research Grant
CURE CADASIL (to George Brown)

Title: Notch is required for the completion of the late-developing avm branch at the c. elegans nerve ring

Authors: G. BROWN[1], A. LEONARD[2], R. GUERRERO[3], S. EMERSON[4], ***R. EL BEJJANI**[5]; [1]medical college of georgia, augusta, GA; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Univ. of Florida, Gainesville, FL; [4]Neurosci., Vanderbilt Univ., Nashville, TN; [5]Davidson Col., Davidson, NC

Abstract: Most studies to date have examined axon growth and guidance during early development but less is known about these processes during later stages. The conserved Notch signaling pathway regulates key developmental processes and remains active after development is completed. We show that Notch is required for the growth of an axonal branch that connects the anterior touch neurons in *C. elegans* in the last larval stage, after most other neurons have completed their development. The late-developing AVM mechanosensory branch exhibits defects in all Notch pathway mutants tested. The defect is a failure in branch formation during late development and not a result of degeneration of a previously formed branch or of developmental delay. Tissue specific rescue experiments suggest that Notch functions non-autonomously, in tissues other than the adjacent body wall muscles. Interestingly, initial ventral guidance of the AVM neuron is not affected in Notch mutants, suggesting that Notch specifically affects the formation of the late, anterior branch.

Disclosures: G. Brown: None. **A. Leonard:** None. **R. Guerrero:** None. **S. Emerson:** None. **R. El Bejjani:** None.

Poster

P023. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P023.07

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Howard Hughes Medical Institute support

Boehringer Ingelheim Fonds PhD student fellowship (Charalampia Koutsioumpa)

Title: Developmental specification of glabrous and hairy skin innervating mechanosensory neurons and its skin dependence

Authors: *C. KOUTSIOUMPA, C. SANTIAGO, B. P. LEHNERT, D. SCHMENLYUN, D. L. PAUL, D. D. GINTY;
Dept. of Neurobiology, Howard Hughes Med. Inst., Harvard Med. Sch., Boston, MA

Abstract: Our sense of touch is essential for life and relies on Low-Threshold MechanoReceptors (LTMRs) whose cell bodies reside in dorsal root and trigeminal ganglia. Interestingly, LTMR subtypes characterized by early embryonic expression of Ntrk2 (TrkB) exhibit morphological and physiological properties that are different depending on the skin region they innervate - hairy skin or hairless (glabrous) skin. In glabrous skin, $TrkB^+$ LTMRs terminate within Meissner corpuscles, while in hairy skin $TrkB^+$ LTMRs form longitudinal lanceolate endings around hair follicles. $TrkB^+$ LTMRs that innervate glabrous skin are Aβ RA1-LTMRs with fast conduction velocities and responsivity to vibration and gentle indentation. $TrkB^+$ LTMRs that innervate hairy skin, on the other hand, are Aδ-LTMRs (D hair cells) with intermediate Aδ conduction velocities and responsivity to indentation and also hair deflection in a directional manner. It is unclear whether embryonic neurons that share TrkB expression are genetically specified to become Aβ RA1-LTMRs and Aδ-LTMRs or whether the interaction of embryonic $TrkB^+$ neurons with different skin regions controls the development of skin region-specific $TrkB^+$ LTMR subtypes. Sparse genetic labeling experiments demonstrate that the morphological specializations of glabrous skin and hairy skin of paw innervating $TrkB^+$ neurons arise at nearly identical times during postnatal development. Interestingly, many $TrkB^+$ neurons terminate along the border of glabrous and hairy paw skin, and individual "$TrkB^+$ border neurons" exhibit branches that formed both lanceolate endings and Meissner corpuscles. Transcriptomic profiling and RNAscope experiments show that neonatal $TrkB^+$ DRG neurons that innervate glabrous skin and hairy skin are transcriptionally very similar, although they are distinct from other DRG neuron types. Lastly, using mouse mutants that have either ectopic glabrous skin or ectopic hairy skin we find that $TrkB^+$ neurons that innervate the ectopic skin regions of these mutants form ending types (either lanceolate or Meissner corpuscle endings) in accordance with the ectopic skin type. Together, these findings support a model in which embryonic $TrkB^+$ DRG neurons are poised to become either Aβ RA1-LTMRs of Meissner corpuscles or Aδ-LTMRs associated with hair follicles, and that glabrous skin and hairy skin differentially instruct the maturation of neonatal $TrkB^+$ neuron axonal endings. This model implies that neuronal identity in the peripheral nervous system is flexibly determined by target tissue.

Disclosures: C. Koutsioumpa: None. **C. Santiago:** None. **B.P. Lehnert:** None. **D. Schmenlyun:** None. **D.L. Paul:** None. **D.D. Ginty:** None.

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.01

Topic: B.07. Synaptic Plasticity

Support: Howard Hughes Medical Institute

Title: Role of Behavioral Timescale Synaptic Plasticity in Contextual Remapping

Authors: *S. P. VAIDYA, R. A. CHITWOOD, J. C. MAGEE;
Howard Hughes Med. Inst., Baylor Col. of Med., Houston, TX

Abstract: In rodents, the CA1 area of the hippocampus is known to manifest distinct maps or neural representations of the same environment based on reward contingencies, task requirements or subtle changes in background cues, a phenomenon known as contextual remapping. While contextual remapping remains a distinct signature of adaptive behavior in rodents, the cellular and network mechanisms underlying the emergence of these divergent maps remain unknown. In this study, we use longitudinal two-photon calcium imaging to characterize the neural dynamics and stability of the emergent maps over a duration of 7 days in the CA1 area of the rodent hippocampus. We show that mice foraging for rewards at distinct cued locations on a linear track form two orthogonal neural representations of the environment that stabilize over the first 2-3 days, after which the maps remain functionally stable across days. We identify distinct signatures of Behavioral Timescale Synaptic Plasticity (BTSP), a cellular plasticity mechanism known to underlie de novo place cell formation in the CA1 area of the hippocampus, in the formation of these divergent maps. To further confirm the role of this plasticity in contextual remapping, we directly manipulate the occurrence of BTSP by application of NMDA antagonist APV in behaving animals across the first two days when the maps emerge and show that in absence of BTSP, the divergence and resolution of the maps is severely impaired and key characteristics of the CA1 maps, like the overrepresentation of reward sites is distinctly absent. Our results suggest a causal role for BTSP in contextual remapping, a key signature of adaptive behavior.

Disclosures: S.P. Vaidya: None. **R.A. Chitwood:** None. **J.C. Magee:** None.

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.02

Topic: B.07. Synaptic Plasticity

Support: MRC Grant ST10985
Wellcome Grant RE13040

Title: Critical brain dynamics emerge during development and are robust to sensory deprivation

Authors: *D. R. W. BURROWS[1], M. P. RICHARDSON[1], M. P. MEYER[1], R. E. ROSCH[1,2];
[1]MRC Ctr. for Neurodevelopmental Disorders, King's Col. London, London, United Kingdom; [2]Dept. of Bioengineering, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Different measures of neuronal function suggest that brain dynamics operate near a phase transition, known as criticality, which can optimise computation. Evidence from in silico studies suggests a role of synaptic plasticity in tuning brain networks to criticality. Given the presence of key

developmental windows during which brain networks are highly plastic and sensitive to sensory input, the stabilisation of networks to criticality may itself be a developmental process which depends on sensory input. However, whether critical dynamics emerge throughout development and are sensitive to sensory input, remains unknown. We perform in vivo 2-photon imaging of whole-brain dynamics in GCaMP6s larval zebrafish throughout development, with and without visual deprivation. We find that key markers of criticality, branching ratio and exponent relation, are subcritical at 3 days, but approach criticality around 6 days. Interestingly, we find that the emergence of criticality is brain region specific with the tectum exhibit faster emergence of criticality than other regions. Critical dynamics do not require visual input, as dark-reared fish also reach criticality at 6 days. These data suggest that critical dynamics emerge as a consequence of developmental network connectivity changes and are robust to sensory deprivation. This work demonstrates the developmental emergence of a balanced state in whole-brain networks in vivo.

Disclosures: D.R.W. Burrows: None. **M.P. Richardson:** None. **M.P. Meyer:** None. **R.E. Rosch:** None.

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.03

Topic: B.07. Synaptic Plasticity

Support: CIHR PJT-153311
CRC 950-231066
Research Centre grant CIRCA
Research Centre grant FRQS
Group grant from Université de Montréal GRSNC

Title: Regulation of hippocampal network and contextual memory by optogenetically-induced long term potentiation of pyramidal cell to somatostatin interneuron synapses.

Authors: *E. HONORÉ, A. ASGARIHAFSHEJANI, F.-X. MICHON, I. LAPLANTE, J.-C. LACAILLE;
Univ. of Montreal Dept. De Neurosciences, Montreal, QC, Canada

Abstract: Hippocampal dependent learning and memory originate from long term synaptic changes in hippocampal network. Somatostatin interneurons (Som-INs) display metabotropic glutamate receptor subtype 1a (mGluR1a) and mechanistic target of rapamycin complex 1 (mTORC1) dependent long-term potentiation (LTP) at their excitatory input synapses coming from local pyramidal cells (PC-Som synapses), that is elicited by fear learning. This PC-Som synapses LTP participates in the regulation of CA1 network metaplasticity and memory consolidation. However, whether LTP at PC-Som synapses is sufficient to regulate CA1 network plasticity and memory remains to be determined. In this work we use an optogenetic approach to examine this question. First, we used optogenetic silencing of Som-INs with dorsal CA1 injection of AAV9.flex.CBA.Arch-GFP.WPRE.SV40 in SOM-Cre mice and found that inhibition of Som-IN activity during memory acquisition impaired contextual fear memory. Thus, we

confirmed that CA1 Som-IN activity during the presentation of the aversive stimuli is necessary for contextual fear memory formation. Second, we developed a paradigm to elicit LTP at PC-Som synapses with optogenetic theta burst stimulation (optoTBS). Using dorsal CA1 injection of AAV-CaMK2a-ChR2 (E123T/T159C)-mCherry in SOM-Cre-eYFP mice and whole cell recordings from Som-INs in slices, we found that optoTBS elicited LTP at PC-Som synapses. This optoTBS induced LTP was dependent of mGluR1 and mTORC1 and regulated the metaplasticity of CA1 network. Third, at the behavioral level, otpoTBS given 30 minutes before contextual fear conditioning, resulted in an impairment of long-term contextual fear memory tested 24 h after. Whole cell recordings of Som-INs 24 h after contextual fear conditioning showed that optoTBS prior to fear conditioning reduced the spontaneous excitatory post synaptic currents (EPSC) frequency and amplitude, as well as evoked EPSC input-output function. Our results suggest that optogenetic induction of LTP at PC-Som synapses before learning may interfere with learning-induced PC-Som synapses LTP and result in contextual fear memory deficits. Thus, LTP at PC-SOM synapses appears sufficient for the regulation of hippocampal contextual memory.

Disclosures: E. Honoré: None. **A. Asgarihafshejani:** None. **F. Michon:** None. **I. Laplante:** None. **J. Lacaille:** None.

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.04

Topic: B.07. Synaptic Plasticity

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NIH 5T32 NS045540
NIH R01 NS108189 diversity supplemental
NIH R01 NS108296

Title: Conditional PTEN deletion in the adult dentate gyrus triggers robust de novo growth of granule cells and the formation of a seizure prone circuit

Authors: *J. M. YONAN, K. D. CHEN, T. Z. BARAM, O. STEWARD;
Univ. of California, Irvine, Irvine, CA

Abstract: Previous studies have documented that deletion of phosphatase and tensin homolog (PTEN) in early development leads to neuronal hypertrophy, aberrant circuitry and sometimes seizures, but consequences of deleting PTEN in mature hippocampal circuits are unknown. Here, we explore structural and functional consequences of PTEN deletion in mature dentate gyrus granule cells of adult mice. Experiments used male and female $PTEN^{f/f}$;$Rosa^{tdTomato}$ mice in which Cre activates expression of tdT and simultaneously deletes PTEN. Controls were $Rosa^{tdT}$ mice. Unilateral injections of AAV-Cre into the dentate gyrus at 2 months of age resulted in focal transfection of granule cells, leaving PTEN expression of input and target neurons intact. Mice survived for 2 weeks, 1, 2, 4 and 6 months following injection

(n=4-6 mice per timepoint). Quantitative analyses were un-blinded because anatomical consequences of PTEN deletion were dramatic, making blinding impossible. PTEN deleted granule cells exhibited approximately 2.3-fold increases in cell body size by 2 months after AAV-Cre injection, with growth occurring earlier in areas of more concentrated transfection. Quantitative assessments of tdT-positive dendrites revealed 1.5-fold increases in apical dendrite length, 1.8-fold increases in dendrite caliber and 1.5-fold increases in spine densities. Despite this dramatic dendritic growth, preliminary BDA tract tracing of perforant path and commissural inputs to PTEN deleted granule cells revealed that specificity of laminar input was maintained. Immunostaining for Znt3, a marker for mossy fibers, revealed that the lamina occupied by mossy fiber terminals from PTEN-deleted granule cells within CA3 increased in width by 150%, but mossy fibers were not evident in the stratum radiatum. Punctate labeling for Znt3 was present in the inner molecular layer in 2/5 mice at 4 months post AAV-Cre and 2/5 mice at 6 months after AAV-Cre indicating supra-granular mossy fibers. To assess for possible seizures in mice with unilateral Cre-mediated PTEN deletion, 7 mice were implanted with recording electrodes at 7 weeks post deletion to allow for intra-hippocampal EEG recordings and simultaneous video recording. Twenty-four hour monitoring revealed onset of electrographic and behavioral seizures beginning around 10 weeks after AAV-Cre injection in 5 mice, with one mouse dying during a seizure. Our results document dramatic *de novo* growth of fully mature dentate granule cells and establish that even unilateral focal deletion of PTEN in the dentate gyrus is sufficient to result in the development of electrographic and behavioral seizures.

Disclosures: J.M. Yonan: None. **K.D. Chen:** None. **T.Z. Baram:** None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder and holds economic interests in the company “Axonis”, which holds a license on patents relating to PTEN deletion and axon regeneration..

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.05

Topic: B.07. Synaptic Plasticity

Support: DA32444
DA15014
DA040519
T32MH079785

Title: Examining how CXCL12/CXCR4 chemokine signaling affects cortical network function using in vitro microelectrode arrays.

Authors: *J. LUCHETTA[1,2], E. IROLLO[1,2], R. BRANDIMARTI[1,2], C.-T. HO[1,2], O. MEUCCI[1,2,3]; [1]Dept. of Pharmacol. and Physiol., [2]Ctr. of Neuroimmunology and CNS Therapeutics, Inst. of Mol. Med. and Infectious Disea, [3]Dept. of Microbiology and Immunol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The chemokine CXCL12 has numerous roles in the adult central nervous system including directing inhibitory neuronal axons, modulating neurotransmission, and promoting synaptic plasticity. Our previous reports demonstrate that CXCL12/CXCR4 G-protein signaling rescues dendritic spine density and cognitive flexibility deficits in an animal model of HIV-associated neurocognitive disorders, suggesting that this approach has therapeutic potential. CXCL12 primarily rescues thin spines, which are highly dynamic and associated with learning. Aligned with this, data from several neurological and psychiatric conditions and their respective animal models suggest that dendritic spines are anatomical correlates to cognitive function. Our studies indicate that CXCL12 regulates dendritic spines through a Rac1/PAK/cofilin signaling pathway, but we have not identified the cellular effectors responsible for CXCL12's beneficial outcomes. Previous reports suggest CXCR4 is only expressed on ~1% of neurons, which are mainly inhibitory. Because these cells have widespread control over network-level activity, we hypothesized that CXCL12/CXCR4 signaling mediates its effect on dendritic spines through consolidating neural network activity into synchronous network bursts in rat cortical neurons. To test this, we implemented a microelectrode array system and were able to measure neuronal culture activity beyond 100 days in vitro (DIV). Experiments in this system suggest that CXCL12 treatment (20 nM) at 28 DIV does not significantly alter synchronous network activity at 3, 6, 24, or 48-hours post-treatment and additional dose-response studies are underway. Ongoing experiments aim to test the possibility that CXCL12 either rescues and/or protects cortical network dysfunction during insult conditions such as APP overexpression or HIV-1 gp120 exposure. Initial results suggest APP overexpression does not alter synchronous network activity but may alter neuronal firing rates after 7 days of exposure. Future studies aim to directly test whether CXCL12's effects on dendritic spines are mediated through inhibitory neurons using a Cre-ON MiR30a shRNA construct combined with mDlx driven Cre expression to knock down CXCR4 specifically in inhibitory neurons in E17 rat cortical cultures. Together, these experiments aim to determine whether CXCL12 modulates neuronal network activity - an action that may be important for CXCL12's effect on dendritic spines and cognition in vivo.

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Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.06

Topic: B.07. Synaptic Plasticity

Support: DA32444
DA15014

Title: Effect of the chemokine CXCL12 on dendritic spines in a rodent model of HIV-associated neurocognitive disorder: is spine clustering involved?

Authors: *C. HO[1,2], E. IROLLO[1,2], O. MEUCCI[1,2,3];
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Abstract: Several neurological disorders, including HIV-associated neurocognitive disorder (HAND), present with dendritic spine loss and synaptic pruning that can lead to cognitive impairment. Previous *in vitro* and *in vivo* work from our lab showed that the chemokine CXCL12 increases dendritic spine density in rat cortical neurons through activation of its cognate receptor CXCR4 and the downstream Rac1/PAK pathway. Importantly, this was correlated with improved cognitive flexibility in an operant learning task. However, it is not clear if CXCL12 regulates spine maturation, or simply stabilizes transient spines. Likewise, we do not know whether the chemokine promotes spine clustering, a phenomenon that has been often associated with learning and memory processes and that positively correlates with mice performance in a number of behavioral tests. To start addressing these questions, we examined the expression and distribution of postsynaptic proteins that are typically present in mature excitatory synapses, e.g. postsynaptic density protein 95 (PSD-95) and the AMPA receptor subunit, GluA1, and measured inter-spine distance in pyramidal neuron cultures treated with CXCL12. Though CXCL12 short-term treatments (20nM; 5 min up to 3hrs) did not significantly alter PSD-95 total protein levels in neuronal lysates, we observe a consistent and significant increase in the percentage of PSD-95^{+} thin spines in cultures exposed to 20 nM CXCL12 for 3hr. At this same timepoint, we observed a similar trend for GluA1^{+} spines and a significant increase in the overall spine density. These results suggest that CXCL12 may promote maturation of the highly dynamic thin spines. Additionally, time course experiments indicate that sustained CXCL12 action greatly depends on its continuous presence in the culture media. Our *in vivo* studies in a rodent model of HAND are in line with these data. Daily *in vivo* treatment with CXCL12 (i.c.v., 25ng/dose/day, 5 days) reduced the inter-spine distance in dendrites of the medial prefrontal cortex neurons with a pattern that is compatible with spine clustering. Ongoing live cell imaging studies in both cultured neurons and brain slices will shed more light on these findings and help determine CXCL12 effects in real time, thus advancing our understanding of CXCL12 regulation of dendritic spines and cognitive flexibility.

Disclosures: C. Ho: None. **E. Irollo:** None. **O. Meucci:** None.

Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P122.08

Topic: B.07. Synaptic Plasticity

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Title: An analog of psychedelics restores functional neural circuits disrupted by unpredictable stress

Authors: *J. LU[1], M. TJIA[1], B. MULLEN[1], B. CAO[2], K. LUKASIEWICZ[1], S. SHAH-MORALES[1], S. WEISER[1], L. P. CAMERON[3], D. E. OLSON[4], L. CHEN[2], Y. ZUO[1];
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Abstract: Stress pervades modern life. It affects various brain functions, posing risks for many psychiatric disorders. However, few therapeutics are available to combat such deleterious effects of stress. One class of candidate drugs are psychedelics. With potent and fascinating effects on the human mind, these drugs have received renewed research interest in recent years. However, their hallucinogenic effects remain a concern for clinical applications. Using a mouse model of unpredictable mild stress, we investigated a novel compound called tabernanthalog (TBG), which is similar in structure to the psychedelic drug ibogaine but free from its hallucinogenic and toxic effects. We found that a single low dose of TBG can correct stress-induced behavioral deficits including anxiety, cognitive inflexibility, and defective sensory processing. In the stressed brain, TBG promotes the regrowth of stress-disrupted connections between cortical neurons and normalizes their baseline and task-associated activity patterns. Our study highlights the potential of using analogs of psychedelics to treat stress-related brain disorders, and provides novel insights into the neural mechanisms underlying their therapeutic effects.

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Poster

P122. Structural Plasticity: Neurons, Networks, and Regulation

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH081060
NIH Grant MH070727

Title: Evaluation of the therapeutic potential of ketamine in Rett syndrome and the role of brain derived neurotrophic factor (BDNF)

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Abstract: Rett syndrome (RTT) is primarily caused by mutations in the X-linked gene methyl-CpG binding protein 2 (MECP2), affecting roughly 1 in 10,000 live female births and representing the second leading cause of intellectual disability in girls and women worldwide. Multiple lines of investigation have implicated the N-methyl-D-Aspartate receptor (NMDAR) in the pathophysiology of RTT, as dysfunction of MeCP2 alters the developmental maturation of NMDARs, contributing to an imbalance of inhibitory and excitatory neurotransmission in the brain. Interestingly, both genetic manipulation and

pharmacological blockade with the noncompetitive NMDAR antagonist ketamine have shown efficacy in reversing such electrophysiological deficits, and a small number of studies have demonstrated an ability of systemic ketamine treatment to rescue behavioral symptoms of RTT and extend lifespan in an animal model. Despite these promising results, a more thorough characterization of ketamine's modulation of RTT symptoms and an investigation into the molecular underpinnings of this effect are warranted. Our lab has previously demonstrated that ketamine administration causes desuppression of brain derived neurotrophic factor (BDNF) protein synthesis in the hippocampus of mice, leading to an enhancement of glutamatergic activity and a reduction of depression-like symptoms. As BDNF is similarly down-regulated in animal models of RTT syndrome, it is plausible that this mechanism may be shared between these two disparate disorders. In this study, we utilized a combination of biochemical, electrophysiological and behavioral paradigms in *Mecp2* knockout mice as well as wild type littermate controls to explore this possibility. Indeed, our findings show an up-regulation of hippocampal BDNF protein expression in both wild type (WT) and *Mecp2* knockout (KO) mice following systemic ketamine treatment. Furthermore, an electrophysiological examination of field excitatory post-synaptic potentials (fEPSPs) revealed a concomitant potentiation of the fEPSP response in both WT and KO animals. Taken together, the results of this study will contribute to the growing investigation of ketamine's therapeutic efficacy and putative molecular action in Rett syndrome.

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Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Program #/Poster #: P251.01

Topic: C.03. Parkinson's Disease

Support: FIS PI19/00298.
Miguel Servet CP18/00038
Fundación Gangoiti

Title: A circuit-based approach to understand hypersexual behaviour in Parkinson's Disease.

Authors: *D. MATA MARÍN[1,3,4], J. A. PINEDA-PARDO[1,3], M. MICHIELS[1,3,4], C. PAGGE[1,3,4], R. MARTÍNEZ-FERNÁNDEZ[1,3], J. MOLINA[5], L. VELA[6], F. ALONSO-FRECH[7], I. OBESO[2,3]; [2]Fundación HM Hospitales Puerta del Sur, [1]HM-CINAC, Mostoles, Spain; [3]Network Ctr. for Biomed. Res. on Neurodegenerative Dis. (CIBERNED), Inst. Carlos III, Madrid, Spain; [4]PhD program in Neuroscience, Autonoma de Madrid Univ., Madrid, Spain; [5]Hosp. 12 de Octubre, Madrid, Spain; [6]Hosp. Fundación de Alcorcón, Alcorcón, Spain; [7]Hosp. Clínico San Carlos, Madrid, Spain

Abstract: BACKGROUND: The balance between cognitive control and enhanced desire towards sexual cues has been hypothesized to be biased toward the latter in individuals with hypersexuality, suggesting possible neurocognitive and connectivity changes along the mesocorticolimbic circuitry. Here, we provide evidence for this hypothesis by comparing the neurobiological substrate of sexual cues disturbance over cognitive control associated to a medication-induced hyperdopaminergic state in

Parkinson´s disease (PD) as a hypersexual acute model.METHODS: We assessed the effect of sexual cues on cognitive control using a novel erotic stop signal paradigm inside an fMRI in 16 hypersexual PD patients, 17 PD patients and 17 controls. Patients were assessed twice on and off medication. In a separate sample of 18 hypersexual patients, we also applied excitatory non-invasive brain stimulation – intermittent theta burst (iTBS) – following a randomized single blind sham-controlled design over the pre-supplementary motor area (pre-SMA).RESULTS: Compared with their non–hypersexual peers, patients with hypersexuality exhibited worse response inhibition in erotic trials, which correlated with medication effects. Inhibition of actions influenced by sexual cues recruited a network involving caudate, pre-SMA, VTA and ACC activity in hypersexual patients while medicated. Dynamic causal modelling revealed distinct best models to account for cortico-subcortical interactions showing reduced task-related inputs in pre-SMA and descending connectivity to caudate in hypersexual compared to non-hypersexual patients. This was sustained by enhanced fractional anisotropy and reduced mean diffusivity in the pre-SMA-caudate pathway. Importantly, excitatory intermittent theta burst stimulation (iTBS) over pre-SMA improved behavioural control when exposed to sexual cues. CONCLUSIONS: We identified a key fronto-striatal and mesolimbic circuitry underlying uncontrolled sexual behaviours in hypersexual PD. Moreover, we demonstrated beneficial acute effects of iTBS in improving inhibitory control in this population, providing valuable insight for future therapeutic options for better management of hypersexuality in PD without compromising patients' motor functioning.

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Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Program #/Poster #: P251.02

Topic: C.03. Parkinson's Disease

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NIH Grant P50 NS062684
NIH Grant NS08608505
NIH Grant MH121069

Title: Dopaminergic medication remediates aberrant cognitive control circuit signaling in Parkinson's disease

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Abstract: Dopaminergic medication is widely used for alleviating motor symptoms in patients with Parkinson's disease (PD), but patients vary greatly in their cognitive responses to medication. It has been

hypothesized that dopaminergic medication impacts cognitive processing in PD by modulating frontoparietal-basal ganglia cognitive control circuits, but little is known about the underlying causal signalling mechanisms and their relation to individual differences in treatment response. Here we use a novel state-space computational model with high temporal resolution fMRI to investigate dynamic causal signalling in frontoparietal-basal ganglia circuits associated with working memory in 36 PD patients (69$\pm$7 yrs; 21F/15M) ON and OFF medication, as well as matched 44 healthy controls (71$\pm$6 yrs; 25F/19M). Our analysis revealed aberrant causal signaling in frontoparietal-basal ganglia circuits in PD patients OFF medication. Importantly, aberrant signaling was remediated by dopaminergic medication and a novel quantitative distance measure predicted individual differences in cognitive change associated with medication in PD patients. These findings were specific to causal signaling measures, as no such effects were detected with conventional non-causal connectivity measures. Our analysis also identified a specific frontoparietal causal signaling pathway from right middle frontal gyrus to right posterior parietal cortex that is impaired in PD (p<0.05). Unlike in healthy controls (r=-0.3, p=0.02), the strength of causal interactions in this pathway did not increase with working memory load and the strength of load-dependent causal weights was not related to individual differences in working memory task performance in PD patients OFF medication (p=0.4). However, dopaminergic medication in PD patients reinstated the relation with working memory performance (r=-0.4, p=0.01). Our findings provide new insights into aberrant causal brain circuit dynamics during working memory and identify mechanisms by which dopaminergic medication remediates cognitive control circuits.

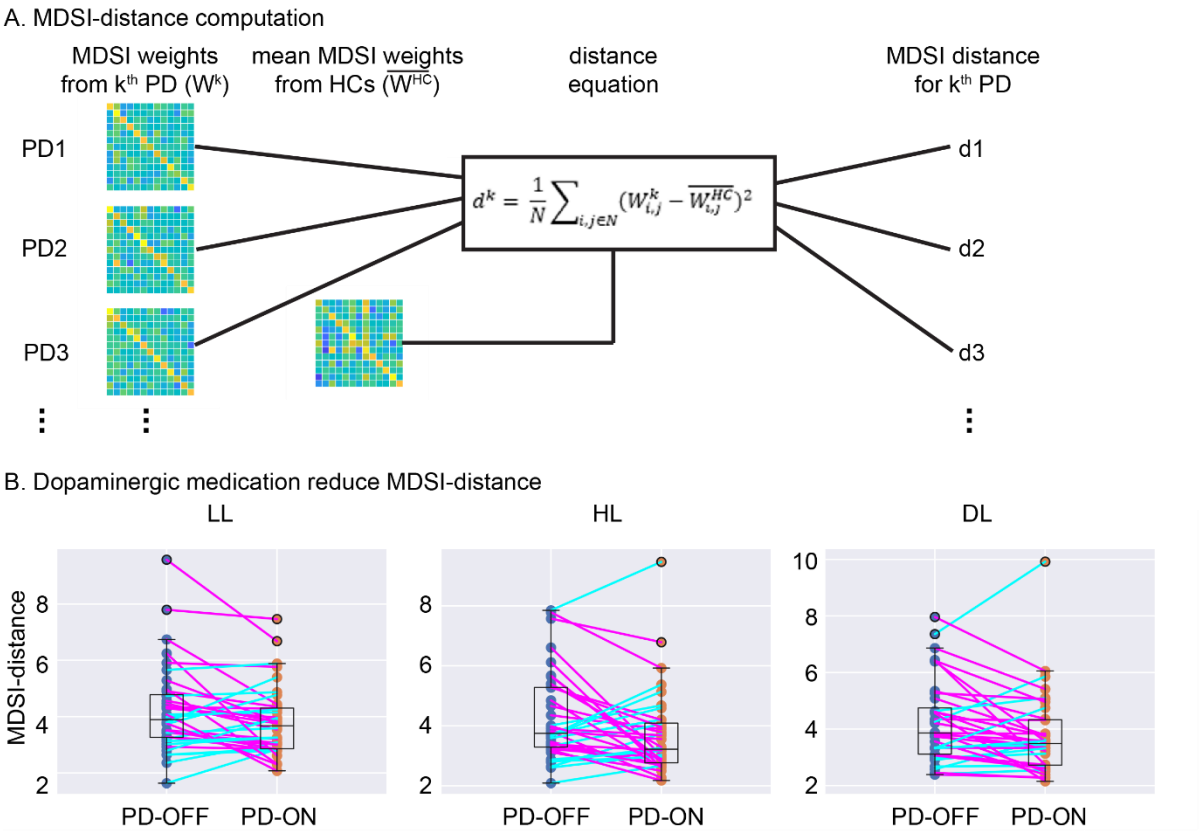


Figure 1. We used a novel multivariate dynamic state-space system identification (MDSI) method to estimate dynamic causal interaction between districuted cortical-subcortical systems during the Sternberg working memory task. (A) Schematic illustration of the algorithm used to compute MDSI-based network-level dissimilarity (distance) in each PD patient. The distance (d) is defined by the sum of the square of MDSI weight difference between each PD patient and the mean of the HC group. Note that d^k is the distance metric for k^{th} PD patient; N is the total number of non-diagonal edge (i,j) in MDSI weight matrix per condition; $W_{i,j}^k$ is the MDSI weight on edge (i,j) for kth PD patient; $\overline{W_{i,j}^{HC}}$ is the mean MDSI weight on edge (i,j) for all HCs. (B) Dopaminergic medication reduces MDSI-based distance, which quantifies the dissimilarity in network-level causal signaling between each PD patient and the HC group, in each task condition, e.g. low load (LL), high load (HL) and distractor load (DL) (all ps < 0.05).

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Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Program #/Poster #: P251.03

Topic: C.03. Parkinson's Disease

Support: Miguel Servet CP18/00038
Proyecto FIS

Title: Everyday life motor habits alter striatal activity in early Parkinson's disease.

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Abstract: Humans can simultaneously and easily shift between automatic/habitual to voluntary/goal-directed modes of behavioural control. Habits (stimulus-response) allows us to perform well-practiced tasks with minimal or no conscious effort. In Parkinson disease (PD), there is a differential loss of dopamine (DA) along the caudal sensorimotor putamen initially transferring to more rostral regions as the disease progresses. Importantly, the sensorimotor putamen is primarily implicated in habitual control therefore possibly explaining some motor deficits in PD such as arm swinging, walking and writing.Our aim was to investigate loss of habitual writing after early dopaminergic cell loss in PD patients. We expected that everyday life motor habits (writing) would be impaired in automatic conditions associated to reduced striatal activities compared to controls. We developed a handwriting task (one of the most well-learned and automatic behaviour) that differentiates between habitual and goal-directed writing components. Writing conditions included automatic (e.g. signature, Spanish) and goal-directed conditions (e.g. Polish, Greek; 10 trials per condition). We considered the following general outcome parameters: writing duration (s), horizontal and vertical amplitudes (mm) of words. The quality and the level of handwriting automation was evaluated by means of the single stroke analysis. A behavioural (30 PD patients; 30 controls) and fMRI (18 PD patients; 25 controls) sessions were performed. Highly asymmetric and early (less than 2 year since diagnosis) PD patients were included and tested while off-medicated. Reduced automatism was seen in the execution of every writing condition compared to controls. This finding was especially true when the most affected side overlapped with hand-dominant side. Neural signals revealed great activity in bilateral posterior putamen in controls in habitual conditions ($p < 0.05$, FWE-corrected). In contrast, in goal-directed conditions, anterior putamen showed increased activity. A similar pattern was seen in PD patients, however, showing reduced posterior putamen activity ($p < 0.001$, uncorrected).Our results suggest that everyday life motor habits is executed with reduced automatic components in every writing condition in PD patients. This was accompanied by reduced posterior putamen recruitment in early PD. Our findings demonstrate a functional dysfunction in posterior putamen that plays a fundamental role in the origin of the characteristic habitual motor deficits of PD.

Disclosures: P. Guida: None. **M.H. Monje:** None. **J.A. Obeso:** None. **I. Obeso:** None.

Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Program #/Poster #: P251.04

Topic: C.03. Parkinson's Disease

Title: Lstm decoding of tremor and movement speed in Parkinson's disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder whose motor symptoms are principally characterized by tremor and bradykinesia. For severe PD, deep brain stimulation (DBS) is an effective treatment, and present efforts are concentrated on closed loop DBS that delivers stimulation in response to a biomarker of the disease. Yet patients often present with complex and specific symptoms, and state-of-the-art approaches to closed loop DBS leverage narrowband spectral estimates of local field potentials and do not yet address the wide variety of motor and non-motor symptoms observed.
Here we utilized full bandwidth recordings from multiple subthalamic and cortical regions in 27 patients with PD to predict moment-to-moment tremor and movement speed using convolutional long short-term memory (LSTM) artificial neural networks. Significant prediction of tremor and speed (empirical labels compared to shuffled) was achieved on a seconds-timescale from subthalamic nucleus (n=92/162 recordings), zona incerta (n=45/86), substantia nigra (n=15/40), as well as somatomotor cortices (30-50%, 25-50 total). We further performed spectral occlusion, in which we filtered the time series into narrowbands, trained new models, and assessed information carried by these bands, which demonstrated that unfiltered time series largely outperformed narrowband spectral estimates. We also demonstrate that multielectrode models could also significantly outperform single electrode models, highlighting the need for improvements in existing concurrent recording technology.
Our LSTM approach required little signal processing and no direct spectral estimation but still leveraged broadband oscillatory activity and may provide the basis for efficient closed loop DBS control policies to address both motor and non-motor symptoms in a patient specific framework.

Disclosures: S. Lee: F. Consulting Fees (e.g., advisory boards); Alpha Omega, Nazareth, Israel. **D. Liu:** None. **P. Lauro:** None. **D. Amaya:** None. **W. Asaad:** None.

Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Program #/Poster #: P251.05

Topic: C.03. Parkinson’s Disease

Title: Posturography in patients with Parkinson´s disease and progressive supranuclear palsy

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Abstract: Introduction: Differential diagnosis of Parkinson's disease (PD) and progressive supranuclear palsy (PSP) might be difficult due to the shared pathophysiology. They might both present with deficits in postural control, even though, in the case of PSP it is typically earlier in the disease course. The pathophysiology of balance difficulties remains elusive, thus, challenging to target with therapy. Static posturography is used to examine a patient's balance and reflects the contributions of the visual, vestibular, and proprioceptive systems to a patient's balance.
Methods: We performed standard posturography in patients with PD (n=9, 3 men, mean age=67,4, range

56-81) and PSP (n=11, 3 men, mean age 69,6, range 58-82) with the history of at least one fall in the previous 3 months with matched disease duration. The posturographic protocol consisted of quiet standing with eyes opened, eyes closed, galvanic stimulation, vibration stimulation of Achilles tendon. Each trial lasted 50 seconds, the stimulation (vibration, galvanic) was applied between 10-20th second, if applicable. Amplitude and velocity of the postural response (separately medio-lateral, anterior-posterior direction), root mean square (RMS) and line integral (LI) was analyzed. The findings for left and right postural responses were combined. All patients were recorded in the best ON state with the absence of interfering dyskinesia. Peripheral neuropathy was excluded.
Results: Statistically significant difference in postural response was found between PD and PSP in the trial with the vibration stimulation of Achilles tendon. The difference was observed after the onset of stimulation (10-20th second of the trial) and reflected in the RMS and LI (p=0,038) with smaller postural responses in PSP. There was no other difference in the rest of the posturographic parameters.
Conclusion: The underlying pathophysiology of postural control might be different in PD and PSP, possibly due to the more pronounced deficit of the proprioceptive system in PSP patients. This might be also discriminative in the differential diagnosis of these entities.

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Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Topic: C.03. Parkinson’s Disease

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NIH RF1-MH117055-01
PF-JFA-1764-02
DIBS Incubator Grant

Title: Parkinson's Advance with DART and DANNCE

Authors: *I. A. WEAVER[1], J. M. ROACH[1], J. R. RAVENEL[2], S.-X. LIM[1], H. YAN[2], B. C. SHIELDS[1], T. W. DUNN[1], M. R. TADROSS[1,2];
[1]Biomed. Engin., [2]Dept. of Neurobio., Duke Univ., Durham, NC

Abstract: Parkinson’s Disease (PD) is a devastating movement disorder caused by the degeneration of dopamine afferents to the striatum. It is known that chronic loss of dopamine alters excitatory (AMPA-R) and inhibitory (GABA-R) synapses in the striatum, and produces a wide range of motor deficits. However, it has been difficult to establish causal relationships between synaptic changes and the behavioral phenotype. One issue is a mismatch in resolution; synaptic changes have been studied in a fine-grain manner, revealing dozens of synaptic alterations in the striatal connectome. In contrast, behavioral assays have been coarse-grain, limited to metrics like velocity, turning, and freezing. Here, we present Compact-DANNCE (Compact 3 -Dimensional Aligned Neural Network for Computational Ethology), which features a floating behavioral arena, a single high-resolution camera mounted below the

arena looking upwards, and optical-grade IR mirrors positioned at the level of the animal chamber to provide 5 angles of view. This system builds upon DANNCE (Dunn, et. al., Nature Methods, 2021), which required multiple cameras in a 10' x 10' room. Here we have compressed the design to a 2' x 2' profile, enabling scalability of the approach. Other key features include observing mice during the active dark phase of their circadian cycle (via IR illumination); visualizing the paws, mouth, and tongue of the animal (via bottom-up view); localizing each body part in 3D space (via concurrent side views), and improved temporal synchronization across views enabling accurate tracking of rapid movements up to 90 Hz (owing to the single-camera design). We are combining Compact-DANNCE with DART (Drugs Acutely Restricted by Tethering), a tool we previously developed to deliver clinical drugs to genetically defined cells (Shields et. al., Science, 2017). Thus far, we have performed a head-to-head comparison of two treatments in a unilateral 6-OHDA mouse model of PD, comparing L-DOPA (replacing dopamine without correcting synaptic pathologies) to AMPAR antagonism of indirect pathway spiny projection neurons (iSPNs) with DART (correcting one synaptic pathology without replacing dopamine). Whereas both treatments qualitatively improve coarse-grain metrics, we resolve pronounced fine-grain differences. L-DOPA restores hunched idling and grooming behaviors but fails to restore rearing. In contrast, iSPN-AMPAR antagonism restores low rearing behaviors similar to those seen in healthy mice. While the results are preliminary, they reveal the power of fine-grain kinematic quantification, and set the stage to examine movement disorders from the perspective of a connectome pathology.

Disclosures: I.A. Weaver: None. **J.M. Roach:** None. **J.R. Ravenel:** None. **S. Lim:** None. **H. Yan:** None. **B.C. Shields:** None. **T.W. Dunn:** None. **M.R. Tadross:** None.

Poster

P251. Parkinson's Disease: Therapeutic Interventions

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P251.07

Topic: C.03. Parkinson's Disease

Title: Effects of exercise on heart rate variability in Parkinson's disease

Authors: *A. A. MEMON[1], **E. B. GEORGE**[2], Y. SUNKARA[3], M. POGWIZD[4], C. CATIUL[5], J. PILKINGTON[5], S. M. POGWIZD[4], A. W. AMARA[5];
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Abstract: Parkinson's disease (PD) is the most common neurodegenerative motor disorder of aging. Although clinical diagnosis requires motor features, non-motor symptoms, including autonomic dysfunction, can present early and adversely affect quality of life in persons with PD (PwP). Indeed, sympathovagal imbalance is present in more than half of PwP. Unfortunately, pharmacological therapies for autonomic dysfunction in PD have limited efficacy and are associated with side effects. Excitingly, exercise rehabilitation has shown potential to enhance autonomic regulation in adults. However, whether exercise improves autonomic modulation in PwP is unclear. Heart rate variability (HRV) is a noninvasive marker of autonomic derangement. Novel insights can be gained from studying this marker during different stages of sleep. Therefore, we hypothesize that exercise will restore sympathovagal balance

during sleep in PwP. To test this hypothesis, we leveraged an existing sleep dataset collected during a recently completed, randomized, controlled clinical trial (RCT) of exercise on objective sleep in PD. In this RCT, 55 participants were randomized to exercise rehabilitation (N=27) or a sleep hygiene, no-exercise control (N=28). All participants underwent laboratory-based nocturnal polysomnography (PSG) at baseline and post-intervention. We analyzed 10 min electrocardiographic recordings (ECG's) during deep sleep (Non-rapid eye movement (NREM) stage 3) and during REM sleep. ECGs were sampled at 512 Hz and exported for analysis using a specially designed Matlab-based program that uses a point process model to assess instantaneous (rather than time-averaged) HRV using a history-dependent inverse Gaussian process. We will use parametric autoregressive modeling to determine power spectral density. We will evaluate frequency domain measures as low-frequency power (LF, 0.04-0.15 Hz), high-frequency power (HF, 0.15-0.40 Hz), and LF/HF ratio. HF reflects parasympathetic/vagally mediated modulation of heart rate, while LF/HF ratio reflects sympathovagal balance. This novel work in progress allows investigation of sleep ECG signatures, a noninvasive and widely accessible measure, as a potential marker to evaluate the effects of exercise on HRV in PwP.

Disclosures: A.A. Memon: None. **E.B. George:** None. **Y. Sunkara:** None. **M. Pogwizd:** None. **C. Catiul:** None. **J. Pilkington:** None. **S.M. Pogwizd:** None. **A.W. Amara:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P289.01

Topic: C.06. Neuromuscular Diseases

Support: 5UG3NS105703-02

Title: Spinal Cord-Chips from sporadic ALS patients reveal disease-specific biomarkers

Authors: *B. ONDATJE[1], D. LALL[1], S. SANCES[1,3], M. LUKASIAK[1], D. WEST[1], A. LAPERLE[1], R. HO[1], M. WORKMAN[1], V. VAIBHAV[2], J. VAN EYK[2], C. SVENDSEN[1];
[1]Regenerative Med. Inst., [2]Advanced Clin. Biosystems, Cedars-Sinai Med. Ctr., Los Angeles, CA;
[3]Translational Sci. and Drug Discovery, Insitro, Inc., South San Francisco, CA

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disorder, with the vast majority of cases being sporadic in nature with unknown genetic cause. ALS is characterized by progressive loss of cortical and spinal cord motor neurons, resulting in muscle weakness and death from respiratory failure typically within 3-5 years of diagnosis. Using induced pluripotent stem cell (iPSC) technology, patient-specific cells can be differentiated into cell types relevant to ALS. Microphysiological systems (MPS), also known as organ-chips, have microengineered three dimensional compartments that enable the co-culture of different iPSC-derived cell types to recapitulate conditions of human physiology *in vitro.* Here we developed an MPS-based model incorporating patient-derived spinal cord motor neurons **(SC-Chip)** to study young onset sporadic ALS. The SC-Chip top channel contains disease-relevant neuronal cells, and the bottom channel contains brain microvascular endothelial cells (BMECs). The porous membrane between the two channels allows for the establishment of a blood-brain barrier.

The primary goal of this project is to establish robust and reproducible biomarkers of this disease by identifying metabolomic, transcriptomic, and proteomic signatures, as well as to test efficacy of candidate therapeutics to ameliorate disease-specific phenotypes. We have detected several biomarkers of sporadic ALS that are consistent across multiple studies in RNA-seq, proteomics, immunohistochemical staining and western blot analysis. These biomarkers were initially detected in a cohort of 5 patient-derived iPSC lines, compared to 5 control lines, and are currently being confirmed in an additional 10 ALS/ control lines. Identified biomarkers for sporadic ALS include increased expression of heavy, medium, and light chain neurofilaments as well as peripherin, an increase in calmodulin binding substrate neurogranin, and a decrease in neural RNA-binding protein ELAV3. We will next administer experimental therapeutics to the vascular side of the SC-Chip to determine (i) transport across the blood-brain barrier and (ii) reversal of disease-specific phenotypes on the neuronal side.

Disclosures: B. Ondatje: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **D. Lall:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **S. Sances:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **M. Lukasiak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **D. West:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **A. Laperle:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **R. Ho:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **M. Workman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **V. Vaibhav:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **J. Van Eyk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **C. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc..

Poster

P289. Motor Neuron Disease: In Vitro Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P289.02

Topic: C.06. Neuromuscular Diseases

Support: E-Rare JTC 2018 project INTEGRALS
Associazione Centro Dino Ferrari

Title: Multi-omics approach on spinal cord organoids to assess new candidate genes/pathways in C9orf72-Amyotrophic Lateral Sclerosis

Authors: N. GALLI[1], B. FRIZZI[1], I. FARAVELLI[1], M. RIZZUTI[2], G. COSTAMAGNA[1], F. BIELLA[2], M. GARBELLINI[2], G. GARRONE[3], M. NIZZARDO[1], P. RINCHETTI[1], E. PAGLIARI[1], M. MENERI[4], G. COMI[1], *S. CORTI[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a rare, idiopathic neurodegenerative disease involving motor system that controls voluntary movement. It is characterized by upper and lower motor neuron (MN) loss, resulting in progressive and relentless muscle paralysis that ultimately leads to death from respiratory failure within a few years. Unfortunately, no effective treatments are available to slow, halt or reverse disease progression. Therefore, improving our knowledge on ALS pathophysiology is crucial for the development of novel therapeutics. Recent evidence indicates that gliosis and mitochondrial dysfunction affect MNs, possibly meaning that alterations in immune and energy metabolism related genes/pathways are associated with ALS. Since 2D cultures are limited in their capability to mimic intercellular interactions, 3D models represent a new tool that recapitulates the complexity of tissue architecture. The primary goal of this proposal is to 1) generate and characterize spinal cord organoids from C9orf72-ALS patient-derived iPSCs and their relative isogenic controls; 2) harness “omics” approaches (with particular focus on transcriptomics and proteomics) to outline the ALS phenotype in this cellular system; 3) identify and validate candidate genes/pathways related to the pathophysiology of the disease. On this basis, we generated spinal cord organoids with a protocol recently optimized in our laboratory and we verified the presence of neural progenitors, post-mitotic neurons, motor neurons, and glia. Organoids were harvested, fixed, and cryosectioned at three time points (day 30, day 45, day 80) and evaluated for their morphology and neurodevelopmental features by immunohistochemistry and qPCR. Specifically, day 80-organoids expressed markers such as MAP2, DCX, OLIG2, PAX6, SMI32, TUBB3, and GFAP. Terminally differentiated spinal cords organoids underwent mass spectrometry to reveal proteins differentially expressed in ALS samples compared to controls. The obtained results showed a number of significantly dysregulated proteins that we are currently evaluating with western blot and qPCR. Preliminary gene ontology analysis displayed alterations associated with cytoskeleton, energetic metabolism, and astrocyte population. Finally, organoids at day 80 were dissociated and cryopreserved to investigate possible aberrant transcriptomic profile related to ALS pathogenesis through single-cell RNA-sequencing. Overall, this project might allow the assessment of novel candidate genes/pathways linked with C9orf72-ALS pathogenesis and their potential as therapeutic targets.

Disclosures: N. Galli: None. **B. Frizzi:** None. **I. Faravelli:** None. **M. Rizzuti:** None. **G. Costamagna:** None. **F. Biella:** None. **M. Garbellini:** None. **G. Garrone:** None. **M. Nizzardo:** None. **P. Rinchetti:** None. **E. Pagliari:** None. **M. Meneri:** None. **G. Comi:** None. **S. Corti:** None.

Poster

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Program #/Poster #: P289.03

Topic: C.06. Neuromuscular Diseases

Support: 1UG3TR003264-01

Title: Modeling C9orf72 ALS/FTD using a new organ-chip model to inform clinical trials

Authors: *D. LALL[1], H. HEMMATI[1], V. GARCIA[1], M. ARTZ[1], B. ONDATJE[1], M. LUKASIAK[1], S. BELL[1], G. LAWLESS[1], W. SEELEY[3], J. VAN EYK[2], C. SVENDSEN[1];
[1]Regenerative Med. Inst., [2]Advanced Clin. Biosystems Inst., Cedars-Sinai Med. Ctr., Los Angeles, CA;
[3]Dept. of Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Frontotemporal dementia (FTD) is a common dementia syndrome in patients under age 65, and amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with the loss of spinal cord and cortical motor neurons leading to paralysis and death from respiratory failure typically within 3-5 years of diagnosis. FTD and ALS have significant overlap clinically, pathologically and genetically. Aggregates of TDP-43 protein are the defining pathology of FTD (FTLD-TDP variant) and nearly all cases of ALS, and the most common genetic cause of both FTD and ALS are repeat expansions in the C9orf72 gene. C9orf72 is expressed in multiple cell types in the brain including in microglia and neurons, and there is strong evidence that disrupted interactions between different cell types underlie pathogenesis in C9-FTD/ALS. In order to model C9-FTD/ALS forebrain, we have developed a microphysiologic system (MPS) that permits the 3D culture of human induced pluripotent stem cell (iPSC)-derived cortical neurons (CNs), astrocytes and microglia in one chamber and brain microvascular endothelial cells in a separate chamber, separated by a porous membrane that provides a blood brain barrier component. Our goal is to validate the robustness of this forebrain MPS (fMPS) model and to identify C9-FTD/ALS-specific biomarkers, which we will then cross validate with the clinical data and pathology from the C9-FTD/ALS patients used to generate the patients iPSCs. In the future, the established fMPS model can be used to discover and validate translatable biomarkers for preclinical efficacy testing, and to assist in patient stratification for clinical trial design.

Disclosures: D. Lall: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **H. Hemmati:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **V. Garcia:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **M. Artz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **B. Ondatje:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **M. Lukasiak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **S. Bell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **G. Lawless:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc.. **W. Seeley:** None. **J. Van Eyk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **C. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc..

Poster

P289. Motor Neuron Disease: In Vitro Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P289.04

Topic: C.06. Neuromuscular Diseases

Support: National Institutes of Health (R01NS105756, R21AG064940),
LiveLikeLou at the Pittsburgh Foundation
Target ALS Foundation

Title: Phosphomimetic TDP-43 shows increased propensity to undergo aberrant liquid-liquid phase separation

Authors: *W. M. TENNANT, J. R. MANN, A. M. GLEIXNER, J. C. MAUNA, C. J. DONNELLY; Univ. of Pittsburgh, Pittsburgh, PA

Abstract: TDP-43 is a predominantly nuclear DNA/RNA binding protein (RBP) where it plays a keyrole in RNA processing, including alternative splicing and RNA trafficking, and is an underlyingneuropathological feature in nearly all Amyotrophic Lateral Sclerosis (ASL) patients. In ALS,TDP-43 is depleted from the nucleus and mislocalized to the cytoplasm where it formshyperphosphorylated and p62 positive insoluble inclusions that strongly correlate with regionsof CNS degeneration. The upstream mechanisms leading to TDP-43 proteinopathy and itscontribution to neurotoxicity remain unresolved and existing approaches to model thispathological event are unreliable. We and others previously showed that TDP-43 undergoesaberrant liquid-liquid phase transitions driven by the C-terminal Low Complexity Domain (LCD)when the protein does not bind its cognate RNA sequences (Mann et al 2019; Gassett-Rosa etal 2019; French et. Al 2019). While hyperphosphorylation of TDP-43 is a hallmark pathology ofALS and other neurological disorders, the physiological and pathological effects ofphosphorylated TDP-43 remain unknown. Here, we generated a 5S>D construct to mimichyperphosphorylated TDP-43 sites in postmortem tissue and found expression results inenriched cytoplasmic localization of the phosphomimetic construct. We next tested the effectof a phosomimetic TDP-43 LCD using the photokinetic optoDroplet approach to study the effecton LLPS of the protein fragment (Mann et al, 2019; Shin et al, 2017) and found repeatedstimulation promotes irreversible protein droplet assembly when compared to WT TDP-43 LCDdisassembly. Furthermore, we find that this optodroplet formation is highly concentrationdependent in the case of the WT TDP-43, however the threshold for LLPS is greatly reduced inthe 5SD construct. Lastly, we also demonstrate that blue light stimulation of full length 5SDoptoTDP-43 results in larger cytoplasmic inclusions when compared to the WT protein. Takentogether these studies indicates that phosphorylation plays a pivotal role in the regulation ofTDP-43 LLPS which could have far reaching implications for TDP-43 both physiologically andpathologically.

Disclosures: W.M. Tennant: None. **J.R. Mann:** None. **A.M. Gleixner:** None. **J.C. Mauna:** None. **C.J. Donnelly:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

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Program #/Poster #: P289.05

Topic: C.06. Neuromuscular Diseases

Support: NIH
ALSA
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CZI
DoD
TEDCO
F Prime

Title: Nuclear accumulation of CHMP7 initiates nuclear pore complex injury and subsequent TDP-43 dysfunction in sporadic and familial ALS

Authors: *A. COYNE[1], V. BASKERVILLE[1], B. ZAEPFEL[1], D. W. DICKSON[2], F. RIGO[3], F. BENNETT[3], P. LUSK[4], J. ROTHSTEIN[1];
[1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Pathology & Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL; [3]Ionis Pharmaceuticals, Carlsbad, CA; [4]Yale Sch. of Med., New Haven, CT

Abstract: Alterations in the nucleoporin (Nup) components and function of the nuclear pore complex (NPC) have been implicated as contributors to the pathogenesis of genetic forms of neurodegeneration including *C9orf72* Amyotrophic Lateral Sclerosis/Frontotemporal Dementia (ALS/FTD). We hypothesized that Nup alterations and the consequential loss of NPC function may lie upstream of TDP-43 dysfunction and mislocalization widely observed in ALS, FTD, and related neurodegenerative diseases. Here, we provide evidence that CHMP7, a critical mediator of NPC quality control, is increased in nuclei of *C9orf72* and sporadic ALS induced pluripotent stem cell (iPSC) derived spinal neurons (iPSNs) and postmortem human motor cortex prior to the emergence of Nup alterations. Inhibiting the nuclear export of CHMP7, triggered Nup reduction and TDP-43 dysfunction and pathology in human neurons. Knockdown of CHMP7 alleviated disease associated Nup alterations, deficits in Ran GTPase localization, defects in TDP-43 associated mRNA expression, and alleviated downstream glutamate induced neuronal death. Thus, our data support a role for altered CHMP7 mediated Nup homeostasis as a prominent initiating pathomechanism for familial and sporadic ALS and highlights the potential for CHMP7 as therapeutic target.

Disclosures: A. Coyne: None. **V. Baskerville:** None. **B. Zaepfel:** None. **D.W. Dickson:** None. **F. Rigo:** None. **F. Bennett:** None. **P. Lusk:** None. **J. Rothstein:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P289.06

Topic: C.06. Neuromuscular Diseases

Support: Dan and Diane Riccio Fund for Neuroscience

Title: Expression of ALS-linked profilin-1 alters the phagolysosomal pathway in iPSC-derived microglia-like cells

Authors: *S. FUNES[1], F. N. U. SHANKARACHARYA[1], J. A. MCDONOUGH[3], W. C. SKARNES[3], J. E. LANDERS[1], D. P. SCHAFER[2], D. A. BOSCO[1];
[1]Neurol., [2]Neurobio., Univ. of Massachusetts Med. Sch., Worcester, MA; [3]The Jackson Lab. for Genomic Med., Farmington, CT

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by loss of motor neurons. Cumulative evidence shows that microglia contribute to disease progression, but the mechanisms underlying this effect are unknown. Several ALS genes are highly expressed in microglia compared to neurons, including profilin-1 (*PFN1*), which encodes an actin-binding protein involved in microglia activation and phagocytosis. To interrogate whether ALS-linked PFN1 mutations affect the intrinsic functions of microglia, we generated mutant human inducible pluripotent stem cells (iPSCs) using CRISPR-Cas9. iPSCs were differentiated into microglia-like cells (iMGs) by a protocol that mimics primitive hematopoiesis in the yolk sac. Isogenic control and ALS-PFN1 iMGs express microglia-enriched markers including P2RY12, TMEM119, and IBA1. Further, iMGs are reactive to LPS and phagocytose disease-relevant material such as human synaptosomes and aggregated mutant PFN1 protein. Using this model, we discovered that ALS-PFN1 iMGs accumulate phagocytosed pHrodo-labeled material over time compared to isogenic control iMGs. Human-synaptosome washout studies indicate that control and ALS-PFN1 iMGs exhibit similar engulfment capacities, but that ALS-PFN1 iMGs retain a higher amount of undigested material at later time points post-washout. ALS-PFN1 iMGs also exhibit an accumulation of CD68 positive structures detected by immunofluorescence, consistent with alterations in the phagolysosomal pathway. To gain mechanistic insight into how mutant PFN1 affects phagocytosis, we performed RNAseq analysis and uncovered an upregulation of *TBC1D15* in ALS-PFN1 iMGs compared to isogenic control iMGs. TBC1D15 regulates the activation state of RAB7, a canonical late-endosomal protein crucial in endosomal/lysosomal pathways. Together, these observations implicate that the degradation machinery of ALS-PFN1 iMGs may be compromised during phagocytosis, leading to an accumulation of undigested material. Our findings provide insight into PFN1 biology and open new perspectives regarding microglia cell-autonomous defects in ALS that may contribute to motor neuron death.

Disclosures: S. Funes: None. **F.N.U. Shankaracharya:** None. **J.A. McDonough:** None. **W.C. Skarnes:** None. **J.E. Landers:** None. **D.P. Schafer:** None. **D.A. Bosco:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P289.07

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant RF1NS114128

Title: Investigating the convergence of altered neuronal activity and C9orf72-linked molecular mechanisms in ALS/FTD

Authors: *L. GHAFFARI, A. BOEHRINGER, T. WESTERGARD, D. TROTTI, A. R. HAEUSLER; Thomas Jefferson Univ., Philadelphia, PA

Abstract: The (GGGGCC)n nucleotide repeat expansion (NRE) in the C9orf72 gene (C9) is the most common genetic cause of ALS and FTD. The presence of the NRE is proposed to lead to neurodegeneration in three ways that may not be mutually exclusive: 1) repeat RNA transcribed from can sequester essential RNA-binding proteins, 2) dipeptide repeat proteins (DPRs), which are unconventionally translated through non-AUG repeat-associated (RAN) translation mechanism in both sense and antisense directions, can produce five distinct DPR species; poly(GA), poly(GR), poly(GP), poly(PA), and poly(PR), and 3) loss of C9ORF72 protein from the NRE-affected allele. Studies using C9-ALS/FTD patient-derived human induced pluripotent stem cell (hiPSC) differentiated into neurons indicate diseased neurons exhibit hyper-excitability, which transitions to hypo-excitability with longer culture time. Furthermore, cortical hyper-excitability is a commonly observed phenotype in ALS patients that typically precedes the onset of lower motor neuron dysfunction. However, the underlying cause and consequence of changes in excitability remain unclear. Since C9-NRE expression can alter neuronal excitability, this could trigger a feed-forward loop of activity-dependent C9-NRE product expression. Our laboratory has recently shown that repetitive trains of depolarization at high frequency (100 Hz) and glutamate-induced excitotoxic stress can trigger RAN translation of DPRs. The effect of altered neuronal activity and C9-NRE products and disease pathogenesis, including DPRs, has just begun to be elucidated by our laboratory and others. However, there is still a critical need to further understand this relationship as it might unravel novel therapeutic targets to ameliorate the DPR burden in C9-ALS/FTD. With these initial findings in mind, I hypothesize that neuronal activity serves as a C9-ALS/FTD pathology modifier. I will dissect the impact of excitatory and inhibitory neuronal activity on molecular mechanisms of C9-ALS/FTD using patient-derived hiPSCs differentiated into glutamatergic cortical neurons.

Disclosures: L. Ghaffari: None. **A. Boehringer:** None. **T. Westergard:** None. **D. Trotti:** None. **A.R. Haeusler:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

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Program #/Poster #: P289.08

Topic: C.06. Neuromuscular Diseases

Support: ICMR grant PGI/IEC/2014/2249

Title: Altered expression of angiogenesis and proteinopathy molecules in North Indian ALS patients and their effects on NSC34 cell line.

Authors: *R. KHOSLA, S. MODGIL, A. TIWARI, K. SHARMA, A. ANAND;
Post Grad. Inst. of Med. Educ. and Res., Chandigarh, India

Abstract: Altered expression of angiogenesis and proteinopathy molecules in North Indian ALS patients and their effects on NSC34 cell line.**AuthorsRadhika Khosla***, Shweta Modgil, Abha Tiwari, Kaushal Sharma, Akshay Anand.
Disclosures Radhika Khosla: None, Shweta Modgil: None, Abha Tiwari: None, Kaushal Sharma: None, Akshay Anand*: None .**Abstract**Amyotrophic Lateral Sclerosis (ALS) is a devastating motor neuron disease which leads to paralysis and total loss of movement with increasing severity of the disease. The diagnostic and prognostic markers are limited. Proteinopathy and angiogenesis (and neuroprotection) have been studied in respect to the disorder. The objective of the study was to analyse the expression of molecules involved in the angiogenesis and proteinopathy as prospective biomarkers in plasma of ALS patients. 89 ALS patients and 98 non neurological controls were recruited in the study. The plasma levels of Vascular Endothelial Growth Factor (VEGF), VEGF Receptor 2 (VEGFR2), Angiogein (ANG), Tar DNA Binding Proetin 43 (TDP 43), Optineurin (OPTN) and Chemokine Ligand 2 (CCL2) were analysed among ALS using ELISA and compared with healthy individuals. Correlation analysis was done for all the markers. To further analyse the effect of the patients' plasma and these molecules on neurons, *in-vitro* analysis was done. NSC34 hybridoma cell line was used as a model. The cell line was stimulated using the patients' plasma to prepare *in-vitro* model of ALS. Appropriate controls were used for cell line experiments in the form of healthy participants' plasma as well as unstimulated cells. The same molecules expression was analysed in the cell line using RT-PCR and ICC experiments. The molecules were found to be significantly reduced in the patients' plasma and were found to be significantly correlated to one another. The plasma caused significant loss of cells after stimulation in *in-vitro* studies. Also the shape of cells was significantly altered. The cells lost their extensions and took circular shape. The expression of the molecules tested was also found to be altered in cell line. The results indicate the importance of the molecules to be studied as prospective biomarkers as a panel as all the molecules were correlated to one another. Studying the effects of plasma on neuronal cell line and study of the neuroprotective and proteinopathy molecules in patients' plasma can be useful in developing appropriate biomarkers for prognosis of the disease. However a limitation of the study is that along with plasma these molecules expression in CSF and plasma-CSF relation are also warranted to be studied as the neurons are in direct vicinity of the CSF.

Disclosures: R. Khosla: None. **S. Modgil:** None. **A. Tiwari:** None. **K. Sharma:** None. **A. Anand:** None.

Poster

P289. Motor Neuron Disease: In Vitro Studies I

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01AR077191
NIH Grant R01NS091540
Amyotrophic Lateral Sclerosis Association
The University of Wisconsin Foundation
UW Stem Cell & Regenerative Medicine Center

Title: Transcriptome analysis using ALS patient iPSC-derived skeletal myocytes reveals Bet1L as a new molecule possibly linked to neuromuscular junction degeneration

Authors: E. M. LYNCH[1], S. ROBERTSON[1], C. FITZGIBBONS[1], M. REILLY[1], C. SWITALSKI[1], A. ECKARDT[1], S.-R. TEY[1], K. HAYAKAWA[3], *M. SUZUKI[1,2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neuromuscular disease in which patients gradually become paralyzed due to loss of motor function. While many genetically inheritable mutations have been linked to ALS, the majority of ALS cases are considered sporadic. Therefore, there is a need for a common therapy that is effective for all ALS patients. Although there is evidence of the disease beginning in the periphery at the neuromuscular junction (NMJ), the specific processes involved in skeletal muscle and at the NMJ are still largely unknown. To study common disease mechanisms in ALS skeletal muscle, we performed RNA sequencing of skeletal myocytes differentiated from induced pluripotent stem cells (iPSCs) of familial ALS (with *C9ORF72*, *SOD1*, or *TARDBP* mutations) and sporadic ALS patients. Compared to healthy control lines, the myocytes from all ALS lines showed downregulation of four genes: *BET1L*, *DCX*, *GPC3*, and *HNRNPK*. We next measured the expression levels of these four genes in hind limb muscle samples from a rat model of familial ALS ($SOD1^{G93A}$ transgenic). Notably, only the Bet1L gene, which encodes Bet1 Golgi Vesicular Membrane Trafficking Protein Like, was commonly downregulated. Bet1L protein appeared to be localized to the basal lamina of the NMJ, with decreased expression over time following disease progression in $SOD1^{G93A}$ transgenic rats. Our results indicate that loss of Bet1L at the NMJ could be of interest for better understanding ALS disease progression.

Disclosures: E.M. Lynch: None. **S. Robertson:** None. **C. FitzGibbons:** None. **M. Reilly:** None. **C. Switalski:** None. **A. Eckardt:** None. **S. Tey:** None. **K. Hayakawa:** None. **M. Suzuki:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P346.01

Topic: C.10. Brain Injury and Trauma

Support: NIH 1R21NS111099
Chuck Noll Foundation
Walter L. Copeland Fund of The Pittsburgh Foundation

Title: Cortical and Hippocampal Reductions in Synaptic Glycoprotein 2 Isoforms in a Rat Model of Traumatic Brain Injury

Authors: K. M. FRONCZAK, Y. LI, M. PARRY, E. HOLETS, J. J. HENCHIR, C. DIXON, ***S. W. CARLSON**;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traumatic brain injury (TBI) can result in chronic cognitive impairments and greatly impact the quality of life for patients living with an injury. Alterations in hippocampal function, including changes in neurotransmission, have been shown to contribute to the manifestation of cognitive impairments in preclinical models of TBI. Neuronal communication is facilitated by the controlled release of neurotransmitters from vesicles in the presynaptic terminal. Synaptic vesicular glycoprotein 2 (SV2) isoforms SV2A and SV2B have been shown to be critical for maintaining the presynaptic vesicular pool and coupling of calcium signaling to the N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, two presynaptic properties we have recently shown to be altered after TBI. The effect of TBI of SV2 isoforms has not been examined. To investigate this, cortical and hippocampal abundances of SV2A and SV2B were assessed at 1, 3, 7 and 14 days after 2.7mm controlled cortical impact (CCI) or sham control injury in rats. Immunoblotting revealed that SV2A and SV2B levels (n=6 / group / time point) were significantly reduced at multiple time points in the cortex and all time points in the hippocampus after CCI. Hippocampal immunohistochemical staining at 14 days post-injury (n=6 / group) revealed significantly reduced immunoreactivity for each isoform in several hippocampal subregions. Overall, reduced SV2 abundance was observed at time points in which injured animals exhibited impaired motor function, as tested by a beam walking task on days 1-5 post-injury, and impaired spatial learning and memory performance, as assessed by the Morris water maze task on days 9-14 post-injury. These findings provide new evidence for the effect of TBI on SV2 isoforms and novel insight into potential contributors to impaired neurotransmission and associated neurobehavioral dysfunction after TBI.

Disclosures: K.M. Fronczak: None. **Y. Li:** None. **M. Parry:** None. **E. Holets:** None. **J.J. Henchir:** None. **C. Dixon:** None. **S.W. Carlson:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

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Program #/Poster #: P346.02

Topic: C.10. Brain Injury and Trauma

Support: NSF-GRFP (JTH) #DGE-1841556
Center for Stem Cells and Regeneration
Center for Zebrafish Research

Title: Prophylactic activation of Shh attenuates TBI sequela by regulation of EAAT2 in adult zebrafish

Authors: *J. HENTIG, D. R. HYDE;
Univ. of Notre Dame, Notre Dame, IN

Abstract: Traumatic brain injuries (TBI) have tremendous and lasting impacts on survivors as these injuries can result in various sequelae. Secondary injury begins within minutes after TBI, with alterations in cellular function, metabolism, chemical signaling contributing to neuro-deterioration. Sonic hedgehog (Shh) is a key signaling pathway that is upregulated following central nervous system (CNS) damage in adult zebrafish and aids in injury-induced regeneration. The Smo agonist purmorphamine, which activates Shh signaling, attenuates various TBI sequelae. Using a modified Marmarou weight drop on adult

zebrafish, we examined post-traumatic seizures (PTS) following blunt-force TBI and Shh modulation. We demonstrate that purmorphamine-induced activation of Shh signaling attenuates TBI-induced sequelae. The inhibition of Shh signaling, by the Smo antagonist cyclopamine, significantly increased the number of TBI fish that experienced PTS, prolonged the timeframe PTS was observed, and significantly decreased survival across all TBI severities compared to severity-matched counterparts. qRT-PCR and immunoblots revealed purmorphamine increased EAAT2 expression in undamaged brains compared to untreated controls. Exposing undamaged fish to 5 mM glutamate in their tank water for 30 mins induced 90% of the fish to experience seizures, with the first seizure recorded as early as 5 mins after exposure. Purmorphamine treatment suppressed the glutamate-induced seizures, with the first recorded seizure at 20 mins and only 25% of the treated fish experiencing seizures. In contrast, cotreating glutamate-bathed fish with purmorphamine and cyclopamine resembled controls, with rapid seizure onset and the majority of the fish experiencing seizures. In contrast, triple-treating (purmorphamine, cyclopamine, and ceftriaxone to transcriptionally upregulate EAAT2) glutamate-bathed fish, rescued the glutamate-induced seizures, with delayed seizure onset and low percentages of fish experiencing seizure activity. In an analogous manner, purmorphamine treatment reduced post-traumatic seizures, edema, and cognitive deficits in TBI fish. In contrast, cyclopamine treatment increased seizure activity, and prolonged elevated edema and cognitive deficits in TBI fish. The increased severity of TBI phenotypes with cyclopamine was significantly reduced by cotreating the TBI fish with cyclopamine and ceftriaxone. Collectively, these data suggest that Shh signaling induces EAAT2 transcription and plays a role in regulating TBI-induced glutamate excitotoxicity and therefore reduces TBI-sequelae.

Disclosures: J. Hentig: None. **D.R. Hyde:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P346.03

Topic: C.10. Brain Injury and Trauma

Support: Military Operational Medicine Research Program, USA

Title: Repeated concussions heightens the vulnerability of brain to blast exposure

Authors: *P. ARUN, D. M. WILDER, A. BATUURE, Y. WANG, J. B. LONG;
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Abstract: A history of repeated concussions is known to cause long-term neurological problems. Typically as a result of contact sports or training exercises, significant numbers of military service members are reported to have a history of concussion before exposures to blast during deployment. No systematic studies have been carried out to determine whether concussion history heightens or decreases the brain vulnerability to blast exposure. In the present study, we have evaluated the effect of repeated concussions on the vulnerability of brain to blast exposure using neurobehavioral functional assessments in rats. Anesthetized rats were subjected to either repeated concussions (two concussions in one week apart using a modified Marmarou weight drop model) or single blast exposure (19 psi peak total pressure,

4-5 msec duration using an advanced blast simulator) or single blast exposure one day after the second weight drop. Sham control rats were not subjected to weight drop or blast exposure. Neurobehavioral changes were monitored at acute, and sub-acute time points using rotating pole test for vestibulomotor functions, open field exploration test for anxiety/depression, and novel object recognition test for short-term memory. Rotating pole test results indicated that the vestibulomotor functions were most disrupted in blast-exposed rats having prior concussions compared to the sham controls or rats exposed to either repeated concussions or blast. The deficits were evident from day 1 post-blast and persisted till one month. Total distance travelled, horizontal/vertical activity, center time and margin time measurements in the openfield exploratory activity test indicated that the rats exposed to both concussions and blast develop more anxious and depression-like behaviors compared to the other groups of rats at both acute and sub-acute time points. The novel object recognition test revealed short-term memory loss at 1 month post-blast in rats exposed to both repeated concussions and blast. The results obtained indicated that the concussion history exacerbated the neurobehavioral functional deficits after blast exposure.

Disclosures: P. Arun: None. **D.M. Wilder:** None. **A. Batuure:** None. **Y. Wang:** None. **J.B. Long:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P346.04

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant MH104632
NIH Grant GM083889
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Google Cloud's Academic Research Credits Program

Title: Repetitive Mild Head Trauma Induces Age-Dependent Sexually Dimorphic Long-term Brain Deficits in a Novel Drosophila Model

Authors: *C. YE[1], J. A. BEHNKE[1], K. H. MOBERG[1], J. Q. ZHENG[2];
[1]Cell Biol., Emory Univ., Atlanta, GA, [2]Cell Biol., Emory Univ., Atlanta, GA

Abstract: Traumatic head impacts, including mild ones such as concussion, represent an environmental risk factor linked to the development of chronic brain dysfunction that can occur years after initial exposure. However, the underlying mechanisms remain poorly understood. A better understanding of the brain's response to mild physical insults and the long-lasting detrimental effects can lend new insight towards the development of neuroprotective strategies. *Drosophila melanogaster* represents an excellent tractable model organism to dissect fundamental cellular and molecular disease mechanisms, including neurodegeneration. With their relatively short lifespan, *Drosophila* enables long-term outcome analyses after initial exposure to mild head trauma. To investigate the life-long effects on brain function and structure after the initial exposure to mild head trauma and the underlying mechanisms, we developed the **H**ead **I**mpact **FL**y **I**njury model (HIFLI) model, in which mild repetitive headfirst impacts to multiple

(10-15 at a time) awake and unrestrained adult flies can be delivered. We showed that young flies (3-5 days old) subjected to our mild and nonlethal injury immediately exhibited concussive-like behaviors such as temporary uncoordinated and seizure-like movements but recovered within 24 hours. However, these injured flies progressively developed impaired startle-induced climbing, brain degeneration, and shortened lifespan throughout their lifetime. Importantly, the behavioral deficits and brain degeneration were more profound in female flies than male flies, indicating that female flies have a heightened vulnerability to mild head trauma. Interestingly, we found that head impacts elicited elevated brain activity, and its acute blockage abrogated some of the detrimental effects in female flies. Lastly, we assessed age as a risk factor for head trauma-induced chronic brain dysfunction by delivering mild head impacts to fly cohorts of different ages (3 days, 2 weeks, and 4 weeks old). We observed substantially worse sensorimotor decline and brain degeneration in the older cohorts, indicating that aging increases vulnerability to mild head injury. Together, our findings validate *Drosophila* as a suitable model system for investigating the long-term effects of head trauma, suggest an increased vulnerability in females and older adults for head trauma-induced brain dysfunction and degeneration, and indicate that early altered neuronal excitability may be a key mechanism linking mild brain trauma to chronic degeneration.

Disclosures: C. Ye: None. **J.A. Behnke:** None. **K.H. Moberg:** None. **J.Q. Zheng:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P346.05

Topic: C.10. Brain Injury and Trauma

Support: VA MERIT 1RX002705-01A1
NIH/NINDS 1R01-NS-101108-01

Title: Traumatic Brain Injury Alters Contextual Fear Extinction But Not Pattern Separation

Authors: *E. R. HALTER[1], C. D. ADAM[2], M. SERGISON[3], O. FRUCHET[3], J. A. WOLF[2];
[1]Univ. of Pennsylvania, PA, PA; [2]Neurosurg., [3]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) are two of the most common ailments afflicting Veterans. However, little is known about the comorbidity of these two disorders, or how they interact and progress over chronic time points. To study the effect of injury on fear memory acquisition and extinction, we subjected rats to a lateral fluid percussion injury (FPI) of 1.8atm or 2.1atm, creating a unilateral mild to moderate TBI. These animals were run through a contextual fear-conditioning and pattern separation paradigm at an acute time point two weeks post-injury (1.8atm n=5, 2.1atm n=3) or sham surgery (n=7). All groups showed an equal affinity for the creation of contextual fear memories as evidenced by similar overall acquisition curves and corresponding high freezing levels in the acquisition context, context A, during the first extinction trial. Similar pattern separation abilities between groups were also displayed by significantly lower freezing levels in a similar, but novel context B, used only for extinction 2, and completed 5min after extinction 1. When a third extinction trial was completed one day later back in context A, sham animals showed a significant reduction in freezing as

compared to extinction 1. This suggests sufficient extinction memory creation and consolidation had occurred. At this same time point, both groups of injured animals did not show decreased freezing but instead displayed freezing at levels statistically similar to the first extinction trial in context A. In the 2.1atm injured group, this high level of freezing in extinction 3 was much more pronounced than the 1.8atm injured animals, suggesting a corresponding larger injury effect. Both groups of injured animals did not show significant extinction in context A until extinction 4, one trial later than seen in the sham group. Our findings suggest that TBI slows the creation and consolidation of fear extinction memories but does not appear to affect the acquisition of contextual fear memories or pattern separation abilities on a short temporal scale. The mild to moderate injury may be disrupting the extinction process due to sleep deficits preventing the consolidation of the extinction memory. This effect appears to increase with injury size. Our data gives us a behavioral basis to further explore the mechanisms underlying this dysfunction using *in vivo* electrophysiological and explore more chronic injury time points using this behavioral paradigm.

Disclosures: E.R. Halter: None. **C.D. Adam:** None. **M. Sergison:** None. **O. Fruchet:** None. **J.A. Wolf:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P346.06

Topic: C.10. Brain Injury and Trauma

Support: Center for Stem Cells and Regenerative Medicine
Center for Zebrafish Research
Indiana Spinal Cord & Brain Injury Research Fund

Title: Studying the regeneration of the zebrafish telencephalon in response to blunt force traumatic brain injury.

Authors: *K. CLOGHESSY, J. HENTIG, D. R. HYDE;
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Abstract: Blunt force traumatic brain injuries (bfTBIs) result in global and diffuse damage to the central nervous system (CNS) and are associated with increased risk of long-term side effects, like memory loss, speech issues, and seizures. Currently, treatments for TBI are focused on managing chronic damage, rather than regenerating cells lost during injury. Activation of endogenous quiescent stem/progenitor cells is a possible therapy for TBI, necessitating a deeper understanding of the genetic mechanism of neuronal regeneration. While the regenerative capacity of mammals is limited, zebrafish (*Danio rerio)* has a robust neurogenic capacity in the CNS, making it ideal to uncover mechanisms involved in endogenous neuronal repair. Our lab modified the Marmarou weight drop model, allowing us to deliver scalable blunt force injury that is centered on the zebrafish telencephalon, homologous to the hippocampus, the center of learning and memory. Following bfTBI, we found that zebrafish recapitulate many of the phenotypes commonly seen in human TBI patients, including an increase in both the number of fish experiencing

seizures and the time required to recover from the bfTBI. There was an increase in the severity of subdermal hematomas, which correlated with the disruption of the blood brain barrier (BBB) as measured with Evan's Blue dye. We also observed cognitive deficits, such as learning in a shuttle box assay, which utilizes an associative-learning test with an adverse electric shock stimulus. Following the bfTBI, we found that both short-term and long-term recall of a learned behavior in the shuttle box were significantly impaired. We determined that the bfTBI induced a gradient of cell death across the entire neuroaxis of the brain, with the maximum numbers of dying cells centered on the region underlying the impact site. Most importantly, we found that the bfTBI also induced cell proliferation in the telencephalon. Thus, zebrafish represents a useful model that recapitulates many of the clinical symptoms described in human bfTBI patients, but unlike mammalian models, also exhibits a robust cell proliferation and neuronal regeneration response. This will allow us to study the genetic mechanisms that induce the quiescent stem/progenitor cells to reenter the cell cycle and regenerate lost neurons following a bfTBI, which could ultimately lead to inducing an analogous regeneration response in humans.

Disclosures: K. Cloghessy: None. **J. Hentig:** None. **D.R. Hyde:** None.

Poster

P346. Animal Models of Brain Injury: Molecular Mechanisms and Other Models

Location: Virtual Only

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Program #/Poster #: P346.07

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant T32DC016853
Indiana CTSI 11917

Title: Mechanisms of Secondary Injury and Auditory Deficits Following Mild Blast Induced Trauma

Authors: *J. FERNANDEZ[1], E. X. HAN[1], E. L. BARTLETT[1], R. SHI[2];
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Abstract: Mechanisms of Secondary Injury and Auditory Deficits Following Mild Blast Induced Trauma

Joseph Fernandez[1,4], Emily Han[1], Edward Bartlett[1,3], Riyi Shi[1,3,41]Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN[2]School of Medicine, Indiana University, Indianapolis, IN[3]Purdue University Interdisciplinary Life Science (PULSe) Program, Purdue University,West Lafayette, IN[4]Dept. Basic Medical Sciences, College of Veterinary Medicine, Purdue University,West Lafayette, IN

Blast-induced hearing difficulties affect thousands of veterans and civilians each year. The long-term impact of blast exposure on the central auditory system (CAS) can last months, even years, without major external injury, and is hypothesized to contribute to many behavioral complaints associated with mild blast traumatic brain injury (bTBI). However, the mechanisms that underlie these long-term impairments are still poorly understood. Although initial mechanical injury likely plays a role in central auditory damage, a secondary molecular mechanism of damage likely results in the chronic auditory deficits following mild bTBI. Oxidative stress has been suggested as a key player in secondary molecular damage

in other models of CNS injury, including other TBIs, and may underlie functional auditory deficits in mild bTBI as well. Here, we examined the underpinnings of auditory deficits following bTBI and compared these results to molecular and anatomical changes observed following injury. We examined changes in markers for cellular membrane damage and acrolein protein adducts for oxidative stress. Additionally, we examined GAD65/67 for changes in cellular inhibition/excitation patterns. These markers were assessed along the auditory pathway, namely, within the superior olivary complex (SOC), inferior colliculus (IC), and auditory thalamus (AT). Increased TMR and acrolein protein adducts staining in blast animals indicate initial mechanical injury within the SOC and ventral axon streams in the brainstem at the 2 day post injury time point. Staining for GAD65/67 shows a reversal of inhibition/excitation within these auditory systems over the course of 14 days. Comparisons of ABR wave amplitudes/ratios and middle latency response, suggest functional changes correlated with these anatomical results. Taken together, our results suggest that an acute cascade of (axonal) membrane damage and oxidative stress results in a temporally dependent inhibition/excitation imbalance over the course of two weeks that is correlated with slight changes in auditory processing.

Disclosures: J. Fernandez: None. **E.X. Han:** None. **E.L. Bartlett:** None. **R. Shi:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: T32NS041234
K01HD084672-04
5R25GM79300

Title: Serotonin sensitivity across injury severities

Authors: *O. SHELTON[1], D. V. BIRCH[2], M. JIANG[1], V. M. TYSSELING[2];
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Abstract: Spinal cord injuries disrupt messages between the brain and the body distal to the injury. This results in paralysis below the injury level and makes daily function very difficult. In addition, most people with spinal cord injury develop hyperreflexia and involuntary muscle contractions, or spasms, that cause even more movement dysfunction as well as pain, contractures, and safety issues. Multiple neuronal tracts are interrupted by SCI. Descending projections from the raphe nuclei innervate the spinal cord and release 5-HT onto spinal neurons. 5-HT alters the excitability of neurons via persistent inward currents. In chronic SCI with long-term deprivation of 5-HT input motoneurons and several species of spinal interneurons change their response to 5-HT by becoming constitutively active or increasing their sensitivity to 5-HT, respectively. In this study we examine whether the difference in intensity of spasms varies with/can be explained by the degree of increase of 5-HT sensitivity of the spinal cord. We used a chronic impact injury mouse model of SCI. We assessed the amount of functional locomotor recovery at 10wks and compared this recovery to the electrical outputs from muscle and nerve tissue in the SCI mice.

To compare how muscle contractions were impacted by our drug interventions we tested spasticity *in vivo* by recording the flexor withdrawal EMG response to an electrical stimulus three months post injury. To directly measure the spinal reflexes, we removed the sacral section of the spinal cord, stimulated the dorsal roots, and then recorded the ENG response through the ventral roots.

Disclosures: O. Shelton: None. **D.V. Birch:** None. **M. Jiang:** None. **V.M. Tysseling:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

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Program #/Poster #: P362.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01-AG044615
NIH R01-HL146114
NIH T32-HL105355

Title: Mitochondrial Adaptations to Diaphragm Muscle Inactivity Imposed by Cervical Spinal Cord Injury

Authors: *A. D. BROWN[1], M. J. FOGARTY[2], G. C. SIECK[3];
[1]Dept of Physiol. and Biomed. Engin., [2]Dept. of Physiol. & Biomed. Engin., [3]Physiol. & Biomed. Engin., Mayo Clin., Rochester, MN

Abstract: Mitochondrial Adaptations to Diaphragm Muscle Inactivity Imposed by Cervical Spinal Cord InjuryAlyssa D. Brown, Matthew J. Fogarty, Gary C. Sieck
2101/2300 characters Type I and IIa diaphragm muscle (DIAm) fibers comprise fatigue resistant slow and fast motor units that are recruited to accomplish breathing. In contrast, type IIx/IIb fibers comprise more fatigable fast motor units that are infrequently recruited only during airway protective and straining behaviors. Thus, there are marked differences in the activity and energetic demand for type I and IIa DIAm fibers compared to type IIx/IIb fibers. Cervical spinal cord hemisection at C_2 (C_2SH) removes excitatory drive for inspiratory activity of the DIAm and thereby imposes prolonged inactivity of type I and IIa fibers. We hypothesize that mitochondrial structure and function in type I and IIa DIAm fibers differs from type IIx/IIb fibers and adapts in response to inactivity induced by C_2SH. After C_2SH, inactivity was confirmed by the absence of DIAm EMG, and after 14 days, the effect of inactivity on mitochondrial structure and function was assessed in type identified fibers. Mitochondria in DIAm fibers were labeled using MitoTracker Green and imaged in 3-D by fluorescence confocal microscopy. Mitochondrial volume density and morphometry were analyzed using ImageJ. In alternate serial sections of the same DIAm fibers, the maximum velocity of the succinate dehydrogenase reaction (SDH_{max}) was determined using a quantitative histochemical technique. Overall, mitochondrial volume density was higher in type I and IIa DIAm fibers and mitochondria were more filamentous compared to type IIx/IIb fibers. Inactivity reduced mitochondrial volume density in type I and IIa DIAm fibers and induced mitochondrial fragmentation. The SDH_{max} values normalized for fiber volume and for mitochondrial volume were both higher in type I and IIa DIAm fibers compared to type IIx/IIb fibers. After 14 days of

inactivity induced by C_2SH, SDH_{max} (normalized for fiber volume and for mitochondrial volume) decreased in type I and IIa. These results are consistent with mitochondrial structural and functional adaptions to the marked reduction in the energetic demand of type I and IIa DIAm fibers imposed by C_2SH.

Disclosures: A.D. Brown: None. **M.J. Fogarty:** None. **G.C. Sieck:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.03

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen #546893

Title: Timeline of changes in key hormones and their receptors associated with spinal cord injury-induced polyuria

Authors: *J. H. GUMBEL, C. YANG, L. E. ZIPPERER, C. H. HUBSCHER;
Univ. of Louisville, Lousiville, KY

Abstract: Timeline of changes in key hormones and their receptors associated with spinal cord injury-induced polyuria
Jason H Gumbel, Cui Bo Yang, Lindsey E Zipperer, Charles H Hubscher
Spinal cord injury (SCI) results in upper and lower urinary tract function deficits, which includes detrusor overactivity, urinary incontinence, detrusor-sphincter dyssynergia, and polyuria. Together, these are among the leading issues that affect quality of life. As the overproduction/passage of urine (polyuria) after SCI has previously been associated with an imbalance in key regulators of body fluid homeostasis, this current study examined the timing of changes in levels of these hormones, peptides, receptors, and channels post-contusion injury in adult male Wistar rats. The results of this study demonstrate significant up or down regulation at various time points, beginning at 7 days post injury, in the levels of urinary atrial natriuretic peptide (ANP), serum arginine vasopressin (AVP), kidney natriuretic peptide receptor-A (NPRA), kidney vasopressin-2 receptor (V2R), kidney aquaporin-2 channels (AQP2) and kidney epithelial sodium channels (ENaC, β and γ but not α subunits). Additionally, the number of AVP-labeled cells/area in the hypothalamus were also significantly decreased at one or more time points, particularly in the suprachiasmatic nucleus which deals with circadian rhythms. Together, the observed significant fluctuations in key components involved in body water/solute homeostasis post-SCI suggests therapeutic interventions (for example, desmopressin, a synthetic analogue of AVP - a hormone known to lose its diurnal rhythmicity post-SCI in humans) should be considered early post-SCI.

Disclosures: J.H. Gumbel: None. **C. Yang:** None. **L.E. Zipperer:** None. **C.H. Hubscher:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

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Program #/Poster #: P362.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant RF1NS110637(JW)
NIH Grant R01NS110635 (AIF/JW)

Title: Sci in aged mice exacerbates neuropathological changes in both spinal cord and brain leading to worsened neurological dysfunction

Authors: *Z. LEI, Y. LI, R. M. RITZEL, H. LI, A. I. FADEN, J. WU;
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Abstract: Approximately 20% of all spinal cord injuries (SCI) occur in persons aged 65 years or older. Older patients with SCI have different features with regard to neurological characteristics after injury. Recent large-scale longitudinal population-based studies showed that patients with SCI are at a higher risk of developing dementia than non-SCI patients, indicating that SCI is a potential risk factor for dementia. Age is known to potentiate inflammation and neurodegeneration at the injured site leading to impaired recovery from SCI. However, no research has been aimed at studying the mechanisms of SCI-mediated cognitive impairment in the elderly. In the present study, young adult (3-month-old) and aged (18-month-old) male mice were subjected to moderate contusion SCI at T10 and their functional outcomes were evaluated using a battery of neurobehavioral tests including motor function [Basso Mouse Scale (BMS)], cognition [Y-maze, novel object recognition (NOR)], and depression [novelty-suppressed feeding (NSF) and social recognition (SR)]. BMS assessment of locomotor function showed marked impairment in aged mice compared to young animals, which were correlated with reduced spared white matter and increased lesion volume. At 2 months post-injury, aged mice displayed worse performance in neurobehavioral tests, as evidenced by lower % of spontaneous alteration in Y-Maze task, reduced novelty preference in NOR test, increased sociability deficits in SR, and elevated latency to detect food in NSF, indicating exacerbated impairment of cognition and depressive-like behavior in aged mice compared to young animals. NanoString analysis with the neuropathology panel identified several age- and injury-specific genes that were differentially expressed in the brain after SCI, including those involved with the inflammation, neurodegeneration, and autophagy pathways. These findings were further validated by qPCR and microscopy. Flow cytometry demonstrated increased microglia and myeloid and lymphocytes infiltration at the injured site from young mice which was exacerbated with age. Moreover, SCI in aged mice altered microglial function and dysregulated autophagy function in both microglia and neurons of the brain, resulting in neurodegeneration compared to young animals. Taken together, our data indicate that aging exacerbates neuropathological changes in both injured spinal cord and remote brain region that is associated with poorer functional outcome. Thus, our studies provide innovative cellular and molecular perspectives on the pathophysiology of age-related deficits after SCI.

Disclosures: Z. Lei: None. **Y. Li:** None. **R.M. Ritzel:** None. **H. Li:** None. **A.I. Faden:** None. **J. Wu:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

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Program #/Poster #: P362.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01NS099076
R01DA03190
R01NS085426
F31DK123840

Title: Spinal dopamine synthesis, release, and regulation of micturition reflexes in female rats with spinal cord injury

Authors: *J. H. DEFINIS[1], E. OATMAN[1], Z. D. BRODNIK[2], C. T. TRUEBLOOD[1], R. A. ESPAÑA[2], S. HOU[1];
[1]Marion Murray Spinal Cord Res. Center, Dept. of Neurobio. and Anat., [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) often results in urinary dysfunction. Although an involuntary micturition reflex can be established to elicit voiding, bladder hyperreflexia and detrusor-sphincter dyssynergia arise to cause incontinence and inefficient expulsion of urine. To date, the mechanisms that underlie the regulation of micturition after SCI are not well understood. We recently observed an increase of a population of tyrosine hydroxylase (TH)+ cells in the rat lumbosacral cord following SCI, which could contribute to the sustention of a low level of dopamine (DA) that modulates the recovered micturition reflex. To further elucidate this spinal endogenous machinery, we employed multiple approaches in female rats with SCI, including qPCR and Western blot to determine the expression of DA-related genes and proteins, fast-scan cyclic voltammetry (FSCV) to test in situ DA release, injection of Bromodeoxyuridine (BrdU) and immunostaining to identify the origin of TH+ neurons, as well as bladder cystometrogram (CMG) and external urethral sphincter (EUS) electromyography (EMG) to examine DA-modulated detrusor-sphincter activity. Three weeks after T10 spinal cord transection, mRNA and protein levels of TH and dopamine decarboxylase (DDC) were decreased, but detectable in the L6/S1 spinal cord segment. Focal electrical stimulation of the region where TH+ cells reside in spinal cord slices evoked DA release. In BrdU injected rats, labeling of mitotic cells showed that no TH+ cells incorporated BrdU. Alternatively, a portion of spinal TH+ cells express PAX2, a transcription factor of inhibitory interneurons. During bladder CMG and EUS EMG, intrathecal (i.t.) administration of the DA precursor, L-DOPA, reduced the number of bladder non-voiding contractions in the filling phase and increased the EUS bursting period during voiding, illustrating the precursor's ability to decrease bladder hyperactivity and improve voiding efficiency. Thus, spinal TH+ cells undergo injury-induced plasticity and are capable of synthesizing and releasing DA following SCI. Newly emerged TH+ cells may develop from a phenotypic switch rather than neurogenesis. Ultimately, increasing DA signaling in the lower cord enhances recovered micturition function after SCI.

Disclosures: J.H. DeFinis: None. **E. Oatman:** None. **Z.D. Brodnik:** None. **C.T. Trueblood:** None. **R.A. España:** None. **S. Hou:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.06

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Characterizing age-dependent alterations in neuron-extrinsic responses after spinal cord injury

Authors: *T. C. SUTHERLAND, D. HORVAT, A. SEFIANI, O. A. GARCIA, M. RIVERA, P. HUNG, C. G. GEOFFROY;
Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Spinal Cord Injury (SCI) is the second most common cause of paralysis, following stroke, and places a significant life-long burden on patients. In the western population, the average age of incidence for SCI has increased, as has the length of survival of SCI patients. This places great importance on understanding SCI in middle-aged and aging patients. Experimentally, SCI is commonly modeled in young adult animals in stark contrast to the aging human population, likely hampering translation of research to the clinic. Axon regeneration after injury is an area of study that has received substantial attention and made important experimental progress, however our understanding of how aging affects this process, and any therapeutic effort to modulate repair, is incomplete. The growth and regeneration of axons is mediated by both neuron intrinsic and extrinsic factors, and both may play a significant role in the age-dependent decline of this capability. Key extrinsic influences on axon regeneration in the include inflammation and astrogliosis, components of the extracellular matrix, and myelin proteins. Alterations in neuron-extrinsic factors with age have received little attention, however, and how the age factor can impact these responses is not well characterized. Alterations in these elements have been observed in the naïve aging CNS and also after SCI. These may compound to result in worse outcomes after SCI in aging populations. Age-dependent alterations in astroglial dynamics are likely to impact the efficiency of astrogliosis, and diminish the ability of astrocytes to quickly sequester the fibrotic scar and inflammatory lesion. There is also evidence of altered inflammation and fibrosis, as well as increases in inhibitory ECM molecules in aging animals. These elements lead to a more severe SCI lesion and will likely result in subsequent decreases in functional recovery. Understanding these age-dependent changes in acute and sub-acute phases of SCI is highly significant to provide strategies to target this early neuron-extrinsic response in aging populations. This will be vital to the development of potential therapeutic avenues to improve injury outcome in an increasingly older SCI population and improve functional recovery after SCI in patients of all ages.

Disclosures: T.C. Sutherland: None. **D. Horvat:** None. **A. Sefiani:** None. **O.A. Garcia:** None. **M. Rivera:** None. **P. Hung:** None. **C.G. Geoffroy:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS107392
NIH Grant R00NS088211

Title: May the force be with regeneration

Authors: *Y. SONG;
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Abstract: Axons in the mature central nervous system (CNS) fail to regenerate after injury, due to the loss of neuronal intrinsic growth potential and the extrinsic inhibitory environment constituted by reactive glial cells. We aim to identify, characterize and manipulate programs in and out of the neurons to achieve axon regeneration and behavioral recovery. We identified a neuronal intrinsic program acting as a brake on axon regeneration by sensing the mechanical force. During axon regeneration, the growth cone physically interacts with the environment such as the glial cells, resulting in the activation of the mechanosensitive ion channel Piezo at the growth cone tip. Opening of the Piezo channels leads to local calcium influx and the activation of Nos (Nitric oxide synthase), which then produces NO. NO functions as a second messenger and propagates to the nucleus where it activates Atr (ataxia telangiectasia and Rad3 related) and its associated complex non-canonically, causing regeneration failure. Atr is a serine/threonine kinase, known to sense single-stranded DNA breaks and activate the DNA damage checkpoint by phosphorylating Chek1, which inhibits Cdc25, causing cell cycle arrest. This pathway has not been implicated in neuroregeneration. We show that in *Drosophila* sensory neurons removing Atr or Chek1, or overexpressing Cdc25 promotes regeneration, whereas Atr or Chek1 overexpression, or Cdc25 knockdown impedes regeneration. Inhibiting the Atr-associated checkpoint complex in neurons promotes regeneration and improves synapse/behavioral recovery after CNS injury. Independent of DNA damage, Atr responds to the mechanical stimulus elicited during regeneration, via the mechanosensitive ion channel Piezo and its downstream NO signaling. Sensory neuron-specific knockout of Atr in adult mice, or pharmacological inhibition of Atr-Chek1 in mammalian neurons *in vitro* and in flies *in vivo* enhances regeneration. Our findings reveal the Piezo-Atr-Chek1-Cdc25 axis as an evolutionarily conserved inhibitory mechanism for regeneration, and identify potential therapeutic targets for treating nervous system trauma.

Disclosures: Y. Song: None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS104194
NIH R21 NS118226

Title: Combination of viral BDNF and daily epidural stimulation to activate locomotor circuits and limit spasticity after complete spinal cord injury in mouse.

Authors: *N. J. STACHOWSKI, D. L. GARCIA-RAMIREZ, S. J. ATOCHE, L. YAO, S. F. GISZTER, K. J. DOUGHERTY;
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Abstract: SCI disrupts motor control below the level of injury, often resulting in paralysis and/or hyperreflexia which remain intractable to current rehabilitation strategies. However, spinal locomotor circuits can be activated to mediate functional stepping in the absence of descending control and serve as therapeutic targets for locomotor rehabilitation. Although excitation of silent pathways is often the focus of SCI studies, a restoration of inhibitory gating of sensory information is essential to prevent aberrant signaling and ensure smooth motor control. BDNF-TrkB signaling has known roles in inhibitory circuit formation and neuronal excitability, and viral overexpression of BDNF after SCI has been associated with locomotor improvements but also pain and spasticity. Epidural stimulation (ES) reduces hyperalgesia and hyperreflexia but additional excitatory modulation is needed to maximize locomotor function. The goals of our study are first to determine if locomotor outcomes can be improved by combining these potentially complementary strategies and then to identify a cellular target by which these strategies exert their beneficial effects for future leveraging. Recent intersectional genetic manipulations have linked inhibitory interneurons (INs) expressing the retinoid orphan receptor β (RORβ), and more specifically expression of TrkB receptors on RORβ INs, with sensory gating of proprioceptive input. Therefore, we hypothesize that exogenous BDNF and ES converge on RORβ INs to enhance inhibition in order to counterbalance concomitant non-specific excitatory effects of BDNF. Here, we use a complete thoracic transection model with viral BDNF treatment alone and in combination with daily ES in adult RORβcre;lsl-tdTomato mice to determine chronic rehabilitative effects *in vivo* and changes in RORβ cellular excitability *in vitro*. We perform weekly measures of locomotor performance and hyperreflexia for 6 weeks post-SCI followed by whole cell patch clamp recordings from RORβ INs in spinal slices. Mice receiving BDNF display weight-supported, alternating stepping but also greatly exacerbated hyperreflexia, but the latter is reduced by ES. RORβ INs from SCI mice have more depolarized voltage thresholds for action potential generation and higher rheobase, whereas cellular properties in neurons from BDNF-treated mice are similar to those of uninjured controls. Taken together, our results suggest that BDNF and ES may have synergistic effects to enhance locomotor improvements when combined and identify RORβ INs as a potential target for restoration of inhibitory counterbalance in sensorimotor pathways after SCI.

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Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.09

Topic: C.11. Spinal Cord Injury and Plasticity

NICHHD, 5K01HD084672-05 (VT)

Neilsen Foundation 649297 (AM)

Title: Muscle spasms following spinal cord injury are driven by changes in synaptic inhibition and motoneuron excitability

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Abstract: The acute phase of spinal cord injury (SCI) is marked by loss of motor function. However, uncontrolled muscle spasms develop in the chronic phase and can interfere with rehabilitation efforts and daily activities. Current pharmacological approaches to manage these spasms depend on global suppression of motor circuit excitability which can equally hinder motor recovery after SCI. To identify more specific therapeutic targets, we investigated chronic changes in synaptic excitation and inhibition in spinal motor circuits, as well as motoneuron intrinsic excitability. We used mouse models of both complete (transected) and incomplete (impact) chronic SCI. Following recovery, animals with incomplete injury were further divided into either low-function or high-function groups based on their BMS score. The whole-tissue sacrocaudal spinal cord along with its ventral and dorsal roots was then extracted and maintained *ex-vivo* and used to evaluate spasm-like activity and its underlying synaptic inputs. Tissue from age-matched animals with no prior spinal injuries was used as a control. Electrical stimulation of the dorsal roots elicited prolonged activity (spasm-like activity) in the ventral roots in all injury models as compared to very brief responses in the control preparations. To study the mechanisms of this activity, we evaluated changes in synaptic inhibition, synaptic excitation, and motoneuron excitability. Synaptic inhibition was estimated indirectly by measuring rate-dependent depression (RDD) of the dorsal root reflex. All SCI groups showed decreased synaptic inhibition compared to control. To evaluate excitatory synaptic currents and motoneuron persistent inward currents (PICs) underlying spasm-like activity, synaptic inhibition was first pharmacologically blocked. Then, individual motoneurons were recorded using single-electrode voltage clamp to measure membrane currents during sensory-evoked spasms. There was no difference in the amplitude of synaptic excitatory currents measured in the injury models compared to control. In addition, motoneuron PICs were slightly increased after injury. Interestingly, when the three chronic injury models were compared to each other, there was no difference in either excitatory synaptic currents or PICs. These results indicate that decreased synaptic inhibition and increased motoneuron PICs drive spasm-like activity in different animal models and thus could serve as better therapeutic targets for managing muscle spasms following SCI.

Disclosures: A. Mahrous: None. **D.V. Birch:** None. **V.M. Tysseling:** None. **C.J. Heckman:** None.

Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P362.10

Topic: C.11. Spinal Cord Injury and Plasticity

Title: The BDNF Val66Met genetic polymorphism increases vulnerability of human motor neurons derived from pluripotent stem cells to an in vitro stretch injury

Authors: S. HE[1], *A. TOGLIATTI[2], K. Y. COTTON[2], Y. BOURICHA[2], I. E. JONES[3], J. D. FINAN[3], C. K. FRANZ[2];
[1]Biomed. Engin., Northwestern Univ., Chicago, IL; [2]Shirley Ryan AbilityLab, Chicago, IL; [3]Univ. of Illinois Chicago, Chicago, IL

Abstract: Traumatic spinal cord injury (SCI) results in various neurological impairments. Most research emphasizes the white matter (axons) loss after the injury. But emerging treatments of SCI like neuromodulation techniques also rely on preserved gray matter (neurons) in the spinal cord. In previous clinical studies, motor neurons loss after SCI varies a lot between patients for several segments above and below the level of injury. Individual patient genetic variation is an elusive factor that may contribute to variable outcomes after SCI. To understand how genetic variation may affect outcomes, we focus on the brain-derived neurotrophic factor (BDNF) since it is an important growth factor in neural development and neural regeneration. The single nucleotide polymorphism (SNP) in the BDNF gene, which results in the substitution of valine by methionine at the 66th residue in the protein (i.e., BDNF Val66Met), has decreased activity-dependent release of BDNF and is associated with altered outcomes in neurological injury such as stroke or traumatic brain injury. It is unknown how Val66Met polymorphism influences outcome after SCI, but approximately 1/3rd of the US population carry it. To test the hypothesis that carriers of the Met allele are more susceptible to motor neuron degeneration after mechanical injury, we use an *in vitro* stretch injury model employing human induced pluripotent stem cell (iPSC)-derived motor neurons from two patients (both are gene-edited to differ by just the presence or absence of the Met allele). We apply different strain levels to isogenic iPSC-motor neurons, then measured the cell viability and neurite length after the injury. The results show that the Met allele carrying motor neurons are more susceptible to neurodegeneration than the Val allele carrier after the injury. Attempts to rescue this phenotype by adding back different amounts of recombinant BDNF could only partially rescue the difference between genotypes before adding even higher amounts resulted in worsening outcomes in both Val and Met groups. Transcriptomic analysis of isogenic iPSC-motor neurons by RNA sequencing reveals differential expression of 1491 genes (613 upregulated, 878 downregulated) with gene ontology enrichment analysis identifying novel cellular processes that may contribute to why the BDNF Val66Met polymorphism is associated with greater susceptibility to neurodegeneration after injury.

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Poster

P362. Spinal Cord Injury: Cellular and Molecular Mechanisms II

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Program #/Poster #: P362.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Cota-Robles Fellowship
Bridge to the Doctorate Fellowship

NINDS: 1 F31NS106742-01
NIAMS: R01 AR064582

Title: The MAP3ks Dlk and Lzk direct diverse responses to axon damage in zebrafish peripheral neurons

Authors: *K. ADULA[1], A. SAGASTI[2];
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Abstract: The MAP3Ks Dual Leucine Kinase (DLK) and Leucine Zipper Kinase (LZK) play diverse roles in axon damage responses. To characterize their functions in axon injury at the single cell level, we generated zebrafish mutants of each gene, labeled single motor neurons (MN) and Rohon-Beard (RB) touch-sensing neurons in live zebrafish, precisely cut their axons with a laser, and assessed the ability of mutant axons to regenerate. DLK and LZK were required redundantly and cell autonomously for axon regeneration in MN neurons, but not in larval RB or adult dorsal root ganglion neurons. Surprisingly, in dlk lzk double mutants, the spared branches of wounded RB axons grew excessively, suggesting that these kinases inhibit regenerative sprouting in injured axons. Uninjured trigeminal sensory axons also grew excessively in mutants when neighboring neurons were ablated, indicating that these MAP3Ks are general inhibitors of sensory axon growth. These results demonstrate that zebrafish Dlk and Lzk promote diverse injury responses, depending on the neuronal cell identity and type of axonal injury.

Disclosures: K. Adula: None. **A. Sagasti:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P378.01

Topic: D.03. Somatosensation – Pain

Support: NIH R01NS087033

Title: Sensory STIM1 is coupled to TRPA1 contributing nociception

Authors: *Y. MEI, B. LEE, N. KAUSHAL, T. ROHACS, H. HU;
Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: The transient receptor potential (TRP) channels play critical roles in sensory modalities, including nociception. TRPA1 is a member of the TRP superfamily. It serves as a noxious chemical sensor and is involved in nociception and chronic pain. TRPA1 is a Ca^{2+} permeable ion channel and located on the plasma membrane. It has been shown that activation of TRPA1 induces intracellular Ca^{2+} release. However, the functional significance of TRPA1-mediated Ca^{2+} release remains unclear. STIM1 is a single transmembrane-spanning Ca^{2+} binding protein and is a Ca^{2+} sensor in the ER to initiate store-operated Ca^{2+} entry (SOCE) when ER Ca^{2+} level is reduced. Our previous studies have shown that STIM1 is expressed in the majority of nociceptors. Whether TRPA1-mediated Ca^{2+} release can activate STIM1 is unknown. In this study, we investigated the involvement of STIM1 in TRPA1-mediated Ca^{2+} response and nociceptive behavior. We transfected the DRG neurons with an ER Ca^{2+} indicator, G-CEPIAer1, and

loaded the transfected neurons with Fura-2 to simultaneously monitor cytosolic and ER Ca^{2+} concentration changes. Our Ca^{2+} imaging data showed that DRG neurons responded to 100 μM AITC, a TRPA1 agonist, in the Ca^{2+} free solution, leading to Ca^{2+} release from the ER, suggesting TRPA1 is likely located in the ER. Using TIRF microscopy, we observed STIM1 puncta formation and translocation after treatment of AITC in the co-transfected STIM1-YFP and TRPA1 HEK cells, suggesting that TRPA1-mediated ER Ca^{2+} release activates STIM1. Moreover, AITC-induced SOCE was significantly reduced in STIM1 KO neurons. To determine whether STIM1 contributes to TRPA1-mediated nociception, AITC-induced nociceptive behavior was examined in WT and STIM1 KO mice. STIM1 KO mice showed a marked reduction of AITC-induced nociception, especially at later time points. Our findings reveal the functional link between intracellular TRPA1 and STIM1. Our study also provides insights into the TRPA1-mediated nociception.

Disclosures: Y. Mei: None. **B. Lee:** None. **N. Kaushal:** None. **T. Rohacs:** None. **H. Hu:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

Location: Virtual Only

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Program #/Poster #: P378.02

Topic: D.03. Somatosensation – Pain

Support: NIH R01NS087033

Title: Store-operated calcium channels are modulated by prostaglandin via the EP1-PKC pathway

Authors: *H. HU[1], D. WEI[2], Y. MEI[1], V. WHITEHEAD[1], A. BEKKER[1];
[1]Rutgers New Jersey Med. Sch., Newark, NJ; [2]Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Store-operated calcium channels are modulated by prostaglandin E2 via the EP1-PKC pathway Huijuan Hu, Dongyu Wei, Yixiao Mei, Victoria Whitehead, Alex BekkerDepartment of Anesthesiology, Rutgers New Jersey Medical School Newark, NJ 07103Chronic inflammatory pain is often caused by peripheral tissue inflammation. Peripheral sensitization is one of the primary mechanisms underlying the pathogenesis of chronic inflammatory pain. However, candidate molecules involved in peripheral sensitization remain unclear. We have shown that store-operated calcium channels (SOCs) are expressed in the dorsal root ganglion (DRG). Whether SOCs contribute to peripheral sensitization associated with chronic inflammatory pain is elusive. Here we report that global deletion of Orai1, a major component of the SOC family, attenuates CFA-induced pain hypersensitivity. To determine the peripheral role of Orai1 in inflammatory pain, we performed patch clamp and Ca^{2+} imaging recordings in wild type (WT) and Orai1 knockout (KO) DRG neurons. We found that thapsigargin (TG, an ER Ca^{2+}-ATPase inhibitor)-induced SOC entry (SOCE) and SOC currents were significantly increased in WT, but not in Orai1 KO DRG neurons from CFA injected mice. Interestingly, the expression level of the Orai1 in L3/4 DRGs was not altered, suggesting that the increased SOCE in DRG neurons is attributed to the functional change of Orai1. To understand how the Orai1 is modulated under inflammatory pain conditions, prostaglandin E_2 (PGE_2), a major inflammatory mediator, was used to sensitize DRG neurons. TG-induced SOCE in DRG neurons was potentiated by PGE_2 in WT, but not Orai1 KO neurons. This

effect was attenuated by a PGE_2 receptor 1 (EP1) antagonist, a Gq/11 inhibitor, PLC and PKC selective inhibitors, indicating PGE_2-induced SOCE enhancement is mediated by EP1 and its downstream Gq-PKC cascade. Consistently, Orai1 deficiency diminished PGE_2-induced thermal hyperalgesia and mechanical allodynia, suggesting that Orai1 is a novel downstream target of PGE2 signaling. Taken together, our findings demonstrate that peripheral Orai1 plays an important role in mediating peripheral sensitization. Our study also provides new insight into molecular mechanisms underlying chronic inflammatory pain.

Disclosures: H. Hu: None. **D. Wei:** None. **Y. Mei:** None. **V. Whitehead:** None. **A. Bekker:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

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Program #/Poster #: P378.03

Topic: D.03. Somatosensation – Pain

Support: MRC-CASE Studentship
Eli Lilly & Company

Title: Kv7.2 is the functionally dominant Kv7 subunit in peripheral nociceptors

Authors: *F. JONES, S. MILNE, N. GAMPER;
Univ. of Leeds, Leeds, United Kingdom

Abstract: Pain is a regular and unavoidable experience that dramatically impacts people's quality of life. Current treatments are often inadequate, expensive or invasive, thus, despite advances, the clinical need is still left unmet and new therapeutic targets are needed. Kv7 ('M') channels may represent such a target as these impose strong control over neuronal excitability. Functional M channels are present in peripheral somatosensory neurons but there is currently no consensus as to what the functionally dominant subunit is. This knowledge is necessary to guide selective therapeutic approaches as various sets of Kv7 subunits express in the brain, muscle and vasculature. Here we combine measures of gene and protein expression with functional patch clamp analysis, behavioural testing and genetic manipulations to ascertain functionally dominant Kv7 subunit(s) in the peripheral nerves. We demonstrated that all but Kv7.1 are expressed in rat and mouse sensory neurons and that Kv7.2, Kv7.3 and Kv7.5 are abundantly expressed. Kv7.2 showed a bias to small-diameter neurons and Kv7.5 toward larger neurons with significant overlap between the various subunits in rats and mice. Effects of Kv7.2/Kv7.3 selective agonist, ICA-27243, and *kcnq2* knockdown on M currents in DRG neurons in vitro suggest Kv7.2 is the predominant subunit controlling M current in TRPV1 positive nociceptors. Thus, *Kcnq2* knockdown significantly reduced the M current amplitude and rheobase in TRPV1 positive neurons and significantly increased the excitability of these neurons. This translated to a reduction in thermal and mechanical pain thresholds and an increased response to acute hyperalgesia when *kcnq2* was knocked down *in vivo.* ICA-27243 also significantly attenuated acute and inflammatory pain with comparable efficacy to retigabine. Knockdown of *Kcnq5* had marginal effects on DRG neuron excitability *in vitro* and on nociceptive transmission *in vivo*. These findings identified Kv7.2 as the functionally dominant Kv7 subunit in nociceptors.

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Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P378.04

Topic: D.03. Somatosensation – Pain

Support: T32 GM008440-24

Title: Pain provoked by a scorpion toxin that targets voltage-gated sodium (NaV) channel 1.3

Authors: *J. SALVATIERRA[1], J. M. BRAZ[2], G. TREVISAN[4], M. SADEGHI[5], M. DEWAARD[6], X. YU[7], F. BOSMANS[8], A. I. BASBAUM[3];
[1]Univ. of California, San Francisco Sch. of Med., San Francisco, CA; [2]Anat., [3]Dept Anat, UCSF, San Francisco, CA; [4]Federal Univ. of Santa Maria, Santa Maria, Brazil; [5]Univ. of California, San Francisco, San Francisco, CA; [6]French Inst. of of Hlth. and Med. Res., Paris, France; [7]Anesthesiol., Univ. of California San Francisco, San Francisco, CA; [8]Ghent Univ., Ghent, Belgium

Abstract: Voltage-gated sodium (Na_V) channels are critical for the excitability and transmission of noxious stimuli of sensory neurons. Although previous studies on nociceptive (pain) processing by sensory neurons focused on $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, here we provide new evidence for a significant contribution of $Na_V1.3$. To reinvestigate the contribution of $Na_V1.3$ to pain processing we identified and synthesized Tf2, a selective $Na_V1.3$ ß-scorpion activator from venom of the Brazilian scorpion Tityus fasciolatus. To identify $Na_V1.3$-expressing dorsal root ganglion (DRG) neurons and to explore their function in pain processing, we performed *in situ* hybridization, immunhistochemistry, *in vitro* calcium imaging, leveraged human-derived iPSC sensory neurons, and conducted a battery of behavioral assays in C57BL/6J mice of both sexes. In contrast to previous reports of minimal expression of $Na_V1.3$ in sensory neurons, we found substantial $Na_V1.3$ mRNA in tyrosine hydroxylase (TH)-mRNA-expressing DRG neurons, a subpopulation generally associated with the transmission of low threshold mechanical inputs (namely CLTMRs). Intradermal hindpaw injection (1µM) of Tf2 in mice induced significantly more nocifensive behaviors (i.e., licking of the hindpaw) than vehicle alone. Injection of Tf2 also induced significant Fos expression in superficial layers of the dorsal horn. Interestingly, the toxin also provoked vigorous behavioral responses indicative of pain of the hindlimb contralateral to the injection, suggesting a rapid development of central sensitization in the spinal cord. Application of Tf2 to dissociated DRG neurons increased Ca^{2+} signals in small- diameter neurons. Importantly, Tf2-induced nocifensive behaviors persisted after ablation of the $TRPV1^+$ nociceptor population with resiniferatoxin. Tf2 (1nM) also significantly and reversibly increased the firing rate of human-derived iPSC sensory neurons. Lastly, injection of Tf2 provoked significant hindpaw swelling and plasma extravasation of Evans Blue albumin, but surprisingly only after ablation of the $TRPV1^+$ population. Taken together our findings suggests that Tf2 induces profound, sensory neuron-mediated effects, possibly via CLTMR afferents, by its binding to and facilitating opening of $Na_V1.3$. It should be noted that previous work by Israel M.R. et al. also reported pain-like behaviors evoked by Tf2, in addition to swelling, but we do not see significant swelling or extravasation in naïve mice with our synthesized Tf2. Future studies will investigate the contribution of $Na_V1.3$ in injury-induced ongoing pain conditions, as well as effects of selective blockade of the channel.

Disclosures: J. Salvatierra: None. **J.M. Braz:** None. **G. Trevisan:** None. **M. Sadeghi:** None. **M. Dewaard:** F. Consulting Fees (e.g., advisory boards); Smartox Biotechnology. **X. Yu:** None. **F. Bosmans:** None. **A.I. Basbaum:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

Location: Virtual Only

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Program #/Poster #: P378.05

Topic: D.03. Somatosensation – Pain

Support: NS055251 (DL)
Warren Alpert Fellowship Award (EJLS)
K99NS116123 (EJLS)
Robert J and Nancy D Carney Institute for Brain Science (AF)

Title: Peripheral voltage gated calcium channels in skin are essential for transient heat hypersensitivity in mice

Authors: *E. J. LOPEZ SOTO[1], D. M. DUBREUIL[2], S. DASTE[1], R. MEIR[1], D. LI[1], A. FLEISCHMANN[1], D. LIPSCOMBE[1];
[1]Brown Univ., Providence, RI; [2]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: $Ca_V2.2$ voltage-gated calcium channels are the dominant Ca_V channel expressed in nociceptors. $Ca_V2.2$ channel blockers applied to the spinal cord relieve pain in humans and rodents, especially during pathological pain. $Ca_V2.2$ channels are expressed at nociceptor pre-synaptic terminals, soma, and peripheral axons, but a biological function of nociceptor $Ca_V2.2$ channels outside pre-synaptic terminals is rarely considered. In this study, we demonstrate that $Ca_V2.2$ channels at nociceptors free nerve endings in skin are required for heat hypersensitivity. We used Hargreaves and automatic von Frey assays to evaluate heat and mechanical sensitivities in female and male wild-type and $Ca_V2.2$-KO mice. Experiments were performed blinded to genotype and treatment. Paw withdrawal latencies to heat and mechanical stimuli were longer in $Ca_V2.2$-KO mice compared with WT controls ($p = 0.001$ and $p = 0.021$, respectively). This is expected as $Ca_V2.2$ channels at nociceptor afferent pre-synaptic termini in spinal cord regulate neurotransmitter release and the transmission of nociception. We then assessed the role of peripheral $Ca_V2.2$ channels in skin, in particular in capsaicin-induced heat and mechanical hypersensitivity. Intraplantar injection of capsaicin (0.1%), a TRPV1 channel agonist, induces transient hypersensitivity to mechanical and heat stimuli at 15 mins which returns to pre-capsaicin baseline responses within 30 mins. Capsaicin-induced heat, but not mechanical, hypersensitivity was 60% reduced in $Ca_V2.2$-KO as compared to WT mice ($p = 0.001$ and $p = 0.994$, respectively). To assess the role of peripheral $Ca_V2.2$ channels in skin we used intraplantar ω-conotoxin MVIIA (1 μM). In wild-type mice, capsaicin-induced heat hypersensitivity was consistently reduced by co-injecting conotoxin with capsaicin, compared to capsaicin alone ($p = 0.041$). By contrast, capsaicin-induced heat hypersensitivity was not altered by intradermal ω-agatoxin IVA, a selective inhibitor of $Ca_V2.1$ channels ($p = 0.130$). Our data reveal that local activation of peripheral $Ca_V2.2$ channels in nociceptor termini in skin *in vivo* are required for capsaicin-induced heat hypersensitivity, but not mechanical hypersensitivity.

Disclosures: E.J. Lopez Soto: None. **D.M. Dubreuil:** None. **S. Daste:** None. **R. Meir:** None. **D. Li:** None. **A. Fleischmann:** None. **D. Lipscombe:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

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Program #/Poster #: P378.06

Topic: D.03. Somatosensation – Pain

Support: DoD Grant W81XWH1810746

Title: Contribution of T-type calcium channels to nociceptors' hyperexcitability and chronic neuropathic pain following spinal cord injury in rats.

Authors: *M. PUOPOLO, H. LIU, J. LAUZADIS, M. KACZOCHA;
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Abstract: A hyperexcitable state and spontaneous activity of nociceptors following spinal cord injury (SCI) have been suggested to play a primary role in the development of SCI-induced neuropathic pain (SCI-pain). Previous work showed that the increased activity of T-type calcium channels induced by the injury is responsible for triggering nociceptors' hyperexcitability and for promoting their spontaneous activity. These observations suggest that the increased activity of T-type calcium channels following SCI may play a critical role in the development of SCI-pain. The aim of this project was to test the hypothesis that TTA-P2 (a blocker of T-type calcium channels) will reduce the hyperexcitable state of SCI-nociceptors and rescue SCI-pain. Sprague Dawley rats (male, 300-350 g) were used in this study. SCI was performed by a midline spinal cord contusion at T10 by using an Infinite Horizon Impactor (150 kilodynes, 1-s dwelling time). The patch clamp technique was used in dissociated dorsal root ganglia (DRG) neurons isolated from SCI, sham, and naïve rats. For voltage-clamp experiments, the external solution was (mM): 151 NaCl, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES; the internal solution was (mM): 125 CsCl, 10 NaCl, 2 $MgCl_2$, 10 HEPES, 10 EGTA, 4 MgATP, 0.3 NaGTP, 14 phosphocreatine, pH=7.2 with CsOH. For current clamp experiments, the external solution was (mM): 151 NaCl, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES; the internal solution was (mM): 125 K-methanesulfonate, 10 NaCl, 2 MgCl2, 0.1 EGTA, 10 HEPES, 14 Tris-creatine PO4, 4 Mg-ATP, and 0.3 Na-GTP; pH 7.2 with KOH. The mechanical allodynia following SCI was assessed with the von Frey filaments by using the up-down method with the 50% threshold. The conditioned place preference (CPP) paradigm was used to assess spontaneous pain. In SCI-nociceptors, we found that T-type calcium channels sustains the bulk (~60%) of the inward current active during the interspike interval. In current-clamp recordings, inhibition of T-type calcium channels with 1 μM TTA-P2 reduced both the spontaneous and the evoked firing in SCI-nociceptors to a level similar to sham-nociceptors. The 50% mechanical threshold dropped from 26.1 ± 3.2 g (pre-injury) to 14.3 ± 1.6 g (post-injury). Intraperitoneal injection of 10 mg/kg of TTA-P2 rescued the to 50% threshold to 26.3 ± 2.4 g (n=6). The difference score measured with the CPP paradigm was 46.4 ± 40.8 s for the drug-paired chamber and -30.8 ± 34.1 s for the vehicle-paired chamber. Taken together, our data suggest that the increased activity of T-type calcium channels induced by the injury

plays a primary role in driving SCI-nociceptors to a hyperexcitable state and contributes to chronic neuropathic pain following SCI.

Disclosures: M. Puopolo: None. **H. Liu:** None. **J. Lauzadis:** None. **M. Kaczocha:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P378.07

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS108087

Title: Localization of Adaptin α2-Subunit to Large Dense Core Vesicles in Mice and Humans

Authors: *R. POWELL[1], V. YOUNG[2], **A. BHATTACHARJEE**[3];
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Abstract: Clathrin-mediated endocytosis (CME) is a critical cellular process that underlies signaling cascades, protein turnover, and general cellular homeostasis. A key facilitator of CME is the heterotetrameric Adaptor Protein Complex 2 (AP2). The AP2 complex is a comprised of α-, β-, σ-, and μ-subunits that display comparable levels of expression across different cell types; however, the α-subunit is unique in that it has two distinct genetic isoforms: AP2α1 and AP2α2. The first characterization of the subneuronal localizations of the two α-subunit isoforms, which showed that AP2α1 was primarily synaptic and AP2α2 was primarily cytoplasmic, occurred over 26 years ago by Ball et al. (PMID: 7593326). Herein, we have expanded upon the work presented in Ball et al. through an immunofluorescent approach to characterize the expression of AP2α2 in mouse and human dorsal root ganglion (DRG) neurons. In mice, surprisingly, we observed a high degree of colocalization of AP2α2 and the neuropeptide calcitonin gene-related peptide (CGRP) at large dense core vesicles (LDCVs) within somas, indicating AP2α2 localizes to LDCVs. In sciatic nerve immunohistochemical analyses, AP2α2 and CGRP co-localization was maintained at mature LDCVs transported down the axon. However, the AP2α2/CGRP colocalization was lost at peripheral terminals where AP2α2 was observed at the very distal neuronal endings within the epidermis, dissociated from CGRP containing LDCVs. Immunofluorescent staining in human DRGs (from one donor) showed similar immunoreactivity patterns that were observed in mice, where AP2α2 colocalized with CGRP as well as TRPV1 at LDCVs. Altogether, we have described an expression profile of AP2α2 in mouse and human DRGs that suggests that AP2α2-CME is functionally distinct from AP2α1-CME in nociceptive peptidergic neurons.

Disclosures: R. Powell: None. **V. Young:** None. **A. Bhattacharjee:** None.

Poster

P378. Pain Mechanisms: Nociceptors: Ion Channels I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P378.08

Topic: D.04. Somatosensation – Touch

Support: NIH NINDS 1R01NS111055

Title: Sensory neuron transcriptomes reveal complex neuron-specific regulation and function of mec-2/Stomatin splicing

Authors: *X. LIANG, C. CALOVICH-BENNE, A. NORRIS;
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Abstract: Alternative splicing (AS) plays a major role in development and function of the nervous system by increasing the diversity and complexity of cellular components. RNA binding proteins are important regulators that control alternative splicing by binding to specific sequences on pre-mRNA. Recent studies from our lab as well as others have showed the alternative splicing is regulated by RNA binding proteins in a cell-specific manner, but it remains unknown to what extent AS contributes to the function of single neurons. MEC-8 is a conserved RNA binding protein, with an essential role in the function of touch neurons in *C. elegans*. However, it is unclear how MEC-8 executes its regulatory function in touch neurons. To this end, we exploited RNA-Seq to profile the transcriptome to get a clear view of MEC-8 regulatory networks in touch neurons. Current single-cell sequencing techniques are limited by low coverage depth, making it difficult to study things like lowly-expressed genes or alternative splicing regulation. By taking advantage of invariant *C. elegans* cell lineage, we isolated thousands of same cells and then performed neuron specific RNA-Seq of wild-type and *mec-8* mutant touch neurons. With this increased depth of coverage in single-neuron profiles we could investigate splicing regulatory in specific neuron type. We noticed a few genes showing different splicing pattern in touch neurons compared to whole animals in wild-type and *mec-8* mutant worms, which suggests their potential roles in touch neurons. Among those genes, a conserved stomatin-related protein MEC-2 was strongly regulated by MEC-8, and *mec-2* mutants show a strong phenotype in touch assays. Furthermore, we found canonical long *mec-2A* isoform is only expressed in six touch neurons while non-canonical short *mec-2B* isoform are expressed in many other neurons in addition to touch neurons. Based on the expression patterns of two *mec-2* isoforms, we uncovered an olfactory role for *mec-2* in addition to its mechanosensory role. Using CRISPR-Cas9 system to force the expression of one or the other isoform of *mec-2* shows that *mec-2A* is functional in touch sensation and olfaction, but *mec-2B* is only functional in olfaction. Putting long isoform of *mec-2* back to *mec-8* mutant can rescue the *mec-8* touch insensitivity phenotype, which indicates the *mec-2* is the primary functionally relevant target of MEC-*8* in touch neurons. Interestingly, by looking carefully of RNA-Seq data, we identified an additional extra-long *mec-2E* isoform, which co-localizes with *mec-2A* isoform, and needs to work together with *mec-2A* to function mechanosensation in touch neurons.

Disclosures: X. Liang: None. **C. Calovich-Benne:** None. **A. Norris:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.01

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant R01 DC018284
NIH Grant F31 DC019292
NIH Grant T32 DC005356

Title: The role of $\alpha_3\beta_4$* nicotinic acetylcholine receptors in modulating the excitability of VIP neurons in the mouse inferior colliculus

Authors: *L. M. RIVERA-PEREZ, J. T. KWAPISZEWSKI, M. T. ROBERTS;
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Abstract: The inferior colliculus (IC), the midbrain hub of the central auditory system, receives extensive cholinergic input from the pontomesencephalic tegmentum (PMT). Activation of nicotinic acetylcholine receptors (nAChRs) in the IC can enhance auditory performance by altering the excitability of neurons. However, how nAChR activation affects the excitability of specific neuron classes in the IC remains unknown. Our lab identified a distinct class of glutamatergic principal neurons in the IC that expresses vasoactive intestinal peptide (VIP). Using VIP-Cre x Ai14 mice and immunofluorescence, we found that cholinergic terminals are commonly located in close proximity to the somas and dendrites of VIP neurons. By using whole-cell electrophysiology combined with pharmacology in brain slices, we found that acetylcholine (ACh) drives a strong, long-lasting excitatory effect in VIP neurons. Application of the muscarinic antagonist atropine did not affect the excitation elicited by ACh. Instead, application of nAChR antagonists revealed that ACh excites VIP neurons via the activation of $\alpha_3\beta_4$* nAChRs, a subtype that is relatively rare in the brain. Furthermore, by blocking the receptors for the main neurotransmitters expressed in the IC, we determined that cholinergic excitation of VIP neurons occurs by activating post-synaptic nAChRs located in VIP neurons themselves and does not require activation of presynaptic inputs. Finally, we found that trains of ACh puffs elicited temporal summation in VIP neurons, suggesting that cholinergic inputs can affect activity in the IC for prolonged periods in an in vivo setting. These results uncover the first cellular-level mechanisms of cholinergic modulation in the IC and a novel role for $\alpha_3\beta_4$* nAChRs in the auditory system, and suggest that cholinergic inputs from the PMT can strongly affect auditory processing in the IC by increasing the excitability of VIP neurons. Since VIP neurons project to the auditory thalamus, the superior olivary complex, and other brain regions, these results further suggest that cholinergic excitation of VIP neurons is likely to have widespread effects on auditory processing and its downstream effects.

Disclosures: L.M. Rivera-Perez: None. **J.T. Kwapiszewski:** None. **M.T. Roberts:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.02

Topic: D.06. Auditory & Vestibular Systems

Support: UMass Startup funds

Title: The contribution of GlyT2$^+$ PnC neurons to prepulse inhibition of the acoustic startle reflex during aging

Authors: *W. HUANG[1], K. FENELON[2];
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Abstract: BACKGROUND:
Prepulse inhibition (PPI) of the acoustic startle reflex (ASR) refers to the inhibition of the startle response by presenting a weak stimulus ("prepulse") prior to the startling stimulus ("pulse"). PPI is a standard operational measure of sensorimotor gating. Reduced PPI is found in patients with schizophrenia, obsessive compulsive disorder and Huntington's disease, and PPI impairments are often associated with deficits in attention (Braff et al, 2001).
The brainstem caudal pontine reticular nucleus (PnC) is at the core of the PPI pathway. Within the PnC, glycinergic neurons are widely distributed among the startle-mediating glutamatergic giant neurons (Lingenhöhl and Friauf, 1992; Koch and Friauf, 1995; Rampon et al., 1996; Zeilhofer et al., 2005). We recently showed that inhibiting these glycinergic PnC neurons reduces PPI (Cano et al., 2021). However, the contribution of these neurons during aging has not been investigated.
Therefore, we used young and old mice to investigate the role of PnC neurons expressing the glycine transporter type 2 (GlyT2) during aging, to determine if the age-related reduction in PPI is associated with a decline in PnC inhibitory function.
METHODS:
Experiments were performed in mice expressing the Cre enzyme in GlyT2$^+$ neurons (i.e., GlyT2-Cre mice), and their control littermates. Animals were classified into two categories: 1- young adults (3-6 months old) or 2- older adults (9-12 months old). To photo-manipulate GlyT2$^+$ PnC neurons, Cre-dependent viral vectors driving the expression of the inhibitory optogenetic tool Archaerhodopsin or the excitatory optogenetic tool Channelrhodopsin, were injected in the PnC. The ASR and PPI were measured 4 weeks after injections, both in the absence and in the presence of neuronal photo-manipulation, in all animals. PPI was used as a behavioral readout of sensorimotor gating and PPI values were compared between genotypes.
RESULTS:
Photo-manipulating GlyT2$^+$ PnC neurons had no effect on ASR in young GlyT2-Cre mice, their control littermates and older GlyT2-Cre mice. In young adult mice, photo-activating GlyT2$^+$ PnC neurons significantly increased PPI ($p=.005$) at 100-1000ms interstimulus intervals (ISI) between the prepulse and the pulse. While photo-inhibiting these neurons resulted in the reverse effect ($p=.033$): PPI was decreased at shorter ISI of 50-100ms. Interestingly, in older adult mice, photo-inhibition of GlyT2$^+$ neurons did not affect PPI.
DISCUSSION:
The findings suggest that: 1) GlyT2$^+$ PnC inhibitory neurons contribute to PPI in young adult mice and 2) such contribution declines with age, providing a possible explanation for age-related PPI alterations.

Disclosures: W. Huang: None. **K. Fenelon:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.03

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant DC015901

Title: Tuning the Excitability of Globular Bushy Cells

Authors: G. SPIROU[1], M. KERSTING[1], B. RAZZAQ[2], C. YAMAMOTO ALVES-PINTO[1], M. MELTON[1], M. H. ELLISMAN[3], P. B. MANIS[4];
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Abstract: The integration of synaptic inputs to generate an action potential is a complex process with multiple control points. These factors include the relative placement of excitatory and inhibitory inputs, the dendritic surface area, and innervation and dimensions of the axon initial segment (AIS). We performed high-resolution, volume electron microscopy (EM) and reconstruction of bushy cells (BC) in the mouse cochlear nucleus in order to quantify these factors. These structural data were converted into compartmental biophysical models and the integration of synaptic inputs was measured using the NEURON simulation environment. 3D reconstructions of cellular compartments were processed to create so-called computational meshes for accurate measurement of surface areas. Dendrite to soma surface area ratios ranged from 2.8-3.6. For the reconstructed BCs (n = 26), somatic surface area ranged in a tight distribution from about 1200 to about 1500 µm² for all except one cell. For dendrites that were completely or nearly completely contained in the image volume (n = 10), surface areas ranged from 3100 to 4700 µm². Large somatic inputs were reconstructed (range 5-12 per cell) and activated individually in the model. Most inputs were subthreshold, but nearly all became suprathreshold following removal of dendrites. For one cell, we mapped every dendritic and somatic synapse, and noted that entire dendritic branches were not innervated but were instead wrapped by glial cells. We also investigated innervation of the axon hillock and axon initial segment (AIS). Large somatic inputs could extend from the cell body onto the hilllock and AIS in most (20/21) cells. The AIS ranged in length from 14.2 to 21.4 µm (n = 16). By assuming a constant density of sodium channels along the initial segment we identify the initial segment length as a contributing factor to cellular excitability. The initial segment was innervated not only by excitatory but also small, likely inhibitory inputs, which ranged a number from 4 to 19. Thus, we identify dendrite to soma surface area ratio, and length and innervation of the axon initial segment as factors controlling neuron excitability. We also suggest that growth of non-innervated dendrites presents another homeostatic mechanism by which individual neurons regulate their excitability.

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Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.04

Topic: D.06. Auditory & Vestibular Systems

Support: 5R01HD088411-04

Title: Synaptic representation of infant distress cries in the auditory cortex

Authors: *J. SUNDARARAJAN[1], D. NEOPHYTOU[2], R. HUSZAR[4], H. V. OVIEDO[3], R. C. FROEMKE[5];
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Abstract: The ability of parental animals to accurately process and respond to infant-related sounds is critical for providing appropriate caregiving responses (Dulac et al., Science 2014). In mice, recent work from our lab and others has shown that maternal experience is accompanied by lateralized auditory cortical plasticity, including enhancement of neuronal responses, and correlation of excitatory and inhibitory inputs in the left auditory cortex (Cohen & Mizrahi, J Neurosci 2015; Marlin et al., Nature 2015). Additionally, responses of individual auditory cortical neurons are enhanced to pup call tempos that occur with higher probability following maternal experience (Schiavo et al., Nature 2020). However, it remains unclear how single auditory cortical neurons reliably compute the behavioral meaning of an infant distress cry, and how infant cries are represented at the level of individual dendritic branches and synapses.Here we use structural and functional 2-photon imaging to ask how populations of synaptic inputs can shape single-neuron responses to infant distress cries in the maternal mouse auditory cortex. We observe that individual auditory cortical neurons exhibit differential tuning to various sounds including pup distress cries with different spectrotemporal characteristics. Additionally, in line with prior work, somatic responses to different pup call tempos are broadened following maternal experience. At the dendritic spine level, our data suggest that individual spines exhibit varying tuning profiles to different pup distress cries, with most individual spines displaying narrow tuning to pup call tempo. We observe that overall somatic response strength is proportional to the number of dendritic spines responding to individual pup calls and pup call tempos suggesting a mechanism by which collective spine responses can influence somatic tuning. We are examining structural synaptic changes that accompany functional changes by tracking excitatory and inhibitory synaptic dynamics during maternal experience. Finally, we are recording from neurons in brain slices that we have imaged in vivo (Ko et al., Nature 2011), to determine the circuit motifs that provide specific auditory inputs to left vs right auditory cortical neurons in male and female mice following parental experience.

Disclosures: J. Sundararajan: None. **D. Neophytou:** None. **R. Huszar:** None. **H.V. Oviedo:** None. **R.C. Froemke:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.05

Topic: D.06. Auditory & Vestibular Systems

Support: NIH grant R01DC013073

Title: Using Microprisms, the 2P Calcium Imaging Revealed a functional distinction between the Dorsal & Lateral Cortices of The Mouse Inferior Colliculus.

Authors: B. IBRAHIM, Y. SHINAGAWA, G. XIAO, A. R. ASILADOR, D. LLANO;
Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: The inferior colliculus (IC) is a critical midbrain structure for the processing of auditory stimuli. The IC is a hub that permits widespread convergence of both bottom-up & top-down projections involving auditory, somatosensory, visual, motor & arousal-related brain regions. Dorsal (DC) & lateral (LC) cortices form the non- lemniscal division of the IC and receive most of the descending projections directed to the IC. LC only contains periodic modules of GABAergic cells & terminals which stain for a range of metabolic markers. Interestingly, the auditory inputs from the auditory cortex or central nucleus of the IC strongly avoid these inhibitory modules & instead form dense projections to the matrix areas that surround the modules. This anatomic distinction between DC & LC could implicate a functional distinction between the two subdivisions. Two-photon imaging was used here to characterize the functional activity of the GABAergic & non-GABAergic cells in the LC as well as in the DC. Consistent with a previous report (Wong and Borst 2019), imaging the surface of the IC showed that both GABAergic & non-GABAergic cells of the DC showed mirror-image tonotopic mapping of high to low & then from low to high frequency along the medial to lateral axis. In contrast, side view imaging of the LC using 45^0 microprisms showed that both GABAergic and non-GABAergic cells were less responsive to the pure tone sound, were not tonotopically organized and were more responsive to amplitude modulated broad band noise. This finding implicates a functional distinction between DC and LC, which functions more to process complex sound.

Disclosures: B. Ibrahim: None. **Y. Shinagawa:** None. **G. Xiao:** None. **A.R. Asilador:** None. **D. Llano:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.06

Topic: D.06. Auditory & Vestibular Systems

Support: Swiss National Science Foundation SNF182504

Title: Activation of basal forebrain parvalbumin neurons exerts frequency dependent effects on auditory processing and behavior in the rat.

Authors: *H. AZIMI, K. THOMAS, M. NADERI, P. VACA SANCHEZ, M. HARVEY, G. RAINER; Dept. of Med., Univ. of Fribourg, Fribourg, Switzerland

Abstract: The basal forebrain (BF) encompasses a collection of deep brain nuclei that have been implicated in higher cognitive functions, such as attention and memory, (Rye et al., 1984), the processing of sensory information, (Bhattacharyya et al., 2013), and sleep and arousal, (Jones, 2003). BF projections to the sensory cortex have now been shown to be segregated according to sensory modality (Kim et al. 2016), with visual, somatosensory, and auditory areas organized along an anterior-posterior axis. While the BF provides the main cholinergic input to the cerebral cortex, it also harbors substantial GABAergic and glutamatergic populations. The diversity of cells types and projections must be taken into account in order to understand how the BF modulates cognitive and sensory processing. We have previously shown that electrical activation of the posterior nucleus basalis (pNB), a BF nucleus associated with auditory processing, enhances response reliability of rat A1 neurons to complex auditory stimuli. Electrical stimulation is expected to activate all pNB projection neurons, so in order to disambiguate the contribution of different BF neuronal subtypes, we utilized a PV-Cre rat line to express channel rhodopsin (ChR2) uniquely in pNB PV neurons. We recorded local field potential and single unit activity simultaneously in the pNB, the thalamic reticular nucleus (TRN), the medial geniculate nucleus (MGN), and the primary auditory cortex (A1), during 40Hz pulse optogenetic activation of the pNB paired with the presentation of complex auditory stimuli in an anesthetized preparation. We have preliminary data from 12 animals. While optogenetic activation of pNB PV neurons had no effect on response reliability, it did result in a frequency specific modulation of firing rates in both MGN and A1. Spiking activity of single neurons at their preferred frequency was suppressed in both A1 and MGN, while responses to non-preferred frequencies in A1 were enhanced. As auditory responses recorded within pNB showed a rough tonotopic organization, we postulate that frequency selective effects of pNB activation on MGN and A1 might regulate neural responses in the auditory pathway via a tonotopic projection pattern. A frequency specific performance deficit in rats that we observed during an auditory detection task for high amplitude targets is consistent with this hypothesis. Both findings support the idea that pNB may modulate auditory processing in a tone-frequency dependent manner according to behavioral demands, selectively dampening high amplitude auditory inputs in a manner opponent to cholinergic BF circuit activity.

Disclosures: H. Azimi: None. **K. Thomas:** None. **M. Naderi:** None. **P. Vaca Sanchez:** None. **M. Harvey:** None. **G. Rainer:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.07

Topic: D.06. Auditory & Vestibular Systems

Support: United States Air Force

Title: A cellular level analysis of the interface between motor and sensory networks in Drosophila

Authors: *K. N. BOONE[1], H. S. J. CHEONG[2], M. M. BENNETT[1], F. A. SALMAN[1], J. F. PHELPS[3], B. MARK[5], J. C. TUTHILL[5], W.-C. A. LEE[4], K. C. DALY[1], G. M. CARD[2], A. M. DACKS[1];
[1]Biol., West Virginia Univ., Morgantown, WV; [2]Howard Hughes Med. Institute, Janelia Res. Campus, Ashburn, VA; [4]Kirby Neurobio. Ctr., [3]Harvard Med. Sch., Cambridge, MA; [5]Univ. of Washington, Seattle, WA

Abstract: The ability for motor and lower order networks to relay information to sensory centers about the behavior state of the animal represents a critical interface between sensory and motor systems. Here, we undertake a circuit analysis of such a sensorimotor interface. Two pairs of ascending histaminergic neurons (AHNs) project from the ventral nerve cord (VNC) of many arthropods to innervate sensorimotor regions in the brain and VNC, and have been demonstrated to function as a corollary discharge circuit in the moth, *Manduca sexta*. However, little is known comprehensively about the connectivity and functionality of these morphologically conserved motor-to-sensory circuits. Using connectomics, transcriptomics and neuroanatomy techniques in *Drosophila melanogaster*, we begin to resolve the connectivity of the mesothoracic and metathoracic AHN pairs (the MsAHNs and MtAHNs, respectively). We demonstrate that each AHN cell pair innervates mostly non-overlapping brain regions (within which they are the sole source of histamine) that process distinct sensory modalities, including auditory and mechanosensory networks. The AHNs receive most of their synaptic input within the tectulum of the VNC with a large proportion of this synaptic input originating from descending neurons. Based on connectomic analyses, the AHNs synapse upon more neurons than were observed to express histamine receptors, suggesting that the AHNs co-release additional transmitters. Transcriptomic and transgenic approaches reveal that the AHNs co-release neuropeptides, including Diuretic Hormone 44 (DH44), implying that these neurons likely have effects over multiple timescales as insect histamine receptors are ionotropic whereas neuropeptide receptors are metabotropic. Downstream targets of the AHNs include several well-characterized cell types including sensory afferents which broadly express the HisClB receptor and second-order auditory neurons which express DH44 receptor 1. Interestingly, there is little overlap in receptor expression of downstream targets, suggesting that the AHNs can have distinct functional roles by way of different transmitter release. Finally, we demonstrate that the AHN pairs differ from each other in a variety of ways including receptor expression, synaptic connectivity, and baseline levels of intracellular calcium regardless of behavioral context. Taken together, this suggests that the AHN pairs likely receive and relay distinct information to downstream targets. Our results provide a detailed circuit-level understanding of a sensorimotor interface that allows descending motor commands to provide feedback to distinct sensory modalities.

Disclosures: K.N. Boone: None. **H.S.J. Cheong:** None. **M.M. Bennett:** None. **F.A. Salman:** None. **J.F. Phelps:** None. **B. Mark:** None. **J.C. Tuthill:** None. **W.A. Lee:** None. **K.C. Daly:** None. **G.M. Card:** None. **A.M. Dacks:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.08

Topic: D.06. Auditory & Vestibular Systems

Title: Correlating transcriptomic markers and morphological features of neurons in the zebrafish startle circuit

Authors: S. A. SEMENOVA, *H. A. BURGESS;
Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD

Abstract: The acoustic startle response is a robust quantifiable behavior that is frequently used to assess the effects of gene mutations on neuronal connectivity and neural circuit function in model organisms. In larval zebrafish, the acoustic startle response starts with statoacoustic ganglion (SAG) neurons receiving an impulse from hair cells of the inner ear and transmitting it to the Mauthner cells, large reticulospinal neurons which trigger body movements by activating motor neurons and interneurons in the spinal cord. Our behavior tests after targeted neuron ablation revealed that populations of neurons in both the anterior and posterior parts of the statoacoustic ganglion contribute to the escapes responses. Tracing of individual fluorescently labeled SAG neurons with subsequent registration to a reference brain revealed a topographic arrangement of cell bodies correlated with the efferent projection pattern. On average, anterior SAG neurons had longer axonal branches than posterior SAG neurons, and suggesting a possible segregation of central targets between these subpopulations. Both anterior and posterior populations had connections to all five hair cell patches. In order to develop new markers for SAG neurons projecting to different central targets, we manually isolated SAG neurons and Mauthner cells and performed transcriptomic analysis using the SMART-Seq v4 protocol. Strong and specific expression of several genes in these neurons was in concordance with previous in situ RNA hybridization data. The neurotransmitter receptor profiles of anterior and posterior SAG neuron populations were distinct, raising the possibility of differential modulation of SAG neuron activity by neuropeptides and serotonin. This data now enables us to develop new transgenic lines for manipulating activity in genetically defined SAG neurons for testing segregation of auditory afferent information to central targets.

Disclosures: S.A. Semenova: None. **H.A. Burgess:** None.

Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

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Topic: D.06. Auditory & Vestibular Systems

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Title: Neural network organization for courtship song feature detection in Drosophila

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Abstract: A key task for auditory systems is recognizing behaviorally relevant acoustic features to drive appropriate reactions. How feature detection emerges along auditory pathways has been difficult to solve due to challenges in mapping the underlying circuits and characterizing responses to behaviorally relevant features. Here we study auditory activity in the *Drosophila melanogaster* brain and investigate feature selectivity for the two main modes of fly courtship song, sinusoids and pulse trains. We identify 24 new cell types of the intermediate layers of the auditory pathway, and using the new connectomic resource FlyWire, we map all synaptic connections between these cell types, in addition to connections to known early and higher-order auditory neurons. This represents the first map of the auditory pathway. We also determine the excitatory vs. inhibitory nature of most synapses in the auditory connectome. We find that auditory neurons display a continuum of preferences for courtship song modes, and that neurons with different song mode preferences are highly interconnected in a network that lacks hierarchical structure. Among this network, frequency tuning is centered on the range of frequencies present in song, whereas pulse rate tuning extends to rates outside of song, suggesting that these neurons form a basis set for downstream processing. We evaluate a linear model for predicting neural responses to acoustic stimuli from a given neuron's synaptic inputs. Ongoing efforts will probe the roles of key nodes in the network by inactivating individual cell types in females during natural courtship behaviors and while imaging from downstream neurons.

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Poster

P438. Auditory Processing: Circuits, Synapses, and Neurotrasmission II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P438.10

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant R01DC019341

Title: Cytology and connections of nucleus angularis in the Western ratsnake (Pantherophis obsoletus)

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Abstract: Snakes lack a tympanum; instead, their columella connects the oval window to the quadrate bone of the jaw. Despite this adaptation, the function and connections of their central auditory system has received little attention. Here we describe a well-defined first order cochlear nucleus, nucleus angularis (NA), in the auditory brainstem of the Western ratsnake (*Pantherophis obsoletus*). Injections of Neurobiotin were made in the basilar papilla, superior olivary nucleus, and torus semicircularis of 16 snakes. NA was identified by location, and by retrograde label following injections into the torus

semicircularis. NA occupies the most dorsal and lateral portion of the acoustic tubercle. It extends rostrally to the cerebello-medullary junction, and caudally borders nucleus vestibularis ovalis. In contrast to lizards, NA does not extend to the medial edge of the medulla. The dorsal part of the posterior branch of the VIIIth nerve terminates in bouton-like terminals in NA. This terminal field is separated into a larger, more medial region and a smaller extension close to the entry of the auditory nerve. NA contains a heterogeneous population of projection neurons which project to the ipsilateral superior olive, the contralateral superior olive and torus semicircularis. The ipsilateral superior olive projects back to NA. Our results reveal similar projections to those observed in lizards. Although snakes are insensitive to airborne sound, and respond best to low-frequency vibrations, the well-defined NA provides a potential substrate for encoding sound intensity as in other reptiles.

Disclosures: D. Han: None. **B.A. Young:** None. **C.E. Carr:** None.

Poster

P467. Visual System: Responses During Behavior II

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Topic: D.07. Vision

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FLAG-ERA JTC 2015 CANON
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Amsterdam Brain and Mind Project

Title: Task contingencies prolong the causal involvement of visual cortex in perception

Authors: *M. N. OUDE LOHUIS[1], J. L. PIE[1,2], P. MARCHESI[1], J. S. MONTIJN[3], C. P. J. DE KOCK[2], C. M. A. PENNARTZ[1], U. OLCESE[1];
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Abstract: The transformation of sensory inputs into behavioral outputs is characterized by an interplay between feedforward and feedback operations in cortical hierarchies. In primary sensory cortices, this is observed when stimulus presentation triggers an early response component (driven by thalamic bottom-up input) and, often, a late component thought to result from reverberating activity through areal interactions. This late phase is engaged by attention and stimulus complexity, and also encodes sensory-independent factors, including movement and report-related variables. However, despite its pervasiveness, the nature and function of late activity in perceptual decision-making remain unclear. Here, we tested whether the function of late activity depends on the complexity of a sensory change-detection task. We trained three cohorts of mice in an audiovisual change detection paradigm with the same stimulus configurations, but different reward contingencies: noncontingently exposed (untrained), unisensory trained (detecting visual, but not auditory), or multisensory trained (detecting both visual and auditory). While visual hit rates were

similar for both trained cohorts, multisensory-trained mice responded more slowly to the same visual stimuli than unisensory-trained mice. Laminar recordings in V1 revealed that early-latency, sensory-related activity was similar across cohorts, whereas late, report-related activity only emerged in trained mice and was associated with decreased noise correlations in V1. To test whether this late activity was causal to perception, we optogenetically silenced V1 bilaterally either at stimulus onset (0 ms) or after a delay (200 ms). Early silencing indiscriminately abolished perceptual report, but delayed silencing selectively affected experimental sessions (primarily in multisensory-trained mice) with slow reaction times and a late onset of report-related activity in V1. We confirmed this result in a second multisensory task with different requirements. The temporal window in which V1 is necessary for perceptual decision-making was therefore extended when we increased task complexity, independently of the presented visual stimulus. Thus, although early visual response components encode all sensory information necessary to solve the task, V1 is not simply relaying information to higher-order areas transforming it into behavioral responses. Rather, task complexity determines the temporal extension of a loop of recurrent activity, which overlaps with report-related activity and determines how perceptual decisions are built.

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Poster

P467. Visual System: Responses During Behavior II

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Title: Cortico-tectal circuits involved in motor preparation and navigation

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Abstract: Cortico-tectal interactions are thought to mediate a range of multimodal behaviors, including navigation, attention, orientation and decision making. Layer 5 pyramidal neurons distributed in

widespread cortical areas connect cortex to superior colliculus (SC) and collicular output targets higher order thalamic nuclei. The thalamo-cortical neurons then generate feedback in cortex. How and when these circuits interact to generate complex behavior is not known. When head-fixed mice navigate a plus-maze, they orient their body to the maze. They coordinate the movement of their torso and limbs with the movement of their whiskers and eyes (Dominiak 2019; Bergmann 2021), with the whiskers and eyes moving in a look ahead fashion, and separately predicting the turn direction that mice impose on the maze. Here we begin to test the hypothesis that the cortico-collicular loop is causal in planning and execution of these behaviors. Our first aim was to look for activity in motor cortical areas (secondary motor cortex, MOs) and colliculus that was related to these behaviors. Activity recorded in all layers of SC and in MOs with high density Neuropixels probes showed that neurons in both areas fire in relationship to movement direction of the mouse. Furthermore, neurons in sensory and motor layers of colliculus fire when eye movement was elicited by whisker stimulation with air puffs. We are currently assessing whether activity in the superior colliculus or cortex is associated with motor preparation or is causal in generating the entire sequence of movements associated with navigation.

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Poster

P467. Visual System: Responses During Behavior II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P467.03

Topic: D.07. Vision

Title: Weber, Fechner and Stevens can co-exist under Fisher's roof

Authors: *J. ZHOU[1], L. R. DUONG[2], E. P. SIMONCELLI[3,4];
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Abstract: In 1834, Weber observed that just-detectable stimulus perturbation (perceptual threshold) for many sensory attributes is proportional to stimulus intensity. Fechner later proposed that this lawful behavior arose from a logarithmic internal representation of stimulus intensity, which when differentiated gives rise to Weber's observation. In apparent contradiction to Fechner’s logarithmic proposal, Stevens showed that observers' rated stimulus intensity are typically power functions of stimulus intensity, with exponents that vary substantially for different stimulus attributes. These two conflicting descriptions of the relationship between stimulus intensity and internal representation are each supported by different types of experimental evidence, and the discrepancy remains unresolved. We show that this quandary can be resolved in a framework that incorporates the joint effects of mean and variance of an abstract internal stimulus representation. Specifically, we propose that magnitude ratings (as used by Stevens) reflect the mean internal representation of stimulus intensity, whereas discrimination thresholds (as well as super-threshold distances) depend on both the mean and variability, as captured by the measure of Fisher Information. Under this interpretation, Weber's Law is fully consistent with Stevens' Power Law (for all

exponents) when variance of the internal representation grows as the square of the mean, a property that has been observed or proposed for a variety of neural representations.

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Poster

P467. Visual System: Responses During Behavior II

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Program #/Poster #: P467.04

Topic: D.07. Vision

Support: NIH Grant R34NS111669
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Title: Diverse coding of visual and movement signals in V1 of freely moving mice

Authors: *P. R. L. PARKER[1], D. M. MARTINS[2], E. S. P. LEONARD[2], S. L. SHARP[2], N. M. CASEY[2], M. SIDIKPRAMANA[2], E. T. T. ABE[2], C. M. NIELL[2];
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Abstract: Studies of visual processing have traditionally been performed in stationary subjects viewing artificial stimuli on a two-dimensional screen. However, this is vastly different from the typical domain in which our visual system operates, as we constantly move through a complex and three-dimensional environment. Furthermore, recent studies have demonstrated a range of movement-related signals in visual cortex, but the computational role of this modulation is unclear due to the constrained conditions under which visual physiology experiments are generally performed. In order to address this mismatch, we have developed a system to perform visual physiology in freely moving mice. A key challenge in this is determining the visual input, which is no longer under experimenter control but depends on the animal's head and eye position. We solve this by using two head-mounted cameras, one recording the visual scene from the mouse's perspective, and one measuring the eye position. By combining this information with high density silicon probe recordings of up to 100 simultaneous neurons, we are able to measure visual receptive fields during free exploration through a three-dimensional environment. In addition to this visual coding, we also find that a large fraction of neurons in V1 encode combinations of eye or head position, as well as saccadic and compensatory eye movements. Finally, recording from the same neurons under head-fixed conditions allows us to relate these freely moving measures to standard measures of visual processing, such as orientation and direction selectivity.

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Poster

P467. Visual System: Responses During Behavior II

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Topic: D.07. Vision

Support: NIH Grant EY029438

Title: Robust representations of 3D motion in macaque FST, but not MT

Authors: *L. W. THOMPSON[1], B. KIM[1], B. ROKERS[2], A. ROSENBERG[1];
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Abstract: Determining the movement of objects through three-dimensional (3D) space is a critical function of the visual system. Recent work identified activity in the macaque superior temporal sulcus that potentially reflects 3D motion processing. However, such modulations could alternatively reflect lower-level selectivity for 2D retinal motion that naturally covaries with 3D motion. To distinguish these possibilities, we measured the responses of macaque middle temporal (MT) and fundus of the superior temporal sulcus (FST) neurons to 3D motion during a 'towards'/'away' discrimination task. The stimuli consisted of dots that moved towards or away from the cyclopean eye within a volume (3° diameter; ±1° of disparity) and contained: (1) combined stereoscopic and perspective cues, (2) stereoscopic cues only, or (3) perspective cues only. Critically, the left- and right-eye perspective cues had opposite net 2D retinal motion directions for both directions of 3D motion. We found that roughly 50% of both MT and FST neurons showed significant direction tuning in the combined and stereoscopic cue conditions. To distinguish if that tuning reflected 2D or 3D motion selectivity, we compared the combined and stereoscopic cue responses to those in the perspective cue conditions. In MT, preferences for the combined and stereoscopic cue stimuli were positively correlated with the perspective cue preferences measured from the dominant eye and either negatively correlated or uncorrelated with those from the non-dominant eye. In contrast, the combined and stereoscopic cue preferences of FST neurons were positively correlated with both eye's perspective cue preference. These results suggest that MT neurons largely represent 2D retinal motion signals, whereas many FST neurons represent 3D motion. To further test if 3D motion could be robustly decoded from either neuronal population, we trained linear decoders using the combined-cue responses and then tested the decoders on each of the cue conditions. In MT, cross-cue testing revealed that 3D motion was conflated with the 2D motion signals and ocular dominance, such that only responses to the dominant eye's perspective cues could be accurately decoded. Decoding performance using MT responses to the non-dominant eye's perspective cues was at chance level. In stark contrast, cross-cue decoding from FST was accurate across all cue conditions. Thus, robust decoding of 3D motion was possible in FST, but not MT. These results suggest that a crucial 2D-to-3D visual motion transformation occurs along the MT to FST pathway.

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Poster

P467. Visual System: Responses During Behavior II

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Program #/Poster #: P467.06

Topic: D.07. Vision

Support: NSERC

Title: Topological and dynamical features of source localized EEG networks in presaccadic visual processing

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Abstract: The topology and dynamics of cortical networks involved in the generation of presaccadic neural signals remain poorly understood. In particular, how they interact with simultaneously presented visual stimuli. Here, we used different approaches in graph theory analysis (GTA) and electroencephalography (EEG) to evaluate topology and dynamics of functional brain networks in the perisaccadic interval. EEG was recorded via 64 channels in two behavioral conditions (fixation or saccade). Participants (N=21) were pre-cued with a series 1-3 grids (three horizontal lines, 10° by 10°) located 5° below the central fixation-point. 100ms later, a stimulus (three vertical lines; same size/location) was briefly presented (for 70ms). In the saccade condition, a left/right shift of the fixation-point during the interstimulus interval triggered a saccade after the second stimulus. Source localization (SL) was performed on the 200ms period following the saccade cue, or the equivalent time during fixation trials. Lagged coherences were calculated between all pairs of 84 Brodmann areas. SL/GTA both identified major network hubs near the frontal and parietal eye fields, with widespread cortical connectivity. Other GTA measures (clustering coefficient, global efficiency, energy, entropy) showed that network segregation, integration, synchronizability, and complexity were enhanced during the perisaccadic interval. Further, these network properties significantly interacted with stimulus repetition, altering both hubs and network topography. These data suggest a network mechanism for enhanced visual information processing and propagation in the presaccadic interval. Acknowledgements: Grant Support: an NSERC Discovery Grant and VISTA Fellowship, funded by CFREF.

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Poster

P467. Visual System: Responses During Behavior II

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Topic: D.07. Vision

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Title: Quantifying the effects of saccadic eye movements on visual responses and receptive field measurements in V1 of the awake mouse.

Authors: *A. NWANKPA[1], C. BARNES[2], D. BARSON[2], J. A. CARDIN[2], M. J. HIGLEY[2];
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Abstract: In the visual system, many species possess the ability to move their eyes rapidly in order to scan their surroundings. For mice, which lack a foveal region of the retina, the function of these saccades in visual processing is not well understood. In addition, neurons in the mouse primary visual cortex (V1) respond preferentially to relatively large stimuli, in contrast to primates and carnivores, potentially reducing the impact of small changes in eye position on visually evoked neural activity. Thus, the consequences of saccades for visual processing in the mouse are unclear. Here, we developed a novel method for calculating gaze shifts in awake, head-fixed mice presented with visual stimuli comprising either sinusoidally drifting gratings or filtered noise patterns. We used 2-photon calcium imaging of GCaMP6s-expressing neurons in V1 to quantify visually-evoked single cell response magnitudes and receptive field structure. We simultaneously monitored spontaneous variation in the animal's behavioral state, measured by pupil diameter, facial movements, and locomotion. We then asked whether including estimates of eye position significantly improved response measurements. Our results suggest that saccades are temporally coupled to changes in behavioral state. Moreover, changes in eye position are capable of altering the response to visual inputs, suggesting a behaviorally relevant function for these movements. Overall, these findings indicate that eye position should be considered in experimental studies of visually-evoked activity in the mouse and that, as in other species, mouse vision represents an active process of acquiring information about the external environment.

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Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P552.01

Topic: E.05. Brain-Machine Interface

Support: NINDS Grant NS053603

Title: Low-dimensional neural manifolds describing natural behaviors

Authors: *E. ALTAN, S. A. SOLLA, L. E. MILLER, E. J. PERREAULT;
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Abstract: Across many brain areas, the activity of populations of neurons is constrained to low-dimensional subregions of the neural space known as neural manifolds. Recent studies of the primary motor cortex (M1) suggest that the population activity on the low-dimensional neural manifold represents the computations required for planning and executing motor behaviors. However, low dimensional manifolds have only been studied in constrained laboratory settings. Is the underlying simplicity suggested by the low dimensionality of M1 manifolds simply a byproduct of the constrained laboratory

environment? If so, is the dimensionality of M1 manifolds corresponding to natural behaviors such as crawling and feeding higher than that of grasping tasks in the laboratory? The dimensionality of the neural manifold determines the number of neurons that need to be sampled to construct accurate brain-to-behavior decoders: the higher the dimensionality of the neural manifold, the more neurons need to be sampled to faithfully represent the behavior. Therefore, establishing the dimensionality of the neural manifold corresponding to natural behaviors is crucial to the design of brain-machine interfaces, a rehabilitative technology that converts neural signals into control commands to restore movement to paralyzed patients. In this study, our first objective was to establish the dimensionality of the M1 manifolds across a range of motor behaviors in different contexts. Our second objective was to use dimensionality reduction to find the neural manifolds and assess whether it is possible to decode EMGs from them. We used Parallel Analysis and Two Nearest-Neighbors as linear and nonlinear estimators of dimensionality, respectively. We found that the linear dimensionality of neural manifolds associated with unconstrained natural behaviors ranged between 7 and 13, while the nonlinear estimates were between 5 and 6. The linear dimensionality of manifolds associated with laboratory tasks ranged between 7 and 15, while the nonlinear estimates were between 5 and 6. Our results suggest nonlinearity in both contexts and that the dimensionality of laboratory behaviors is similar to that of natural tasks. Next, we used two common dimensionality reduction tools, PCA (linear) and UMAP (nonlinear), to find the neural manifolds. EMG prediction accuracies were similar when we used all recorded neurons, PCA embeddings, and UMAP embeddings. Our results suggest that low-dimensional neural manifolds exist in richer, natural behavioral contexts as they do for the constrained laboratory environment, and that these low-dimensional manifolds are associated with motor behaviors across contexts.

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Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Topic: E.05. Brain-Machine Interface

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Title: Tracking long-term changes in high-dimensional ECoG BCI control using deep autoencoders

Authors: *N. NATRAJ[1], R. ABIRI[2], S. SEKO[1], Y. GRAHAM[1], N. HARDY[3], E. F. CHANG[4], K. GANGULY[5];
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Abstract: For individuals with paralysis, Brain Computer Interfaces (BCIs) have the potential to restore lost function through the decoding of neural activity to control external assistive devices. Typically, the control signal in BCIs are low-dimensional as they comprise the imagined motor movements of a single end-effector (such as imagined right arm movements). However, recent work in invasive, spike-based

intracortical recordings has shown that the whole-body can be represented from a single cortical region such as the “hand-knob area”. This suggests that BCI recordings can allow decoding of much higher-dimensional representations, with the potential to translate to complex control of assistive devices with higher degrees of freedom. In this study, we sought to understand whether high-dimensional BCI control signals can be decoded using mesoscale electrocorticography (ECoG). We first established separable control signals using diverse discrete imagined actions, resulting overall in a 12D control signal from the single ECoG grid. A discrete classifier was initialized on these imagined data to classify individual imagined actions using the envelope of three neural oscillations: delta band (0.5-4Hz), beta band (12-30Hz) and high-gamma (70-150Hz), all binned at 8Hz. Then, by leveraging the stability of ECoG, we tracked the consolidation of the high-dimensional control signal with practice over many weeks. Specifically, stable decoding of the high-dimensional control signal was achieved through closed-loop decoder batch updates from online sessions over many sessions of practice. As a result, our subject was able to robustly control a high-degree of freedom virtual robotic device. To understand how neural activity evolved to consolidate the control signals, we used a deep autoencoder to uncover the latent space that captured the refinement of the high-dimensional control signals with long-term BCI training. Overall, our results show that high-dimensional control signals can be stably represented in mesoscale ECoG recordings, without any rigid somatotopy and outside of the hand-knob area of primary motor cortex. Notably, we are able to track changes in the latent space representations; this allowed the user to more easily control the BCI system.

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Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Title: Stabilizing brain-computer interfaces through nonlinear manifold alignment with dynamics

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Abstract: Intracortical brain-computer interfaces (iBCIs) can restore voluntary movement to people with paralysis by translating brain activity into a control signal for an external device. Currently, iBCI performance declines over time due to instabilities at the neural interface, such as shifts in electrode position. Such instabilities result in a degradation of decoding performance that can only be recovered by retraining with additional data. To solve this problem, an emerging class of methods seeks to find a population-level latent manifold structure that has a stable mapping between brain activity and behavior. In recent proofs of concept, Farshchian et al (2018) and Degenhart et al (2020) found that unsupervised manifold alignment can achieve stable iBCI decoding without supervised decoder recalibration. However, these methods do not incorporate nonlinear dynamics models, which have outperformed other methods in retaining the behavioral information necessary for high-performance iBCI decoding (Pandarinath et al., 2018). Thus, we developed a platform for nonlinear manifold alignment with dynamics (NoMAD) that seeks to stabilize iBCI decoding following discovery of nonlinear neural population dynamics. In NoMAD, manifold discovery is performed by latent factor analysis via dynamical systems (LFADS), a deep learning approach that uncovers manifold structure by modeling the shared dynamics underlying population activity. NoMAD combines LFADS with unsupervised distribution alignment (Dyer et al., 2017; Farshchian et al., 2018) to produce consistent manifold estimates that are robust to changes in the recorded neurons. We tested whether NoMAD could improve the stability of offline decoding for motor cortical activity from a monkey performing an isometric wrist force task throughout 20 sessions spanning over three months. NoMAD achieved stable, high-performance decoding of the monkey's exerted force over all sessions without supervised recalibration. On days where a static decoder applied to smoothed spikes achieved positive decoding performance, NoMAD achieved a mean improvement over the static decoder of 0.48±0.16 R^2. Comparatively, ANMA (Farshchian et al., 2018) and FA-based stabilization (Degenhart et al., 2020) gave average improvements of 0.26±16 R^2 and 0.028±0.19 R^2, respectively. Of the days that had negative decoding performance with a static decoder, NoMAD restored positive performance to 7 of 8, while ANMA restored 3 and Degenhart 4. By combining accurate, nonlinear manifold discovery with unsupervised manifold alignment, NoMAD improves upon current methods, potentially enabling high-performing, stable iBCIs.

Disclosures: B.M. Karpowicz: None. **Y.H. Ali:** None. **L.N. Wimalasena:** None. **M. Keshtkaran:** None. **A.R. Sedler:** None. **K. Bodkin:** None. **X. Ma:** None. **L.E. Miller:** None. **C. Pandarinath:** None.

Poster

P552. Neurophysiology: Decoding and Neural Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P552.04

Topic: E.05. Brain-Machine Interface

Support: NIH Director's New Innovator Award (DP2), Contract DP2MH126378

Title: Intrinsic and nonlinear geometric dynamical modeling of neural population activity

Authors: *H.-L. HSIEH[1], H. ABBASPOURAZAD[1], B. PESARAN[2], M. M. SHANECHI[1];
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Abstract: Neural population activity during naturalistic behavior may evolve on nonlinear low-dimensional geometric manifolds. Thus, identifying this intrinsic geometry and incorporating it explicitly in the dynamical model are critical for investigating neural representations but remain elusive. We develop a novel data-driven framework to learn a nonlinear geometric dynamical model for the temporal evolution of neural population activity. Prior work has shown that a prevalent feature of cortical dynamics across datasets is rotational patterns that can be seen with various dimensionality reduction techniques. Motivated by this broad observation, we hypothesized that neural population activity may evolve on nonlinear manifolds containing holes, which may explain why linear projections of this activity onto hyperplanes show rotations in time. We thus developed our framework to identify multi-dimensional nonlinear manifolds with holes, learn an intrinsic coordinate system for the manifold, and then learn a dynamical model for the temporal evolution of population activity on top of the manifold. We applied this framework to motor cortical population dynamics in non-human primates performing motor tasks. We found that the manifold underlying neural population dynamics was indeed nonlinear and contained a hole yet was multi-dimensional. Moreover, our derived manifold-based intrinsic coordinates described the population activity better than the linear embedding coordinates. This geometric dynamical modeling framework for neural population activity has the unique ability to identify the underlying intrinsic geometry and to build the dynamic model on top of it. Thus, it provides a novel tool to explain and model neural population activity and its intrinsic geometric dynamics.

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Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P552.05

Topic: E.05. Brain-Machine Interface

Support: Weijerhorst Foundation Grant (UTAP)
INTENSE Grant NWO17619

Title: Decoding movement using riemannian geometry in stereotactic-EEG recordings.

Authors: *M. C. OTTENHOFF[1], M. VERWOERT[1], S. GOULIS[1], J. P. VAN DIJK[2], A. COLON[2], S. TOUSSEYN[2], L. WAGNER[2], P. KUBBEN[3], C. HERFF[1];
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Abstract: A brain-computer interface (BCI) allows users to interact with a computer without any physical movement and could improve independence of paralyzed patients. By using neural data as direct input into a predictive model, one can control assistive technologies such as robot arms, spelling computers or speech synthesizers. A small but growing subgroup of BCIs use invasive stereotactic-EEG (sEEG) electrodes, often implanted for focal localization in patients with refractory epilepsy. These electrodes

provide high temporal and spatial resolution in a sparse brain-wide coverage, including deeper structures like the insula and hippocampus.
As sEEG electrodes are currently only implanted for clinical purposes, the contact locations are different for each patient and thus it is not straightforward to combine or compare data between patients. However, combining data would increase the amount of available data and could significantly decrease decoder calibration times. To combine data in the dispersed coverage of sEEG, we explore the use of Riemannian manifolds. By mapping the data to a higher dimensional manifold, large scale neural dynamics might be captured that are partially covered by implanted electrodes in each participant. Riemannian geometry is receiving increasingly more attention in scalp EEG, driven by state-of-the-art results in BCI decoding competitions and promising results in transfer learning. This work describes a first attempt to apply Riemannian Geometry in a movement decoder using sEEG recordings.
Ten epileptic patients undergoing presurgical assessment for resection surgery participated in our study. Participants were instructed to continuously open and close either their left or right hand for 3 seconds, followed by 3 second rest period. The experiments included 30 trials per hand in randomized order, resulting in a total of 60 trials. First, the neural data was detrended, demeaned and filtered for 50 Hz line noise. Then, we extracted the alpha, beta and high gamma band envelope and windowed the data. From the resulting [*windows* x *samples* x *channels*] matrix, we extracted the regularized sample covariance matrices (rSCM) per window. The Riemannian decoder was developed on a 3-class problem using 10-fold cross-validation. Predictions were made by calculating the minimum Riemannian distance of the rSCM to the class mean. Our results show that this approach achieves comparable results to previous work that uses a linear discriminant analysis classifier. These results implicate that a non-parametric approach can achieve similar performance as a parametric approach, reducing the risk of overfitting through hyper parameter estimation.

Disclosures: M.C. Ottenhoff: None. **M. Verwoert:** None. **S. Goulis:** None. **J.P. van Dijk:** None. **A. Colon:** None. **S. Tousseyn:** None. **L. Wagner:** None. **P. Kubben:** None. **C. Herff:** None.

Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Program #/Poster #: P552.06

Topic: E.05. Brain-Machine Interface

Support: H2020-EIC-FETPROACT-2019-951910-MAIA

Title: Simultaneous decoding of reaching goals and task phases from medial parietal areas using a hidden Markov model

Authors: F. E. VACCARI[1], S. DIOMEDI[1], *M. GAMBERINI[1], M. FILIPPINI[1,2], P. FATTORI[1,2]; [1]Univ. of Bologna, Bologna, Italy; [2]Alma Mater Res. Inst. for Human-Centered Artificial Intelligence, Bologna, Italy

Abstract: The fronto-parietal network includes areas involved in generation and control of the motor behaviour. We recently showed that the activity of neurons of V6A and PEc areas, localized in the

posterior parietal cortex of macaque, progresses through a sequence of neural states during a reaching task similarly to what has been observed also for frontal regions. Here, we first investigated the neural states within the parietal PE area, contiguous to PEc, to test whether it shows the same sequence of activation patterns as the caudal areas PEc and V6A. To this purpose, we recorded neurons during a delayed reaching task in which the monkey had to reach 9 different targets placed at eye-level, the same task used to study V6A and PEc. Then, we explored the feasibility to embed an HMM algorithm as neural decoder for Brain Machine Interface (BMI) applications to simultaneously decode task phase and target position from these three areas. We found that a Hidden Markov model (HMM) was able to detect in PE the same main states that we previously found in V6A and PEc. To decode these common neural dynamics, we merged several HMMs separately pre-trained in a unique boosted model that was able to detect the initial phase of the task, in which the animal could freely move the eyes and it was not aware of the future target, plus the three main subsequent task phases (i.e., waiting time, movement execution and target hold period). With this model, we achieved epoch decoding accuracies up to 86 and 88% from V6A and Pec. This was significantly lower, but still above chance level, from PE (67%). Once estimated, the same state sequence could be exploited to also extract information about the reaching goal. In this case, the accuracy of the HMM algorithm was extremely good for V6A and PEc, whereas it decreased for PE (82 and 70% for vs 36%). Spatial information extracted by the three areas peaked during movement and rapidly decreased during the holding phase, suggesting a relative low influence of pure proprioceptive signals. Finally, we tested the algorithm in sub-optimal conditions simulating a neuron loss through several days of recordings without re-training the algorithm. HMM showed a reliable robustness losing on average only the 10% of performance against a 20% drop in the neural population. We demonstrated that HMM can be efficiently used to decode neural activity and to extract spatio-temporal information that could be used to drive a finite state BMI. Our work also confirms that the posterior parietal cortex is interesting to support BMI implants, but, due to the heterogeneity of these areas, careful investigations should be carried on to identify the best source of the information needed.

Disclosures: F.E. Vaccari: None. **S. Diomedi:** None. **M. Gamberini:** None. **M. Filippini:** None. **P. Fattori:** None.

Poster

P552. Neurophysiology: Decoding and Neural Processing II

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Program #/Poster #: P552.07

Topic: E.05. Brain-Machine Interface

Support: H2020-EIC-FETPROACT-2019-951910-MAIA

Title: Evidence for motor-related neural states in posterior parietal cortex

Authors: S. DIOMEDI[1], F. E. VACCARI[1], C. GALLETTI[1], K. HADJIDIMITRAKIS[1,2], *P. FATTORI[1,2];
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Abstract: The parieto-frontal network enables us to perform optimal reaching movements by combining the multisensory integration and state estimation function of the parietal cortex with the muscular and motor planning functions of the motor and premotor cortices. Fundamental for these interactions are neural population patterns within the nodes of the network. In fact, whereas there are theoretically infinite possible activations, in practice, due to plasticity and anatomical connectivity, these patterns are reduced to only a small number of 'neural states', especially in typical, stereotyped laboratory tasks. Here, we examined whether in posterior parietal cortex it is possible to trace back the heterogeneity of neural discharges to a limited number of 'neural states'. We thus recorded from two *Macaca fascicularis* monkeys, 209 and 176 neurons from V6A and PEc areas respectively while the animals were performing a delayed reaching task toward 9 targets placed at different directions and depths in darkness. In addition, we also recorded 92 neurons from V6A area from 2 other animals during a delayed reaching task towards 3 targets placed on a fronto-parallel plane, both in light and dark conditions. To characterize different ensemble activity patterns, we applied an unsupervised machine learning method, the Hidden Markov Model. In the reaching task performed in the dark, both areas were found to encode several neural states. We divided the decoded states in 'micro and 'macro' based on their overall relevance on population activity. The three 'macro' states corresponded to the three main task epochs, already observed in motor and premotor cortices, i.e. waiting for the go signal, reaching execution and holding the target. 'Micro' states represented smaller task temporal intervals: the reaction time period before the action, an initial and a final part of the movement and the first part of the hold epoch. We further investigated the nature of these 'macro' states and tested whether they represented the pure motor plans processing and movement execution or whether they reflected underlying computation principles characteristic of the parietal cortex, invariant to task conditions. We found that visual input added in the reaching task performed in the light did not alter the state sequence, but rather, besides slight differences, a generalization analysis between light/dark conditions allowed to decode the same population patterns. These results suggest that dynamics in posterior parietal cortex are mainly shaped by motor and premotor cortices activity, reflecting the timing of action unfolding.

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Poster

P568. Afferent and Descending Control

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.01

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant IOS 1456866

Title: Gamma-aminobutyric acid receptor alpha subunit control of hyperactive behavior in developing zebrafish

Authors: *W. BARNABY[1], H. DORMAN BARCLAY[3], A. NAGARKAR[3], G. TEICHER[4], M. PERKINS[5], J. TRAPANI[5], G. DOWNES[2];
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Massachusetts, Amherst, Amherst, MA; [4]Biol., Univ. of Massachusetts, Amherst Mol. and Cell. Biol. Program, Amherst, MA; [5]Biol., Amherst Col., Amherst, MA

Abstract: Neural networks in the vertebrate hindbrain and spinal cord rely upon a balance of excitatory and inhibitory neurotransmitter systems to orchestrate locomotive behaviors. Classically inhibitory, GABA is recognized as a key regulator of these neural networks. Despite its importance, the precise roles and molecular mechanisms of GABA remain unclear due to the complexities of GABA signaling. $GABA_A$ receptors ($GABA_ARs$), which mediate the rapid responses to GABA, are ionotropic, ligand-gated heteropentamers, constituted from combinations of 19 and 22 different subunits in mammals and zebrafish, respectively. The molecular diversity, potential for compensatory mechanisms, and few isoform specific pharmacological agents have challenged efforts to better understand how $GABA_AR$, and hence GABA, regulate locomotor networks.In developing zebrafish, bath application of $GABA_AR$ antagonists results in hyperactive swimming by 48 hours post-fertilization (hpf) and all later stages of development, indicating that $GABA_ARs$ regulate locomotor behavior from early larval stages. We hypothesize that during these early larval stages, a limited number of $GABA_AR$ isoforms regulate locomotor networks. To test this hypothesis, we performed a CRISPR-Cas9 somatic mutation screen targeting individual or combinations of all 8 α subunit genes, which are obligatory receptor components, then we analyzed the escape behavior of these 'crispants' at 48 and 96 hpf. This analysis revealed that at 48 hpf, combinations that targeted α3, α4 and α5 generated different types of hyperactive behavior, suggesting that these subunits play a prominent and subtype-selective roles in regulating locomotion. At 96 hpf, a hyperactive phenotype due to this subset was drastically attenuated in both mosaic and germline lines, suggesting that homeostatic mechanisms are effective at later stages of development.α3 is expressed in discrete sets of cells in the hindbrain and spinal cord at 48 hpf, which provides the opportunity to identify specific cell types that are able to regulate swimming behavior. We are currently determining the identity of these α3 expressing cells and assessing the importance of the hindbrain versus the spinal cord in performing hyperactive swimming behavior. Taken together, these data provide a platform to identify how $GABA_ARs$ regulate vertebrate locomotion. Moreover, given that $GABA_AR$ dysfunction is a central aspect of epilepsy and larval zebrafish are an increasingly recognized epilepsy model, we are creating new resources to investigate this disorder.

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Poster

P568. Afferent and Descending Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.02

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NINDS 900023

Title: Role of Dopaminergic Descending Neuron in the control of locomotion in Drosophila

Authors: *N. WANG, V. BHANDAWAT;
Drexel Univ., Philadelphia, PA

Abstract: Neuromodulatory descending neurons (DNs) – neurons that project from the brain to the spinal cord/thoracic ganglia play an essential role in the control of locomotion. Their importance is well-established, in part, through the demonstration that exogenous applications of neuromodulators produce fictive locomotion. However, the mechanism of descending neuromodulation *in vivo* remains poorly understood: both how these DNs are recruited and how they affect the components of the motor circuit *in vivo* are unclear. This study aims to fill this critical gap by investigating the role of dopaminergic descending neurons (DADNs) in fly locomotion. Specifically, we will take advantage of the extensive genetic tools in flies, the availability of electron microscopy data for the entire fly brain and thoracic ganglia, *in vivo* electrophysiology, and calcium imaging in behaving *Drosophila* to elucidate the role of DADNs in the control of locomotion. In *Drosophila*, there are only two DADNs. We started by performing whole-cell patch-clamp recordings from these two neurons while tracking leg movements. We found that in the absence of leg movements, DADNs exhibit tonic activity, which transforms to burst activity during some but not all leg movements. There also exists a prolonged inhibition in DADNs after the termination of locomotion. Next, we measured the activity of DADNs when the fly was walking on a trackball; in this experiment, the activity in DADNs was highly correlated with yaw rotations. While these results establish the DADN activity is related to locomotion, it was also clear that the relationship between leg movements and DADNs' neuronal activity is complex. The complexity likely represents multiple diverse inputs into dopaminergic neurons. To further characterize presynaptic input into DADNs, we reconstructed DADNs in a publicly available electron microscopy dataset. The identified presynaptic partners suggested that DADNs receive 1) inputs from other descending neurons in the brain and 2) feedback from thoracic ganglia. By optogenetically stimulating presynaptic neurons in both the brain and thoracic ganglia, we found that both sets of presynaptic inputs can individually activate DADNs. Together, these studies show that DADNs integrate both feedforward and feedback signals to influence locomotion.

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Poster

P568. Afferent and Descending Control

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Program #/Poster #: P568.03

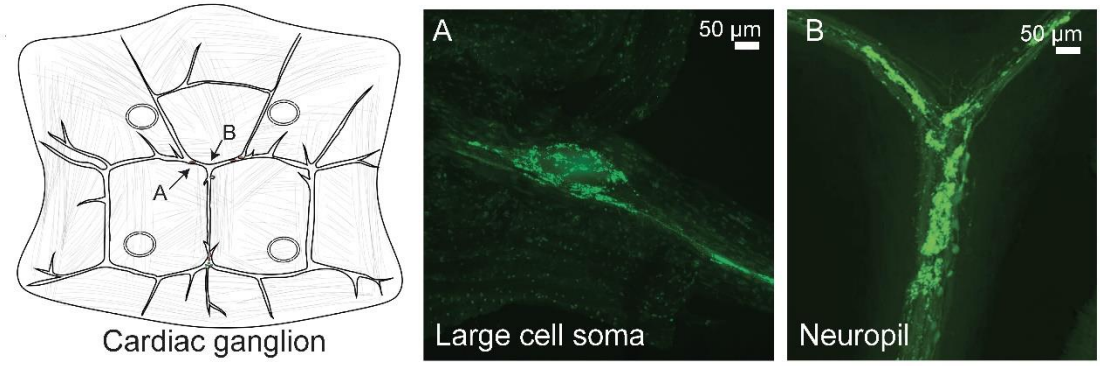
Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R35 NS097343
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Title: Characterizing Chemical Synapses in the Cardiac Ganglion of Cancer Borealis

Authors: *N. K. BAAS-THOMAS, M. C. RUE, P. IYENGAR, E. MARDER;
Brandeis Univ., Waltham, MA

Abstract: The heart contractions in *Cancer borealis*, or the Jonah crab, are initiated by the cardiac ganglion (CG) which innervates the heart tissue. The CG is composed of only nine neurons, five large cell (LC) motor neurons and four small cell pacemakers. These neurons fire synchronously to produce stereotyped rhythmic impulses, which are stable yet flexible in response to perturbations. The CG is the direct target of multiple neuromodulators whose effects on the normal CG rhythm are well established. Characterizing the identity and location of the circuit's chemical synapses is key to understanding its flexible motor output. Using an antibody against synapsin, a presynaptic protein, we found that chemical synapses were clustered around the LC somata (Figure A) and at the neuropil (Figure B). This implicates the soma as a key site of synaptic integration which is unexpected in invertebrates like the Jonah crab. We next performed double immunostains for chemical synapses and several neuromodulators with different actions on CG output to understand the intersection between morphology and function in this circuit. Stains for inhibitory neuromodulators revealed GABA-like and AST-B-like immoreactivity which was nearly completely colocalized with chemical synapses near the LCs. We next looked at excitatory neuromodulators, proctolin-like, FMRFamide-like, and RPCH-like immunoreactivity, and found little or no overlap at the chemical synapses near the LCs. These results provide morphological evidence that inhibitory input is preferentially integrated at neuronal cell bodies. Conversely, all the neuromodulators studied only partially overlapped with the chemical synapses present at the neuropil. This suggests that there are specialized regions of integration for different modulatory inputs. For several of these neuromodulators, we have also identified which nerve provides afferent input into the ganglion. Our findings provide a topographical organization for multiple inhibitory and excitatory modulators that alter the rhythmic output of this semi-autonomous motor circuit.



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Poster

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.04

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Alternating Rhythmic Finger Tapping is Strongly Correlated with Rudimentary Grasping Pattern

Authors: *S. MANOHARAN, H. PARK;
Electrical & Computer Engin., Texas A&M Univ., College Station, TX

Abstract: Neurotraumas often result in catastrophic loss of motor function. The retrieval of impaired grasping function is one of the major focuses of motor rehabilitation, since manipulation through grasping underlies most physical interactions with the world around us. In order to effectively accomplish this goal, there arise two distinct needs: 1) a deeper understanding of the driving neural mechanisms behind grasping and 2) a quantifiable physiological metric to evaluate the grasping function. Studies suggest that rudimentary grasping has a higher influence of subcortical control, while complex grasping has a higher influence of cortical control. Also, prior works indicate similarity between finger tapping patterns and rudimentary finger grasping patterns. Although the connection between the finger tapping and the rudimentary finger grasping has not been investigated with sufficient detail, finger tapping can provide a framework to evaluate the grasping capability, with a strong relationship in between. Notably, it is still challenging to quantitatively evaluate the grasping function, due to the variations caused by the complexity of grasping tasks and the varied levels of cognitive influence involved. In this study, we investigated factors and metrics to facilitate the quantitative evaluation of rudimentary grasping patterns using rhythmic finger tapping patterns. We employed alternating and simultaneous rhythmic finger tapping between two adjacent fingers among the thumb, index, and middle fingers. Ten healthy subjects were asked to tap neighboring fingers alternatingly or simultaneously as fast as possible while maintaining a clear trajectory, to minimize the cognitive intervention while maintaining the data reliability. We first identified that asymmetric patterns underlying alternating rhythmic finger tapping patterns for the Index-Middle and Thumb-Index pairs are skewed towards the rudimentary grasping pattern ($p<0.01$). Second, the degree of asymmetry during alternating rhythmic finger tapping is larger for Index-Middle pair than Thumb-Index pair ($p<0.01$), which is congruent to their respective temporal separation established in rudimentary grasping patterns. No such similarity between tapping and grasping was observed in simultaneous rhythmic finger tapping. Conclusively, we observe that alternating rhythmic finger tapping follows the rudimentary grasping pattern - therefore, we expect to apply these methods and metrics of alternating finger tapping in grasp diagnostics and rehabilitation.

Disclosures: S. Manoharan: A. Employment/Salary (full or part-time):; Texas A&M University. **H. Park:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

P568. Afferent and Descending Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.05

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Independent research fund, Denmark

Title: Effects of the paradoxical “freezing” response to stimulation in the Pedunculopontine nucleus (PPN) on the lumbar spinal interneurons in freely moving rat

Authors: *J. KAUR[1], N. BERTRAM[1], E. NAJARRO[1], R. W. BERG[2];
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Abstract: It is well-known that the mesencephalic locomotor region (MLR) plays an important role in initiating and regulating movement, and electrical stimulation can induce locomotion. Nevertheless, it was recently discovered that optically stimulating a subset of neurons in the pedunculopontine nucleus (PPN), which is a part of the MLR, paradoxically induces a whole-body halt of movement rather than movement initiation (Carvalho et al., 2020). To investigate this new phenomenon and the effect of this PPN stimulation on spinal motor circuits, we chronically implanted Multi-Electrode Arrays (128-channels) in the lumbar spinal cord of adult rats. Further, we stimulated the PPN using a photosensitive genetically expressed sodium channel (ChrimsonR), using CamKIIa as a promotor in an AAV virus, that was injected along with an implanted optical fiber. Contrary to the anticipated locomotor response, the photo-stimulation induced a strong arrest of movement where the whole body of the rat "completely froze". Measurements of motion were performed using accelerometers and video recording. The recordings of lumbar units indicated that PPN stimulation reduced the neuronal spiking activity in some of the spinal neurons. The PPN neurons inducing the "freezing behavior" were likely glutamatergic based on preliminary histology, which is still ongoing.

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Kentucky Spinal Cord and Head Injury Research Trust
Commonwealth of Kentucky Challenge for Excelle
Craig F. Neilsen Foundation CNF546714

Title: Swallow network modularity is revealed in the optically-recorded germline-GCaMP6F mouse

Authors: T. PITTS[1], N. SALTSMAN[4], K. E. ICEMAN[2], B. GOURÉVITCH[5], J. CAI[6], ***N. MELLEN**[3];
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Abstract: Swallow must be coordinated with breathing to prevent aspiration, but the mechanisms of this coordination are poorly understood. In the sagittally sectioned rodent hindbrain (SSRH) preparation, control networks for swallow are exposed at the dorsomedial edge of the preparation. In vitro swallow is defined as a burst at the hypoglossal nerve (XIIn) unaccompanied by phrenic (C4) motor output. Here we

used transgenic mice in which the genetically encoded Ca^{2+} indicator GCaMP6F was expressed in the germline, enabling optical recording from all cells exposed at or near the sagittal surface of the SSRH. At the end of each experiment, the tissue was fixed, and a 400 µm section was cut from the sagittal face, for immunohistochemical processing to identify $ChAT^+$, $phox2b^+$, and SST^+ neurons. Using this preparation, we identified a novel population of neurons rostral to the pre-Bötzinger complex (PBC) and dorsal to nucleus ambiguus (NA) that is immediately activated following stimuli. Seconds after stimulus offset, a discrete population of neurons in NA become active, and their activity is accompanied by a burst on XIIn unaccompanied by C4 activity, occurring immediately before or just after the inspiratory burst, consistent with adaptive intercalation of breath and swallow. Unlike the diffuse activity seen along the ventral respiratory column during fictive respiration, networks activated during swallow are spatially compact with sharp, well-defined borders, consistent with modularity. This functional anatomical organization is supported by immunohistochemistry: strong phox2b and ChAT expression with sharp boundaries was found to overlap with the population of neurons strongly activated during stimulation, and the delayed activity associated with fictive swallow overlapped precisely with the well-defined ChAT- and phox2b-positive populations within NA. These findings highlight divergent strategies between the swallow and respiratory pattern generators and lay the groundwork for a detailed investigation of adaptive central coordination of swallow with breathing.

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Poster

P568. Afferent and Descending Control

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University of Iowa, Old Gold Summer Fellowships

Title: Shape and timing: using variational analysis to dissect motor robustness

Authors: *Y. WANG[1], J. P. GILL[2], H. J. CHIEL[2], P. J. THOMAS[3];
[1]Dept. of Mathematics, Univ. of Iowa, Iowa City, IA; [2]Dept. of Biol., [3]Dept. of Mathematics, Applied Mathematics, Statistics, and Biol., Case Western Reserve Univ., Cleveland, OH

Abstract: Motor systems show an overall robustness, but because they are highly nonlinear, understanding how they achieve robustness due to their different components such as sensory feedback and biomechanics is difficult. In many rhythmic systems, robustness against perturbations involves response of both the shape and the timing of the limit cycle trajectory. This makes the study of robustness even more challenging.
To understand how a motor system produces robust behaviors in a variable environment, we consider a

neuromechanical model of triphasic motor patterns in the feeding apparatus of the marine mollusk Aplysia californica developed by [Shaw et al., J. Comput. Neurosci 2015] and [Lyttle et al., Biol. Cybern. 2017]. We established in [Wang et al., SIADS 2021] the tools needed for studying combined shape and timing responses of both continuous and nonsmooth limit cycle systems under sustained perturbations and applied them to study robustness of the neuromechanical model against an increased mechanical load. Interestingly, we discover that nonlinear biomechanical properties confer resilience by immediately increasing resistance to applied loads. In contrast, while the sensory feedback also immediately responds to the perturbation, the effect of changed sensory feedback signal is significantly delayed by the firing rates hard boundary properties. Our analysis suggest that sensory feedback contributes to robustness primarily by shifting the timing of neural activation and specifically increasing the duty cycle of the neural pool involved in retraction. This enables the system to generate stronger retractor muscle force to compensate the increased force and hence achieve strong robustness.
The approaches that we are applying to understanding a neuromechanical model in Aplysia, and the results that we have obtained, are likely to provide insights into the function of many other motor systems that encounter changing mechanical loads and hard boundaries, both mechanical and in neuronal firing.

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Poster

P568. Afferent and Descending Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.08

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Differential activation of reflex motor pathways by 10kHz vs. single pulse spinal cord stimulation

Authors: *D. LEE, K. LEE, D. WANG, Z. KAGAN, K. BRADLEY;
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Abstract: High frequency (10kHz) spinal cord stimulation (SCS) is well-established and expanding neuromodulatory technique for treating chronic pain as well as activating motor circuits to restore motor function. Despite clinical success, the cellular mechanism of 10kHz SCS for activating neurons is still not fully understood. We aimed to study the activation of reflex motor pathways by 10 kHz SCS vs. single pulses in the spinal circuits. SCS was applied via a micro-sized, in-line quadripolar electrode array positioned epidurally over the L5-L6 dorsal spinal segments (innervating the left hind paw). We applied 10kHz SCS (symmetric biphasic; pulse width: 20us; duty-cycled: 3ms ON with 5s OFF), as well as single pulse SCS (symmetric biphasic; pulse width: 200us; frequency: 0.2Hz). Both strategies were applied at different times on the same two stimulating contacts (configuration: bipole). Needle electromyograms (EMG) were taken of compound muscle action potentials (CMAP) from the hindlimb thigh (biceps femoris) and paw plantar toe flexor muscle (flexor digitorum brevis). We investigated the recruitment curve of these two different muscles by 10kHz SCS and single pulse SCS strategies, in terms of recruitment slope and peak-to-peak (PtP) CMAP amplitude. The recruitment curve was obtained by increasing stimulation amplitude from threshold (observable defection of EMG) to 130% of it. Within this range of amplitude, there was clear pattern that one muscle was more selectively recruited than the other

one. Using 10kHz SCS, the recruitment curve of the thigh muscle CMAP increased at a greater (slope:10.4±2.4 uV/uA, PtP:0.8±0.04 mV) than the toe muscle (1.5±0.15 uV/uA, 0.16±0.06 mV). Using single pulse SCS, the thigh muscle showed more gradual recruitment (4.5±2.1 uV/uA, 0.3±0.1 mV) than the toe muscle (21.8±14.8 uV/uA, 1.15±0.05 mV) We observed that 10kHz SCS activated the thigh muscle selectively, with very little activation by single pulse SCS. The toe muscle showed a similar but opposite selectivity, where single pulse SCS resulted in more selective activation of the toe than 10kHz SCS. Given that both strategies were applied to the same stimulating contacts, i.e., the same spatial location in the spine, these results suggest that 10kHz activates a different set of specific afferent fibers and/or reflex pathway different from that activated by a single pulse. This may represent a new tool for stimulation selectivity, and 10 kHz stimulation may expand potential targets in spinal circuits for pain and motor control beyond those commonly understood for conventional low frequency stimulation.

Disclosures: D. Lee: A. Employment/Salary (full or part-time):; Nevro. **K. Lee:** A. Employment/Salary (full or part-time):; Nevro. **D. Wang:** A. Employment/Salary (full or part-time):; Nevro. **Z. Kagan:** A. Employment/Salary (full or part-time):; Nevro. **K. Bradley:** A. Employment/Salary (full or part-time):; Nevro.

Poster

P568. Afferent and Descending Control

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P568.09

Topic: E.07. Rhythmic Motor Pattern Generation

Title: The influence of proximal & distal muscle activation on bimanual interference

Authors: *Y. WANG[1], O. PINTO NETO[3], M. M. DAVIS[1], R. J. CASTRO[1], T. WRIGHT[1], D. M. KENNEDY[2];
[2]Hlth. & Kinesiology, [1]Texas A&M Univ. - Site 2, College Station, TX; [3]Anhembi Morumbi Univ., São Paulo, Brazil

Abstract: The influence of proximal and distal muscle activation on bimanual interference Wang, Y.[1*], Pinto Neto, O.[2]; Davis, M.M.[1], Castro, R.J. [1], Wright, T.J.[1]. & Kennedy, D.M.[11]Department of Health & Kinesiology, Texas A&M University, College Station, TX[2]Center of Innovation, Technology and Education, Anhembi Morumbi University, São Paulo, SP
Neuroanatomical and neurophysiological differences between proximal and distal muscles suggest that the effects of neural crosstalk may be stronger in proximal than distal muscles. The current investigation was designed to compare coordination dynamics between bimanual force tasks performed with proximal and distal muscles. Right limb dominant participants (N=12, mean age = 21.9) performed rhythmic patterns of isometric force in 1:1 symmetric and 1:2 asymmetric patterns using proximal (triceps brachii (TRI)) and/or distal (First Dorsal Interosseous (FDI)) muscles. Lissajous plots and movement templates were provided to guide performance. Participants performed 10 trials per muscle combination (TRI-TRI, TRI-FDI, FDI-TRI, FDI-FDI) for each coordination pattern in a counterbalanced order. Muscle activity from the TRI and FDI were recorded using sEMG. The behavioral results indicated very effective temporal performance of the goal coordination patterns regardless of the muscle combination used to

perform the task. The results also indicated consistent perturbations in the forces exhibited by the non-dominant limb that could be attributed to the forces produced by the dominant limb during the asymmetric task. However, similar distortions were not observed in the symmetric task. The harmonicity results also indicated that more adjustments, hesitations, and/or perturbations in the left limb than the right limb during the 1:2 task regardless of the muscle combination used to perform the bimanual task. However, left limb harmonicity was significantly lower for the TRI-TRI condition than the other muscle combinations. These results are consistent with the notion that neural crosstalk exerts a stronger influence on the non-dominant limb than the dominant limb and this influence is greater with proximal than distal muscles activation.

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Poster

P568. Afferent and Descending Control

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Program #/Poster #: P568.10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01 NS085387
NSF DBI 2015317

Title: Optogenetic activation of 5-HT neurons in the raphe pallidus: effect on sensory-evoked responses in lumbar motoneurons of the neonatal mouse

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Abstract: The brainstem raphe pallidus (RPa) is an important source of serotonin (5-HT). Many of the 5-HT-producing neurons in the RPa project to the spinal cord (raphespinal) and profusely innervate the ventral region of the spinal cord where motoneurons are located. Electrical stimulation of the RPa in the cat has been shown to depolarize and recruit lumbar motoneurons, both when given alone or in combination with sensory afferents stimulation (Fung and Barnes 1989). Because RPa also contains non-5-HT raphespinal neurons, it is still unclear whether motoneuron excitation can be attributed to the activation of 5-HT raphespinal neurons. In this study, we use channelrhodopsin-2 (ChR2) optogenetics for precise manipulation of RPa 5-HT neurons and calcium imaging for recording activity in individual lumbar motoneurons. We found that RPa activation did not recruit motoneurons and substantially reduced dorsal root (DR)-evoked responses in these motoneurons. The inhibitory effect of RPa activation on DR-evoked responses was completely abolished by spinal application of the 5-HT2 receptors antagonist ketanserin but not by application of the 5-HT1 receptors antagonist WAY-100135. These results unmask a previously unreported 5-HT2-dependent inhibitory role of RPa serotonergic neurons in the modulation of sensory-evoked responses in lumbar motoneurons, highlighting the need for a systematic re-evaluation of the serotonergic contribution of the different raphe nuclei to the modulation of spinal motor circuits.

Disclosures: A. Giorgi: None. **M. Perreault:** None.

Poster

P568. Afferent and Descending Control

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Program #/Poster #: P568.11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BIOSIGNE
ANR

Title: Diversity and specialization of brainstem V2a neurons in the control of orientation and locomotion

Authors: *G. USSEGLIO[1], E. GATIER[1], A. HEUZÉ[2], J. BOUVIER[2];
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Abstract: The brainstem reticular formation (RF) is key for controlling and orchestrating motoractions. Indeed, reticular neurons interface multiple sensory and cognitive modalities upstream,with supra-spinal and spinal executive motor circuits downstream. However, their functionaldiversity is still poorly resolved. In particular, are reticular neurons an unified controller ofmultiple motor circuits, or do they comprise specialized subsets based on their inputs and/oroutputs to control component motor actions individually?We recently showed that a genetically-defined class of glutamatergic neurons in themedial reticular formation, the V2a neurons (Chx10-expressing), encompasses at least twodistinct spinally-projecting subsets: a cervical-projecting subset whose activation controls headrotation movements and imposes a change of locomotor trajectory, and a lumbar-projectingsubset that depresses locomotor speed (Usseglio et al., 2020). V2a reticular neurons thuscomprise distinct functional subsets defined by projection and whose functional outcome mayowe to the targeted cell type.Previous work suggested that lumbar-projecting V2a neurons exert a functionalinhibition on locomotion via local inhibitory neurons in the spinal cord (Bouvier et al., 2015).Using a rabies-based transsynaptic strategy on newborn mice, we demonstrate here that thecervical-projecting subset instead directly forms synapses with spinal motoneurons controllingthe axial musculature of the neck. Furthermore, using circuit optogenetics, we reveal that V2areticular neurons not only control head turning and locomotor velocity and trajectory, but alsoother inherent components of orienting behaviors whose executive circuits are located in thebrainstem. These include conjugate eye movements, snout deflections and breathingmodulation. Importantly, we show that these latter functions are not dependent on spinally-projecting V2a neurons but are supported by brainstem-projecting V2a subsets.Our work highlights that V2a neurons in the gigantocellular reticular nucleus act as anorchestrator of orienting motor actions and can be subdivided in two macro-categories,anatomically and functionally, i) one that controls ocular, orofacial and respiratory movementsthrough supra-spinal projections, and ii) another one that controls trunk and limb movementsthrough spinal projections. Within each, a further specialization by projection site andpostsynaptic targets supports the control of individual motor components.

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Poster

P568. Afferent and Descending Control

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: SCNIP studentship Award
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Wings for Life
Frank Leblanc Chair in Spinal Cord Injury

Title: Uncovering the descending dopaminergic inputs to the medullary reticular formation

Authors: *J. R. GRAMS[1,2], T. L. NELSON[4], M. A. TRAN[3], D. A. ELLIOTT[1], P. J. WHELAN[1,3]; [1]Hotchkiss Brain Institute, Univ. of Calgary, Calgary, AB, Canada; [2]Dept. of Neurosci., [3]Dept. of Comparative Biol. and Exptl. Med., Univ. of Calgary, Calgary, AB, Canada; [4]Cumming Sch. of Medicine, Univ. of Calgary, Calgary, AB, Canada

Abstract: Dopamine is a key neurotransmitter involved in motor control, which has been shown to mediate locomotor behaviors through the nigrostriatal pathway. Although this pathway is well understood, a growing body of literature suggests that parallel descending pathways contribute to the modulation of locomotion. Dopamine neurons have been shown to project directly to motor circuits within the mesencephalic locomotor region (MLR). Neurons within the medullary reticular formation (MRF) also contribute to locomotor control and integrate modulatory input. However, the dopaminergic projections to the MRF have not been well documented. We used a combination of immunohistochemical and viral tracing techniques in DAT-IRES-Cre;td-Tomato and TH-IRES-Cre transgenic mice to map dopaminergic inputs to the MRF. Retrogradely labelled neurons were identified across numerous dopaminergic brain regions including the A13 and A11 nuclei, the periaqueductal grey (PAG) and the locus coeruleus (LC). Our preliminary results suggest that the primary source of dopaminergic input to the MRF originates from the A11 region. Intriguingly, projections from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) to the MRF were sparse. Next, using an anterograde viral approach, we found that dopaminergic neurons from the A11 region project to and form putative synaptic connections with neurons in the MRF. We compared the overall fiber length and synaptic density across the rostrocaudal extent of the MRF and found multiple projection sites in the caudal pontine reticular nucleus (PnC) and Gigantocellular Reticular Nucleus (GRN), which are key sites involved in locomotor control. Putative synaptic connections were formed with excitatory reticulospinal neurons. Lastly, using D1-IRES-Cre;td-Tomato transgenic mice, we found evidence of D1 dopamine receptor expression in the MRF. Altogether, our study suggests that the primary source of dopaminergic input to the MRF originates from non-canonical neurons in the A11 region. These preliminary findings support the idea that dopaminergic neurons of the A11 region contribute to the modulation of locomotor behaviour through descending projections to motor circuits in the MRF.

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Poster

P568. Afferent and Descending Control

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Program #/Poster #: P568.13

Topic: E.07. Rhythmic Motor Pattern Generation

Support: The Edward Jekkal Muscular Dystrophy Research Fellowship (DLGR)
NIH R01 NS104194 (KJD & SG)
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Title: Spinal cord injury-induced plasticity of sensory afferent input pathways to Shox2 interneurons following epidural stimulation in mouse

Authors: *D. GARCIA-RAMIREZ, N. J. STACHOWSKI, S. J. ATOCHE, L. YAO, S. GISZTER, K. J. DOUGHERTY;
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Abstract: Lumbar spinal neuronal circuitry generates the locomotor rhythm and pattern even in the absence of descending input from the brain and sensory afferent inputs. However, the initiation and adaptation of locomotion to the environment requires descending and sensory afferent control. Most spinal cord injuries (SCIs) occur above the location of the spinal locomotor neurons so descending modulation is disrupted but the spinal circuitry remains relatively intact. Therefore, stimulation of afferent fibers, such as with epidural stimulation (ES), is used as a strategy to counteract the deficit of the descending modulation after SCI and subsequently gain locomotor control. In mice, lumbar interneurons (INs) expressing the transcription factor Shox2 have been linked to locomotor rhythm generation and patterning. Therefore, studying the effects of ES on Shox2 INs represents an opportunity to understand the therapeutic mechanisms and further improve current strategies to recover locomotor function after SCI. Previously, we stimulated dorsal roots while performing whole cell patch clamp recordings targeting Shox2 INs in lumbar spinal slices from uninjured adult Shox2::Cre;Rosa26-lsl-tdTomato mice and found that Shox2 INs received inputs mediated by both excitatory and inhibitory sensory pathways. In slices from mice 6+ weeks after complete thoracic spinal transection, Shox2 INs received almost exclusively excitatory inputs in response to dorsal root stimulation. However, in mice in which ES wires were implanted at lumbar spinal level L2 and sub-motor-threshold ES was delivered while mice were weight-supported on a treadmill starting 1 week after SCI and electrode implantation surgery, afferent-evoked inhibitory inputs to Shox2 neurons were observed more often than excitatory inputs. The aim of this study is to identify whether sub-motor-threshold ES alone is sufficient to revert or prevent the SCI-induced changes in afferent pathways to Shox2 neurons, as observed with ES during weight-supported treadmill sessions. We compared the SCI-induced plasticity of sensory afferent input to Shox2 INs in groups of mice receiving sub-motor-threshold ES in the home cage, weight-supported treadmill sessions without ES, and ES on the treadmill, with that of untreated SCI mice. We found afferent-evoked inhibitory and excitatory inputs to Shox2 INs in mice that received ES in their home cage, while Shox2 INs from mice placed on the treadmill with weight support but no ES received mainly excitatory input, similar to the untreated SCI group. This suggests that ES alone is sufficient for the recovery or maintenance of inhibitory sensory pathways to locomotor-related neurons.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

Location: Virtual Only

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Program #/Poster #: P637.01

Topic: F.08. Biological Rhythms and Sleep

Support: Israel Science Foundation (ISF) grant 1326/15 and 51/11
Adelis Foundation
European Research Council (ERC-2019-CoG 864353)

Title: Impaired feedback auditory processing despite extensive single-neuron responses during human sleep

Authors: *H. HAYAT[1], A. MARMELSHTEIN[1], A. J. KROM[2], Y. SELA[1], A. TANKUS[3], I. STRAUSS[3], F. FAHOUM[3], I. FRIED[4], Y. NIR[1];
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Abstract: Reduced behavioral responsiveness to environmental stimuli is a hallmark of sleep, yet how responses along cortical sensory pathways during sleep compare to those during wakefulness remains unclear. Specifically, previous studies have yet to resolve where along the sensory hierarchy, in which signals, and what factors affect sensory responses during sleep. Here, we recorded intracerebral EEG, microwires LFPs, and neuronal spiking activity along with polysomnography in 13 drug-resistant epilepsy patients implanted with clinical depth electrodes, while intermittently presenting auditory stimuli (e.g. words, click-train, music) during wakefulness and sleep. We found that auditory spiking and LFP induced high-gamma (80-200Hz) power showed robust auditory responses during sleep across the temporal lobe well beyond the primary auditory cortex, exhibiting moderate attenuation in response magnitude while maintaining their selectivity profiles and their tight locking with soundwave envelopes. By contrast to spiking/gamma responses, LFP alpha-beta (10-30Hz) power decrease was prevalent in wakefulness but strongly disrupted in sleep. Entrainment to 40 Hz click-trains was comparable across REM sleep and wakefulness but reduced in NREM sleep. In conclusion, our results establish the presence of extensive and robust auditory responses during sleep while LFP alpha-beta power decrease, likely reflecting top-down processes, is deficient. More broadly, our findings suggest that feedback signaling is key to conscious sensory processing.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

Location: Virtual Only

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Program #/Poster #: P637.02

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant EY031705
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NIH Grant R01EY027841
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Title: Reduction of the glutamate concentration in the ventromedial prefrontal cortex during human sleep

Authors: *T. YAMADA[1], M. TAMAKI[2], B.-D. TYLER[1], S. KHAN[1], J. WATERS[1], T. WATANABE[1], Y. SASAKI[1];
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Abstract: Neurochemical mechanisms underlying wake-sleep regulations in the human brains are poorly understood. It has been suggested that regions that span from the subcortical regions to the medial prefrontal region are involved in arousal systems in humans (Maquet et al., 2000; Nofzinger et al., 2004, 2005), possibly through glutamatergic signaling (Weigend et al., 2019). Animal models have suggested that circuits using glutamate and GABA neurotransmitters in the subcortical regions regulate wake and sleep (Brown et al., 2012; Saper & Fuller 2017). In the rats' cortex, glutamate levels increased during prolonged wakefulness and during REM sleep, whereas glutamate levels decreased during NREM sleep (Dash et al., 2009). However, to our knowledge neurochemicals processing regulating wake and sleep in the human brain has never been clearly revealed. As an initial work to address this question, specifically we measured the concentrations of glutamate (Glx) in the ventromedial prefrontal cortex (vmPFC) and early visual areas (EVA) during sleep to test whether the Glx concentration changes in these regions, using simultaneous magnetic resonance spectroscopy (MRS) and polysomnography (PSG). Healthy young adults, ranging 18-30 years old, participated in the experiment. Approximately one week after an adaptation session conducted for them to be familiarized with sleeping inside an MRI bore, the subjects were again asked to sleep inside the MRI bore for about 90 min. During this 90-min sleep session, a 10-min MRS scan was repeated 9 times to collect Glx concentrations from the vmPFC in one group or EVA in the other group. We then calculated how much Glx concentrations changed during NREM sleep and REM sleep relative to wakefulness in the vmPFC or EVA region. While the Glx concentration was decreased during NREM sleep and REM sleep in the vmPFC, it was not decreased during either NREM sleep or REM sleep in EVA. The relative Glx concentration in the vmPFC was significantly lower than that in EVA during both NREM sleep ($p=0.001$) and REM sleep ($p=0.012$). Moreover, the amount of reduction of Glx concentration in the vmPFC during NREM sleep was significantly correlated with the sleep onset latency ($p=0.015$): Namely, the larger amount of reduction of Glx concentration in the vmPFC, the shorter the sleep onset latency. However, in EVA, the Glx concentration was not correlated with the sleep onset latency. These results are consistent with the hypothesis that the vmPFC is a part of the human arousal system, in which reduction of the glutamate level plays a role in initiating sleep, whereas the glutamate level in EVA is not involved in the human arousal system.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

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Program #/Poster #: P637.03

Topic: F.08. Biological Rhythms and Sleep

Support: Searle Scholars Award
NIH R00-MH111748
NIH R01-AG070135

Title: Consistent Temporal Patterns of Thalamocortical Activity during Slow Global Events detected with High Resolution EEG-fMRI

Authors: *Z. DIAMANDIS[1], B. SETZER[2], L. D. LEWIS[1];
[1]Biomed. Engin., [2]Grad. Program for Neurosci., Boston Univ., Boston, MA

Abstract: Sleep reflects a state of decreased arousal important for cognitive function and memory consolidation. Sleep is marked by specific oscillatory interactions across cortical and thalamic structures as well as large fluctuations in the global fMRI signal that are coupled to both neural activity and autonomic arousal. While previous studies have shown that brain-wide propagated activity reorganizes during sleep, the fine-grained thalamocortical dynamics that underlie these global events remain unknown. In the past, studies have been limited by the spatiotemporal resolution of conventional imaging methods, which cannot capture dynamics in individual thalamic nuclei. We used previously published simultaneous electroencephalography (EEG) and fast functional magnetic resonance imaging (fMRI) (TR=367ms) data to investigate the interaction between thalamocortical dynamics and EEG activity during slow global cortical events. Then, we used ultra-high field fMRI at 7 Tesla (TR=247ms) to specifically examine the dynamics of individual thalamic nuclei during these events. We found a consistent sequence of cortical EEG and thalamocortical fMRI activity associated with troughs in the global cortical fMRI signal, wherein EEG slow waves precede cortical fMRI troughs which are in turn followed by analogous thalamic activity with a 1-2s lag. Further, we found evidence of a specific sequence of activation across individual thalamic nuclei, subsequent to the dip in the cortical signal. These results demonstrate a specific, consistent pattern of thalamocortical activity coupled to the global cortical fMRI signal and shed further light on how fMRI signal fluctuations relate to electrophysiology and arousal state.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

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Program #/Poster #: P637.04

Topic: F.08. Biological Rhythms and Sleep

Title: Analysis of the disruption of DMN synchronicity under effects of Sevoflurane and contributions of VTA-DMN FC to the emergence from general anesthesia

Authors: *J. ZIMMERMANN[1], R. NUTTALL[2], D. GOLKOWSKI[3], G. SCHNEIDER[2], A. RANFT[2], R. ILG[4], C. SORG[2], A. WOHLSCHLÄGER[2];
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Abstract: Disruption of the intrinsic connectivity of the Default Mode Network (DMN) has been associated with Sevoflurane general anesthesia. However, whether its integrity or disruption is the key for consciousness remains unclear. Studies in rodents suggest that the dopaminergic ventral tegmental area (VTA) might be involved in the process of emergence from general anesthesia with a halogenated ether. We propose that a sevoflurane-induced unconscious state is characterized by the loss of synchronization in the DMN, and that a dopaminergic VTA functional connectivity towards the DMN is crucial for reestablishing its synchronization. We used rs-fMRI data from 15 male volunteers (mean, 26yr), under Sevoflurane general anesthesia. Then, we calculated the Fano Factor (FF) and its distribution across 34 regions of the DMN. The FF captures higher order correlation and global synchrony between discrete events and allows to quantify if the observed neural variability compares with the expected variability for a Poisson process. Gamma distributions were fitted to the FF distributions yielding shape and scale factors for each subject and session. We conducted a VTA seed-based functional connectivity (sb-FC) analysis, as a proxy of the dopaminergic interaction between VTA and DMN. To control for anatomical accuracy and RSN specificity, we added 8 further midbrain nuclei and 5 further resting state networks. Finally, we used a mediation analysis to test whether the recovery of synchronicity in the DMN can be explained by first the recovery of VTA-DMN connectivity. Our results showed that the scale factor of the FF distribution as well as sb-FC of the VTA to the DMN were significantly reduced under sevoflurane. Furthermore, the effect of anesthesia on the scale factor was totally mediated by the sb-FC: **Indirect Effect: -0.49** CI: [-0.9185 - -0.0368], **Direct Effect: -0.14** CI: [-0.2956 - +0.0202], **Total Effect: -0.24**CI: [-0.3808 - -0.1066], which is suggested by the mediation analysis. Our findings suggest that the FF distribution is sensitive for detecting resting state fMRI signal changes in synchronicity related to sevoflurane general anesthesia. We could also demonstrate that large-scale synchronization patterns were disrupted, specifically in the DMN. This implies that a well-organized and integrated DMN is a signature for consciousness and that its recovery might depend on an intact dopaminergic VTA-DMN interaction.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

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Program #/Poster #: P637.05

Topic: F.08. Biological Rhythms and Sleep

Title: Getting a good night's sleep: Sleep duration is associated with default mode network connectivity in youth

Authors: *A. HEHR[1], A. MORALES[1], B. BORG[1], J. EVANSKI[1], E. HUNTLEY[2], H. A. MARUSAK[1]; [1]Dept. of Psychiatry and Behavioral Neurosciences, Wayne State Univ. Sch. of Med., Detroit, MI; [2]Survey Res. Center, Inst. for Social Res., Univ. of Michigan, Ann Arbor, MI

Abstract: Sleep plays an integral role in healthy development. Inadequate sleep has been linked to poorer emotion regulation and increased risk of psychopathology. Alarmingly, 58% of middle school children are sleeping less than the recommended amount of 9-12 hours based on guidelines from the American Academy of Sleep Medicine. Prior neuroimaging studies in adults link poor sleep to variation within and between key neurocognitive networks, particularly connectivity of the default mode network (DMN). The DMN is implicated in self-reference and rumination, and disruptions in DMN connectivity are associated with risk of psychiatric disorders. Importantly, many psychiatric disorders begin during childhood and adolescence, and functional connectivity within and between neurocognitive networks undergo dramatic changes across childhood and adolescence. However, few studies have examined the impact of sleep on DMN connectivity in youth. This study included 3798 youth (11.9±0.6 years, 47.5% female, 78.9% White, 12.3% Black American, 4.5% Asian) from the Adolescent Brain Cognitive Development (ABCD) study, a longitudinal experiment across 21 sites in the United States. To maximize sample size with both neuroimaging and objective sleep data (Fitbit watch activity tracker), we included data from the ABCD 2-year follow-up time point. Within and between network resting state functional connectivity (rsFC) was measured between the DMN and core neurocognitive networks (i.e., dorsal attention network [DAN], frontoparietal network [FPN], and salience network [SN]). Average sleep duration was measured over 13.1±6.5 days. Pearson's R correlations were used to test for associations between sleep duration and within and between network rsFC of the DMN. On average, youth slept 7.4±0.7 hours (range: 3-14.1 hours), which is below the recommend 9-12 hours. Total sleep duration was positively correlated with within-network DMN rsFC and negatively correlated with rsFC between the DMN and the DAN and FPN. Sleep duration was not associated with rsFC between DMN and the SN. These findings are consistent with a previous neuroimaging study of sleep deprivation in adults, showing similar patterns of altered within and between network connectivity of the DMN. Given that altered DMN connectivity has been associated with risk of psychopathology, altered DMN connectivity during development may play a role in the link between poor sleep and the development of psychiatric disorders. This study contributes to a growing body of research demonstrating the importance of healthy sleep habits in youth. Future directions will include behavioral indices and additional measures of sleep quality.

Disclosures: A. Hehr: None. **A. Morales:** None. **B. Borg:** None. **J. Evanski:** None. **E. Huntley:** None. **H.A. Marusak:** None.

Poster

P637. Sleep, Arousal, and Anesthesia: Systems

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Program #/Poster #: P637.06

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NS094062

Title: Evidence of a supplementary role of monoaminergic disfacilitation in the suppression of hypoglossal motoneuron activity during hypoxic REM sleep

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Abstract: The present study was undertaken to explore the neurochemical mechanisms that control motor activity during REM sleep under hypoxic conditions, such as those that arise during obstructive sleep apnea. Specifically, we aimed to determine whether monoaminergic disfacilitatory mechanisms (withdrawal of excitatory noradrenergic and serotonergic inputs) participate in the suppression of hypoglossal motoneuron activity during REM sleep under hypoxic conditions. Accordingly, noradrenergic and serotonergic antagonists were microinjected into the hypoglossal nucleus, and their effects on the hypoglossal nerve activity were examined during hypoxic REM sleep. Adult cats were prepared for monitoring behavioral states of sleep and wakefulness, and for extracellular recordings from the hypoglossal nerve. A breathing mask was placed over the animal's nose and mouth to induce single episodes of hypoxia (SpO2 = 70-75%) via a ventilator that regulates on-off flows of nitrogen gas and air into the mask. The real-time oxyhemoglobin saturation level (SpO2) was continuously monitored and recorded. A mixture of prazosin (a noradrenergic antagonist) and methysergide (a serotonergic antagonist) were microinjected, ipsilaterally, into the hypoglossal nucleus during hypoxic non-REM sleep and wakefulness. Prior to the microinjection of drugs, hypoglossal nerve activity decreased by 23.4±2.6% (n=13) during REM sleep versus non-REM sleep under hypoxic conditions (pretreated hypoxia). Following the microinjection of prazosin+methysergide, there was a mean decrease of 12.2±1.3% (n=17) in the nerve activity during hypoxic REM sleep (treated hypoxia). The effect of drug treatment during hypoxic REM sleep was statistically significant compared to pretreated hypoxia ($p<0.001$; unpaired t-test). After 50 minutes of postinjection, recovery from drug effect occurred with a decrease of 19.0±2.3% (n=12) during hypoxic REM sleep (recovery hypoxia), which was significantly different from that of treated hypoxia ($p=0.009$), but not different compared to pretreated hypoxia ($p=0.217$). Our data demonstrates that blockade of hypoxia-induced monoaminergic drives attenuates the suppression of hypoglossal nerve activity during REM sleep. This validates our hypothesis that monoaminergic disfacilitation contributes partially to the suppression of hypoglossal motoneuron activity during hypoxic REM sleep. Therefore, we propose that monoaminergic disfacilitation, in addition to glycinergic postsynaptic inhibition, are responsible for atonia during REM sleep under hypoxic conditions (e.g., obstructive sleep apnea).

Disclosures: C.D. Tobin: None. **S.J. Fung:** None. **M. Xi:** None. **M.H. Chase:** None.

Poster

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Program #/Poster #: P637.07

Topic: F.08. Biological Rhythms and Sleep

Support: NIH K08 NS 099425-01

Title: Parabrachial nucleus glutamatergic neurons are not necessary for wakefulness

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Abstract: Lesions in the brainstem tegmentum can cause coma in humans and experimental animals, but the specific cell types and neural connections that sustain wakefulness have not yet been identified. Coma-causing lesions overlap the parabrachial nucleus (PB) and disrupting glutamatergic PB neurons decreases wakefulness. We hypothesized that glutamatergic parabrachial neurons are necessary for wakefulness. We selectively ablated Vglut2-expressing PB neurons by injecting a Cre-conditional apoptotic vector (AAV-DIO-Casp3-TEVP), bilaterally into the PB of Vglut2-IRES-Cre mice that also had a GFP Cre-reporter (R26-LSL-L10GFP). This approach deleted glutamatergic neurons in the PB region, while leaving neighboring neuronal populations in the laterodorsal tegmental nucleus and locus coeruleus intact. As controls, mice with the same genotype were injected with a Cre-conditional mCherry vector (AAV-DIO-TVA-mCh). Bilateral stereological counts of GFP-expressing neurons remaining in the PB revealed that this approach was highly effective (2,770 ± 2,732 versus 19,072 ± 2,003 GFP+ neurons in ablation versus control mice).
In our first cohort, we used a novel infrared camera-based assay to measure the locomotor activity of mice. We found no statistical difference between our ablation and control groups (p=.73, 41.5 ± 7.2% versus 37.5 ± 8.0% epochs with movement in n=10 ablation versus n=7 control mice). In a replication cohort, we used video-electroencephalography and electromyography (vEEG/EMG) to more rigorously measure wakefulness. Once again, we found no statistically significant difference (p=0.90, 50.1 ± 6.6% versus 53.3 ± 6.9% wakefulness in n=9 ablation versus n=8 control mice), and wakefulness did not correlate with the number of remaining PB neurons (r^2=0.06). We also did not find statistically significant differences in amount of time spent in non-REM sleep (p=0.65). Several mice in the ablation group had unusually short bouts of REM sleep, and this group spent significantly less time in REM sleep (p=0.042, 4.8 ± 2.8% versus 6.2 ± 1.2%). These results are not consistent with our hypothesis that glutamatergic parabrachial neurons are necessary for wakefulness.

Disclosures: F. Grady: None. **S. Graff:** None. **J.C. Geerling:** None.

Poster

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Program #/Poster #: P637.08

Topic: F.08. Biological Rhythms and Sleep

Support: Sleep Research Society Foundation, Career Development Award

Title: Spectral features of limbic network activity during cataplexy in narcoleptic mice

Authors: *Z. SABRA[1], A. A. ROGERS[2], L. M. AIANI[2], J. T. WILLIE[3], N. AU YONG[1];
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Abstract: Introduction: Orexin-deficient narcolepsy type 1 (NT1) is characterized by sudden attacks of REM sleep with associated loss of muscle tone (cataplexy) triggered by strong emotional stimuli. Although autoimmune-mediated loss of orexin neurons in the lateral hypothalamus causes NT1, the precise circuit-level disturbances that link emotional triggers to precipitous lapses into REM sleep remain unknown.**Methods**: Using orexin/ataxin-3 transgenic mice, a model of NT1, we studied the dynamic variation of limbic network activity during wake, sleep, and cataplexy by recording local field potentials (LFPs) in the infra- and prelimbic (IL/PrL) cortex and amygdala in freely behaving mice. Continuous video recording was performed in 6 mice for 24-48h while collecting frontal-parietal neocortical EEG, nuchal EMG, IL/PrL LFPs, and amygdala LFPs. Spectral analysis was performed to determine oscillatory features associated with behavioral transitions.**Results**: We demonstrate that transition from wakefulness to cataplexy is associated with 1) enhanced low frequency oscillations (1-30Hz) with a prominent theta (4-8Hz) component and 2) simultaneous attenuation of high frequency oscillations (30-100Hz). These changes appear earlier in the IL/PrL cortex compared to neocortex. Analysis of coherence between the amygdala and IL/PrL cortex showed highest coherence in the theta range. Using spectral Granger causality analysis, the spectral changes associated with cataplexy in the IL/PrL cortex precede and predict those in the amygdala and neocortex. **Conclusion:** Cataplexy in narcoleptic mice is associated with an increase in low frequency oscillations within the IL/PrL cortex that precedes and possibly drives subsequent responses within the amygdala and neocortex. Characterization of circuit-level biomarkers of narcolepsy may be used to inform novel neuromodulatory interventions.**Support**: Sleep Research Society Foundation, Career Development Award to JTW.

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Poster

P637. Sleep, Arousal, and Anesthesia: Systems

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Program #/Poster #: P637.09

Topic: F.08. Biological Rhythms and Sleep

Title: Spectral electroencephalic features of a slow propofol induction in mice

Authors: D. KILLING, T. HAPPE, D. P. OBERT, M. KREUZER, F. NOWAK, G. SCHNEIDER, *T. FENZL;
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Abstract: Despite the vast use of anesthetics, many questions regarding the underlying mechanisms leading to loss of consciousness remain, upon today, unanswered. While working towards better understanding, rodents have become the predominant animal model. Yet there is only minimal knowledge on the effects of propofol, one of the most commonly used intravenous general anesthetics, on the mouse

brain. In the present study we investigated spectral EEG changes during slow induction of propofol anesthesia in mice in order to improve face validity and constructive validity of this animal model. Seven adult, male mice (C57BL6) were included in this study. We established a chronic central venous access via the right external jugular vein, and implanted 9 chronic epidural electrodes (ECOG), one of them serving as grounding. After 14 days of recovery, we performed a propofol anesthesia (propofol 2%), increasing the flow rate every two minutes by 0,5µl/min. After loss of righting reflex (LORR) the infusion rate was held constant for 5 minutes before stopping. Observation periods were split into two phases: start of anesthesia to LORR; and LORR to EEG burst suppression. We used descriptive statistics and a paired Wilcoxon test for analyses. Mice lost righting reflex 1320 s [IQR: 204] after start of anesthesia at a flow rate of 5.7 µl/min [IQR: 1.0]. Around LORR, delta power increased in all cortical areas, as did alpha, especially in the somatosensory cortex. When comparing the EEG at the start of induction vs. the EEG shortly before burst suppression, we found a decrease in delta power in all cortical areas. The alpha power decreased as well, except in the somatosensory cortex. In this work we show mouse-specific spectral electroencephalographic changes upon induction of propofol anesthesia. However, these changes differ in some points from observations in humans. While, around LORR, an increase in delta power, reflecting a slowing of the EEG, can also be found in humans and other primates, we could not observe an increase in alpha power in the frontal cortices only, but a global increase. These differences may be due to different species, but also could be attributed to the induction speed. We performed a slow induction, to optimally observe EEG changes, which stands in contrast to bolus injections in humans. This study depicts advantages and potential limitations of a mouse model for propofol anesthesia. As many questions regarding neuroscientific features of anesthetic induced loss of consciousness can only be answered using animal models, our data, including the newly established vein access, provides important basis for further research.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant F32-GM137491
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Title: Chemogenetic activation of GABAergic neurons in the rostromedial tegmental nucleus decreases arousal and increases sensitivity to general anesthetics

Authors: *O. A. MOODY, K. F. VINCENT, R. KATO, E. R. ZHANG, K. SOLT;
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Abstract: During states of unconsciousness, like sleep and general anesthesia, the brain has multiple areas that are actively suppressed to reduce wakefulness. The rostromedial tegmental nucleus (RMTg) is

one GABAergic midbrain nucleus that sends inhibitory projections to the ventral tegmental area (VTA). Previous research has shown that activating dopaminergic neurons in the VTA increases wakefulness, and inhibiting these neurons can increase non-rapid eye movement (NREM) sleep. We hypothesized that activating GABAergic neurons in the RMTg would decrease wakefulness and make the brain more susceptible to anesthetic-induced unconsciousness. Excitatory designer receptors exclusively activated by designer drugs (DREADDs) expressed in transgenic Vgat-ires-cre mice were used to target the GABAergic RMTg neurons specifically. Mice expressing excitatory M3Dq receptors in the RMTg travelled significantly shorter distances and spent more time immobile in the open field test after receiving CNO (3 mg/kg, i.p.) compared to saline ($p < 0.05$, n=8). These mice also took more time to recover the righting reflex after 50 minutes of 2.5% isoflurane after receiving CNO (3 mg/kg, i.p.) compared to saline. Finally, mice given CNO (3 mg/kg, i.p.) before propofol (100 mg/kg, i.p.) had increased time to return of righting compared to when given saline prior to propofol. In addition, several mice that did not lose righting after saline and propofol, did lose righting for over 40 minutes after receiving CNO and propofol. Together these data suggest that activating GABAergic neurons in the RMTg reduces overall motor activity and makes the brain more susceptible to anesthetic-induced unconsciousness. The RMTg may play an important role in actively suppressing arousal during states of unconsciousness.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: NSF grant 1749500

Title: The Portal System of the Suprachiasmatic Nucleus

Authors: *Y. YAO[1], A. B. TAUB[2], J. LESAUTER[2], R. SILVER[1,2,3];
[1]Dept. of Psychology, Columbia Univ., New York City, NY; [2]Dept. of Neurosci. and Behavior, Barnard Col., New York City, NY; [3]Dept. of Pathology and Cell Biology, Grad. Sch., Columbia Univ. Med. Sch., New York City, NY

Abstract: Transplantation of the suprachiasmatic nucleus (SCN) into the third ventricle (3V) restores circadian rhythms in an SCN-ablated animal. Even when placed within a semipermeable polymeric capsule, which allows diffusion of hormonal signals but prevents neural outgrowth, the SCN restores circadian rhythmicity with the period of the donor rather than that of the recipient host (Silver et al., 1996) demonstrating that the brain clock produces effective diffusible signals. Ex vivo studies confirm that diffusible signals can set the phase of SCN oscillators in organotypic slices (Maywood et al., 2011). However, a challenge raised by Schibler et al. (2003), is how the small SCN can produce sufficient amounts of humoral signals to set the phase of extra-SCN oscillators unless the target is very nearby. To

explore the possibility of nearby targets, we examined the SCN's vascular organization in male C57BL/6NJ mice (n=27) to explore possible output pathways for humoral signals. The SCN lies at the base of the brain, adjacent to the fluid-filled 3V, making it difficult to study its vasculature in sectioned material. To acquire whole mount images of SCN vasculature we combined iDISCO+ brain clearing and light sheet microscopy using antibodies type IV collagen, smooth muscle actin, and arginine vasopressin to label blood vessels, arteries and the SCN respectively. Surprisingly, we discovered portal vessels connecting the capillary beds of the SCN and the organum vasculosum lamina terminalis (OVLT), a circumventricular organ (CVO). The portal vessels join the rostral-most SCN and the ventral-most aspect of the OVLT superficial plexus. Additionally, the SCN shell has a significantly higher branch density of capillaries ($8.7\pm0.7\times10^{-6}$ nodes/μm^3, n=6) than the core ($4.6\pm1.8\times10^{-6}$ nodes/μm^3). This clock-OVLT portal system enables high concentrations of diffusible signals from the SCN to reach nearby targets without being diluted by returning to the systemic circulation. Prior to this report, the only known portal system in the mammalian brain was the pituitary portal system, first described by Popa & Fielding (1933). Unravelling the function of the pituitary portal system and the neural signals it carries took decades, and continues to be a topic of investigation (Harris, 1948; Guillemin & Schally, Nobel Prize 1977; Trudeau & Somoza, 2020). Like the pituitary portal system, the SCN-OVLT portal system encompasses a highly fenestrated CVO and provides "a window" to the brain. These findings of a new portal system expand opportunities to explore how the SCN communicates with target brain regions and helps to explain how this small nucleus can impact rhythms throughout the body.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

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Title: Rapid state reversibility from deep dexmedetomidine sedation induced by photoactivation of lateral preoptic GAD2 neurons in mice

Authors: *T. YAMAGATA[1,3], S. N. PEIRSON[1], E. O. MANN[2], R. G. FOSTER[1], V. V. VYAZOVSKIY[1,2];
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Abstract: Dexmedetomidine (Dex) is an agonist of alpha2-adrenergic receptor hence it acts as a powerful sedative by counteracting noradrenaline-mediated arousal. Dex-induced sedation is characterized not only by EEG patterns characteristic of NREM sleep, but also reduced body temperature. Here we investigated whether the probability of awakening from Dex sedation is related to the degree of hypothermia, assessed

using thermal imaging of skin temperature in freely behaving mice. To induce awakenings from Dex sedation, we used an established paradigm which consisted in optical activation of GAD2 neurons in the lateral preoptic area in mice ($GAD2^{LPO}$, n=6), which we and others have shown to reliably result in an immediate awakening from physiological sleep. As expected, shortly after Dex administration (100 mg/kg), the animals stopped moving, assumed a prone position, and the frontal EEG was dominated by high amplitude slow waves, concomitantly with a progressive reduction of skin temperature. During the early phase of sedation (first 1h after administration), photoactivation of GAD2 neurons using 10Hz stimulation for 2 min initially provoked a drop in SWA without behavioral arousal and eventually induced behavioral awakening, while the latency to awakening was still substantially higher during stimulation under sedation as compared to spontaneous NREM sleep (NREM: 5.3 ± 1.6 s, Dex: 31.4 ± 5.5 s, n=6, $p<0.05$, two-tailed paired t-test). Once the 2-min stimulation was terminated, the animals returned to a sedated state within 0.5 ± 0.3 min and high amplitude SWA was re-established. We observed that stimulation during the late phase of sedation (2-3 hours after administration), when the peripheral body temperature dropped to nearly room temperature and the EEG amplitude was very low, still resulted in rapid behavioural awakening, and, unexpectedly, the latency to awakening was significantly shorter as compared to trials performed during the initial Dex sedation ($p=0.0021$). These results indicate that GAD2 neurons in the lateral preoptic hypothalamus have a wake-promoting role during both sleep and Dex-induced sedation. Intriguingly, depth of sedation reflected in elevated threshold for awakening was not associated with the degree of hypothermia, suggesting that reduced metabolism is not incompatible with behavioural wakefulness and arousal.

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Poster

P657. Threat/Fear: Neural Circuits II

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Program #/Poster #: P657.01

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01-MH117791

Title: Responding to predicted and surprising foot shock outcome in ventral pallidum and nucleus accumbens core

Authors: *M. MOADDAB, M. H. RAY, M. A. MCDANNALD;
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Abstract: The ventral striatopallidal system, a basal ganglia network, includes the ventral pallidum (VP) and the nucleus accumbens. The involvement of different nodes within the ventral striatopallidal system in mediating reward has been well-studied, yet little is known about the contribution of such circuitry to threat processing. Recently, we reported the VP and nucleus accumbens core (NAcc) as neural sources of threat signals. We did this using a discrimination procedure consisting of cues predicting unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.25), and safety (p = 0.00). We showed dynamic

relative threat signaling during cue presentation within the VP, and specific threat signaling within the NAcc. Here, our aim was to examine firing patterns following the delivery and omission of foot shock outcomes in each region. We observed diverse neural signals for aversive outcome in each region. Further, we found the VP and NAcc to be composed of very similar functional neuron types. Many VP and NAcc neurons are shock responsive, showing equivalent responding following danger and uncertainty shock. However, many other VP and NAcc show differential firing to surprising and predicted foot shock on uncertainty shock and danger trials. This firing pattern is indicative of positive prediction error - a signal to strengthen cue-shock associations. Additionally, both the VP and NAcc contain neurons showing differential firing to surprising and predicted foot shock omission on uncertainty omission and safety trials. This firing pattern is indicative of negative prediction error - signal to weaken cue-shock associations. Neither regions contain a substantial number of neurons showing a fully signed prediction error. Our observation of similar aversive outcome responding raises the possibility that both the VP and NAcc receive inputs from the same areas involved in foot shock-related processing. A complete analysis of VP and NAcc outcome firing will be presented.

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Poster

P657. Threat/Fear: Neural Circuits II

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Topic: G.01. Fear and Aversive Learning and Memory

Support: Hungarian Brain Research Program Grant (2017-1.21-NKP-2017-000002)
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Title: Dissecting the amygdalar microcircuitry

Authors: *Á. BABICZKY, F. MÁTYÁS;
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Abstract: The amygdala is a central hub in the brain circuit that controls behavioral responses to the environmental changes via the well-accepted lateral (LA)/basal(BA)→central amygdala (CeA) route. Accordingly, CeA controls a line of motor and autonomous brain centers regulating behavioral responses. In addition, recent discoveries have refined this canonical functional organization by identifying valence-specific LA/BA pathway avoiding the CeA suggesting that CeA is not the only output region of the amygdalar complex. Therefore, our main goal was to provide a comprehensive anatomical map with connectivity principles of the amygdalar subregions participating in emotional response. First, we combined anterograde and retrograde tracer microinjections with fluorescent immunohistochemistry to investigate the afferent and efferent connections of different amygdala subnuclei. We selectively labelled the LA, BA, the basomedial (BM), centrolateral (CeL) and centromedial (CeM) subnuclei, as well as the amygdalostriatal transition area (Astr) and the intercalated inhibitory cells. Then we investigated the

localization of labelled axons and neurons and compared their relative densities in each subnuclei. Our results indicate that there are several, rather non-overlapping pathways within the amygdala which contradicts the traditional serial information flow model. For example, there is no prominent connection between LA and BA, and their intra-amygdalar targets are also different (BM, Astr and CeM, respectively). Notably, both LA and BA projections avoid CeL and only weakly target CeM, suggesting only a limited intra-amygdalar connection between the cortical-like and striatal like amygdala. Next, we investigated the major excitatory, namely the cortical and thalamic inputs to the amygdala. Furthermore, using cortical layer- and thalamic subnuclei-specific cre mouse lines, we further detailed these pathways in a cell type-specific manner. We found that the cortical and thalamic afferents selectively innervate amygdalar subnuclei, suggesting the existence of functional link between cortical/thalamic input and the separate intra-amygdalar routes. Specifically, LA and BA as well as CeL and CeM connectivities largely differ. Taken together, our findings highlight the existence of separate (rather than serial) information flow within the amygdala defined by their intra-amygdalar and cortical/thalamic innervation which could provide a framework for future studies on understanding amygdalar function.

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Poster

P657. Threat/Fear: Neural Circuits II

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Program #/Poster #: P657.03

Topic: G.01. Fear and Aversive Learning and Memory

Support: SNSF Grant 31003A_176332

Title: A posterior insular cortex - lateral amygdala circuit in fear learning

Authors: S. PALCHAUDHURI, D. OSYPENKO, A. KHUBIEH, O. KOCHUBEY, *R. SCHNEGGENBURGER;
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Abstract: Associative learning allows animals to evaluate environmental cues, and to generate appropriate behavioral responses. During aversively motivated learning, a neutral sensory cue like an auditory stimulus (the conditioned stimulus, CS) acquires an aversive meaning when paired with an aversive reinforcing stimulus (the unconditioned stimuli, US). The lateral amygdala (LA) is a convergence point for CS-US association, and for plasticity of a CS representation. Nevertheless, the role of specific long-range afferents to the LA in these processes still remain elusive. The posterior insular cortex (pInsCx) is a multimodal sensory area which processes auditory, somatosensory / nociceptive, as well as interoceptive information; in rats, the pInsCx projects to various amygdalar regions including the LA (McDonald 1998; Shi & Cassell 1998). Using retrograde and anterograde tracing techniques, we provide anatomical evidence in mice that the granular and dysgranular regions of the pInsCx project to the anterior LA. Optogenetically-assisted circuit mapping shows robust glutamatergic EPSCs in principal neurons of the anterior LA after the expression of Chronos in the pInsCx, providing evidence for a functional glutamatergic pInsCx → LA connection. Furthermore, optogenetically-evoked EPSCs at this

connection showed increased AMPA/NMDA ratios in mice that received paired CS-US stimulation as compared to various control groups, suggesting an involvement of this pathway in fear learning. *In-vivo* optrode recordings showed that a subpopulation of pInsCx neurons develop a CS response which persists on the fear memory retrieval day, suggesting a role of the pInsCx in fear learning. Optogenetic silencing of LA-projectors in the pInsCx during the US (using retrogradely-expressed Arch1.0), showed a moderate, but significant decrease of fear memory when tested one day later. *In vivo* Ca^{2+} imaging experiments, combined with optogenetic and/or chemogenetic silencing of pInsCx neurons, are underway to study the impact of pInsCx afferents on LA neuron activity during the transmission of US information, as well as for the transmission of learned CS information. In summary, our study suggests a role of pInsCx afferents to the LA in fear learning, and begins to unravel the mechanistic role of this afferent connection to the LA during key phases of fear learning.

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Poster

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Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH114961

Title: Stress Enhanced Fear Learning in Juvenile and Adult Male and Female Rats

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Abstract: Stress Enhanced Fear Learning (SEFL) is a paradigm used to investigate key characteristics of Post-Traumatic Stress Disorder (PTSD) such as exaggerated fear expression that does not rely on associative learning. There are few studies that have investigated the effects of age and sex in reference to SEFL. To further explore how stress intensity, developmental age, and sex affects the development of SEFL, we used the SEFL method developed by Fanselow and colleagues under three levels of stress in rats. Using no, low, moderate, and high stress groups, rodents at either P24 or P90 underwent four days of SEFL training and testing. Our preliminary findings for P24 rats showed that females exhibited SEFL under moderate and high levels of stress, while age- and litter-matched males only exhibited SEFL under high levels of stress. However, in stark contrast, we observed the opposite effect in high stress P90 rats where males, but not female rats exhibited SEFL.

Disclosures: S.R. Hetherington: None. **A.M. Poulos:** None.

Poster

P657. Threat/Fear: Neural Circuits II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P657.05

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01MH114961

Title: Acute restraint stress enhances context encoding in fear conditioning

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Abstract: Various forms of stressors have the capacity to influence cognitive and emotional processing in ways that can enhance learning in mammals ranging from humans to rodents. Context fear learning is a task that requires the use of cognitive systems to create a context representation that can then be associated to a fear response through affect-based processing systems. This type of learning has been seen to potentiate with acute stressors in mice and rats, however, these observations have not yet determined if the potentiation is due to affect-based changes or if this effect could in part be mediated by enhanced context encoding. In the current study we aim to determine if a brief restraint stressor can alter contextual-spatial encoding by using a modified context fear conditioning procedure in adult C57Bl/6J mice and Long Evans rats. Mice were either restrained or transferred to a novel cage for 15 minutes then placed back into their homecage for 15 minutes before being exposed in varying amounts of time to Context A. After 24 hours mice were placed back into Context A for a brief period followed by a single footshock, then immediately removed, and placed back into their homecage. On days 3 and 4 half of the mice were exposed to either the context in which they were shocked or a novel context in a counterbalanced way to test for generalization. Our data demonstrates that presentation of an acute stressor immediately prior to context pre-exposure can enhance contextual-spatial encoding as seen by the enhancement in freezing of stressed mice with little to no generalization. Use of a similar procedure in Long Evans rats will also be conducted to determine if the effect that is seen in mice can also be observed in rats. Preliminary experiments suggest that the same brief restraint stress used in mice is also able to enhance fear learning in rats.

Disclosures: E. Groom: None. **E. Peru:** None. **L.M. Colon:** None. **A.M. Poulos:** None.

Poster

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Program #/Poster #: P657.06

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH114961

Title: Long Term Retention of Juvenile and Adult Context Fear Memory in Female and Male Rats

Authors: N. ODYNOCKI[1], Z. ISSACS[1], L. BARON[2], S. HETHERINGTON[1], ***A. POULOS**[3]; [2]Psychology, [1]Univ. at Albany, SUNY, Albany, NY; [3]Univ. At Albany, SUNY, Albany, NY

Abstract: While the long-term retention of context fear memories has been largely described in adult male rodents, relatively little is known about the dynamic nature of these memories in juvenile male and female rats. In the small but growing body of research aiming to characterize juvenile long-term memory, the results from these studies have identified that young animals are more prone to forgetting. However, the extent to which these juvenile memories can be recovered in both male and female rats is not well understood. Our laboratory has recently shown that as juveniles, female rats exhibit greater context fear conditioning (CFC) than males, but this pattern shifts in adulthood when males exhibit greater CFC than females. In the current set of experiments, Long-Evans male and female rats were context fear conditioned at 24 (juvenile) and 90 (adult) days of age and tested for retrieval at 1 or 60 days later. Adults displayed stable levels of freezing across retention intervals with males exhibiting higher levels of freezing compared to females at both intervals. Juvenile animals, irrespective of sex, showed moderate levels of conditional freezing at the 1-day retrieval test, but showed little freezing at 60 days. We then tested the hypothesis that the forgetting evident in juvenile male and female rats could still be recovered with a test of savings. We found that animals who exhibited forgetting displayed higher levels of context fear expression in a sex dependent manner after a savings trial compared to animals who were not shocked as juveniles. Overall, our results highlight the importance of studying learning and memory processes in both male and female subjects, which are not stagnant across development. Furthermore, we provide evidence that fear memories forgotten as juveniles can be recovered in adulthood after a savings trial. These results may help lay a foundation into further understanding sex differences and development in context fear conditioning.

Disclosures: N. Odynocki: None. **Z. Issacs:** None. **L. Baron:** None. **S. Hetherington:** None. **A. Poulos:** None.

Poster

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Program #/Poster #: P657.07

Topic: G.01. Fear and Aversive Learning and Memory

Support: MH114961

Title: A comparison of ventral CA1 and medial prefrontal cortex efferents in the male and female rat

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Abstract: In rodents the medial prefrontal cortex (mPFC) and the hippocampus are inter-connected and project to the basolateral amygdalar nuclei (BLA) and constitute a major portion of the neural circuit mediating context-mediated fear expression. While these regions associated with context fear conditioning have been well characterized and anatomically defined, the vast majority of research in this area has been conducted in the adult male rat. Mounting evidence suggests that male and female rats differentially recruit distinct regions of this neural circuit during associative learning (Maren et al., 1994, Kudo et al., 2004, Gresack et al., 2009, Keiser et al, 2017). These findings raise the intriguing possibility that sex differences in context fear mediated retrieval result from differences in the neural connectivity of this circuit. Here we characterize and explore the densities and distributions of mPFC and ventral hippocampal (vH) efferent projections in both male and female Long Evans rats using the anterograde tracer *Phaseolus vulgaris-leucoagglutinin* (PHA-L). Transport of PHA-L was visualized using 3,3'-diaminobenzidine immunoperoxidase staining while an adjacent series of Nissl-stained tissue sections were used for cytoarchitectural analysis with reference to atlas templates from 2018; *Brain Maps (BM) 4.0, J Comp Neuro*. Spatial registration of fibers with PHA-L transport in reference to *BM 4.0* allowed for an initial qualitative comparison of densities and distributions across the male and female rat brain. For the comparisons presented here, we have chosen to mainly focus on major regions involved in context fear conditioning, namely prelimbic, infralimbic, anterior cingulate, ventral hippocampus, and amygdalar nuclei. PHA-L injection sites were observed within the boundaries of the prelimbic area and ventral CA1 resulting in visible transport of axonal fibers within basolateral amygdalar nuclei.

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Poster

P657. Threat/Fear: Neural Circuits II

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Topic: G.01. Fear and Aversive Learning and Memory

Support: BoR (LEQSF (2018-21)-RD-A-17)
NIH Grant (R01MH122561)

Title: Direct prefrontal cortical projections to the central amygdala regulate high fear states in mice

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Abstract: Exaggerated responses to perceived threat are associated with several mental illnesses including generalized anxiety, post-traumatic stress and panic disorders. Neuronal circuits in the central nucleus of the amygdala (CEA) are necessary for fear learning and expression of defensive behavior, with a mutually inhibitory circuit motif in the CEA regulating freezing and flight responses. The sources of

excitation to the GABAergic CEA that drive intense fear responses are unsolved. Cortical dysfunction is observed in clinical populations with panic disorder, raising the possibility that direct projections from cortex to CEA could modulate high intensity fear responses. Here, we describe a projection to the CEA from the dorsal peduncular (DP) subdivision of the ventromedial prefrontal cortex. DP-->CEA neurons are glutamatergic and mainly target the medial subdivision of the CEA. Mice were subjected to a Pavlovian fear conditioning paradigm that elicits freezing and flight responses to distinct components of a serial compound stimulus, and Ca^{2+} activity was recorded using open-source miniscopes. We show that DP-->CEA projectors are activated specifically by high-intensity threats. Optogenetic and chemogenetic manipulation experiments demonstrate that inhibition of this pathway is anxiolytic and leads to reduced flight, suggesting that the DP-->CEA pathway is necessary for avoidance behavior. Finally, results from *in vitro* recordings demonstrate that these DP-->CEA projectors have excitatory effects on both corticotropin-releasing factor and somatostatin cells in the CEM. These results are the first demonstration that the prefrontal cortex exerts direct top-down control over CEA neuronal circuits that generate fear-related behavior.

Disclosures: C. Borkar: None. **X. Fu:** None. **M. Dorofeikova:** None. **Q. Le:** None. **R. Vutukuri:** None. **C. Vo:** None. **S. Basavanhalli:** None. **A. Duong:** None. **E. Bean:** None. **A. Resendez:** None. **J.G. Parker:** None. **J.G. Tasker:** None. **J.P. Fadok:** None.

Poster

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Program #/Poster #: P657.09

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01-MH117791

Title: Neuropixels recordings reveal distributed signaling of threat probability and threat-elicited behaviour across rodent midbrain and pons

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Abstract: The generation of suitable threat signals in response to threat stimuli is generally considered to be the domain of the forebrain. These signals are then thought to be relayed to midbrain/pons regions to organize the behavioural aspects of fear and adaptive fear responding. Recording from the ventrolateral periaqueductal gray, a midbrain region commonly implicated in generating fear behavior, our lab has found signals for both threat probability and behavioural output. This suggests that threat probability signaling is not exclusive to forebrain regions. To more comprehensively map midbrain and pons threat signaling, we devised a system for multi-region, high-density recording using Neuropixels probes during a fear discrimination procedure in rats. The one-centimeter Neuropixels probe was implanted such that its path coursed through the superior colliculus, most periaqueductal gray subregions, all dorsal raphe subregions, median raphe and additional regions enroute. We recorded 1812 neurons across 21 regions from 10 rats. Analysis of firing during cue presentation showed that neurons could be clustered into

discrete functional types, with each type distributed across at least several regions. Every functional cluster showed a unique temporal pattern of differential cue firing. From these clusters, a small functional network emerged: consisting of clusters showing short latency firing increases to danger, strong differential firing of danger and safety with firing patterns tightly correlated across clusters. Regression revealed these neurons to initially and rapidly signal threat probability, then giving way to signaling of threat-elicited behaviour. Additional analysis of the period following the outcome indicates these regions also play a role in threat outcome and prediction error signals, expanding even further the potential role of midbrain/pons networks in threat signaling and behaviour. These results suggest that networks of midbrain/pons regions not only generate threat-elicited behaviour in response to threat stimuli, but may also play a role in the generation of threat signals themselves.

Disclosures: J.A. Strickland: None. **M.A. McDannald:** None.

Poster

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Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH K99 NS119783 (CEV)
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Title: Activity and modulation of ventrolateral periaqueductal gray neurons during innate freezing

Authors: *C. E. VAAGA, I. M. RAMAN;
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Abstract: Appropriate behavioral responses (i.e. freezing and flight) to threats within the environment are critical for survival. Such innate defensive behaviors require activation of the midbrain periaqueductal gray (PAG), however, the extent to which distinct sub-columns within the PAG are involved in conditioned vs. innate freezing remains controversial. Our recent work has demonstrated that putative freezing-related neurons (expressing the transcription factor Chx10) in the ventrolateral column of the PAG (vlPAG) are subject to modulation by local dopaminergic neurons, which receive input from cerebellar circuits. Whether these neurons in the vlPAG mediate innate freezing, however, is not known. Here we have begun to test the necessity and sufficiency of activity in vlPAG Chx10 neurons during innate fear responses evoked by visual looming stimuli. Under control conditions, both male and female mice responded to visual looming stimuli with prolonged freezing responses (males: 31.4 ± 4.0 seconds, females: 38.5 ± 3.6 seconds, unpaired t-test $p = 0.2$). In response to repeated stimuli, freezing responses showed robust habituation, but the pattern of habituation depended on the interval between successive stimuli. Habituation was slowed when stimuli were presented within the same behavioral session (inter-trial interval: ~5 minutes), as compared to when stimuli were presented across behavioral sessions (inter-trial interval: 24-48 hrs). To test necessity of vlPAG Chx10 neurons during innate freezing, we optogenetically inhibited these neurons during the presentation of a looming visual stimulus. Optogenetic inhibition significantly reduced the percent time spent freezing during the first 20 seconds post stimulus

(WT: 87.2 ± 2.3%; Chx10::Arch: 41.3 ± 9.3%). These results suggest silencing Chx10 neurons occludes freezing responses, suggesting that vlPAG circuits are responsible for generating innate freezing behaviors. Freezing could also be elicited in head-fixed mice running on a treadmill, setting the stage for electrophysiological recordings of vlPAG neurons during behavior.

Disclosures: C.E. Vaaga: None. **I.M. Raman:** None.

Poster

P858. Timing and Temporal Processing II

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NIH Grant T32-DC010775
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Whitehall Foundation Award 2010-05-84

Title: Medial prefrontal cortex represents ordinal position within a sequence of events

Authors: *G. A. ELIAS[1], A. H. TRAN[1], M. P. SARAF[1], K. W. COOPER[1], B. SHAHBABA[2], N. J. FORTIN[1];
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Abstract: The prefrontal cortex is a key region within a larger network that supports the temporal organization of memory. Our recent work suggests the prefrontal cortex is necessary for animals to track their ordinal position within a sequence of events, but precisely how prefrontal cortex accomplishes this remains unclear. To elucidate the computational and representational mechanisms underlying ordinal position tracking, we recorded single-unit ensembles from the medial prefrontal cortex (mPFC) of rats as they performed an odor sequence memory task. In this task they had to determine whether a presented odor (4x odors, A-D) occurred in the correct ordinal position (4x trials per sequence) or not. First, we observed that individual neurons were selectively active during distinct epochs during trials (individual odor presentations) and modulated their activity levels during these periods according to the trial's ordinal position. Next, using a Bayesian decoding algorithm, we quantified the information contained in the ensemble activity. We found that prefrontal ensembles represented time and ordinal information throughout the sequence, though some moments and positions were more strongly represented than others. Specifically, temporal coding was more accurate during trial periods compared to inter-trial periods and, while ordinal position was reliably decoded throughout the entire sequence, it was strongest for the first and last positions in the sequence. Finally, to disambiguate odor from ordinal coding, we decoded the activity during "out of sequence" trials, in which odors were presented at an incorrect ordinal position (e.g. odor B in position 4). We found that ordinal position was more strongly decoded than the

odor identity throughout these trials. These findings suggest that the prefrontal cortex supports the temporal organization of memory by preferentially representing the ordinal position of sequential events.

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Poster

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IOS-1150292
BCS-1439267
2010-05-84

Title: The sequential organization of hippocampal ensemble activity provides a key temporal signal supporting the memory for the order of events

Authors: *M. SARAF[1], D. HAGHVERDIAN[2], K. COOPER[1], G. ELIAS[1], B. SHAHBABA[2,3], F. NORBERT[1];
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Abstract: The hippocampus is critical to the temporal organization of our experiences. Although this fundamental capacity is conserved across modalities and species, its underlying neuronal mechanisms remain unclear. Previous studies found that hippocampal ensemble activity exhibits sequential firing fields during the presentation of individual stimuli or inter-stimulus intervals (i.e., “time cells”). Although this type of activity has been shown to provide a strong temporal signal within such task events, it remains unclear whether it supports the temporal organization of event sequences. To address this important issue, we recorded CA1 ensemble activity as rats performed a nonspatial sequence memory task. Briefly, the task involved repeated presentations of a sequence of five odors, and rats had to determine whether each odor was presented in the correct order to receive a water reward. We adapted a Bayesian algorithm to quantify the degree of temporal information contained in the spiking activity of simultaneously recorded neuronal ensembles. Consistent with previous reports, we found that hippocampal ensembles provided significant temporal information not just during inter-stimulus intervals, but also during individual stimulus presentations. Importantly, we discovered that this temporal organization was primarily stimulus-specific, reflected sequential relationships among stimuli through a lag effect, and was stronger on correct than incorrect order judgments. We also report that this temporal coding extended across the full sequence of stimuli unfolding over several seconds. Collectively, these findings offer compelling evidence that the sequential organization of hippocampal ensemble activity provides a key temporal signal supporting our ability to remember the order of events within a sequence.

Ongoing analyses are examining whether this form of temporal coding was also present in a compressed form during sharp wave ripple (SWR) events observed during inter-stimulus intervals.

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Poster

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Title: Hippocampal ensembles represent the sequential order of nonspatial events

Authors: *K. W. COOPER[1], L. LI[2], M. P. SARAF[1], G. A. ELIAS[1], P. BALDI[3], B. SHAHBABA[2], N. J. FORTIN[1];
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Abstract: The hippocampus is critical for our ability to remember the sequence of daily life events. Although this capacity is conserved across species and modalities, its underlying neural mechanisms remain unclear. Considerable data from spatial exploration paradigms in rodents indicates that capturing the sequential nature of trajectories is a fundamental coding property of hippocampal neurons. This view is supported by evidence that hippocampal activity can represent sequences of past, present, and future spatial locations during running or a pause at a decision point. To determine whether this function extends beyond the processing of spatial information, we recorded hippocampal activity as rats performed a challenging odor sequence memory task, wherein they had to correctly identify whether each item was presented in the correct sequence position. Using novel statistical decoding methods that account for the graded nature of odor coding in the hippocampus, we quantified the information contained in the activity of simultaneously recorded hippocampal ensembles during odor presentations. To maximize decoding accuracy, we first used a convolutional neural network model and found that, within individual odor presentations, hippocampal ensembles reliably reactivated the sequence of odors experienced. To decode neural activity during specific theta cycles within odor presentations, we then used a logistic regression model, which had better temporal resolution but weaker decoding accuracy. We found that information about past, present and future stimuli was compressed within individual theta cycles, and that this sequential information was linked to the accuracy of order judgments and flexibly incorporated trial-specific contingencies. Finally, at the level of individual neurons, we found a significant proportion of

neurons that exhibited phase precession during odor presentations, as well as neurons that tended to fire in a specific sequence within theta oscillations. Collectively, these results suggest a fundamental function of the hippocampus is to encode, preserve, and predict the sequential order of experience across modalities.

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Poster

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Program #/Poster #: P858.04

Topic: H.08. Learning and Memory

Support: 5R01MH100121-09

Title: Neural representations of temporal schemas in hippocampus and precuneus predict schema-based reasoning

Authors: *N. W. MORTON[1], A. PUDHIYIDATH[1], R. VIVEROS DURAN[1], A. C. SCHAPIRO[2], I. MOMENNEJAD[3], D. M. HINOJOSA-ROWLAND[1], R. J. MOLITOR[4], A. R. PRESTON[5];
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Abstract: Schemas capture patterns across multiple experiences, accumulating information about common event structures that guide decision making in new contexts. Previous behavioral work suggests that schematic knowledge based on the temporal regularities of events affects reasoning about non-temporal properties of event elements. Using fMRI, we measured neural representations of temporal schemas and examined how these representations relate to reasoning behavior. Participants were presented with object sequences that were generated from an underlying temporal community structure and were then asked to make inferences about properties of the objects. Temporal schema representations in perirhinal cortex predicted the subjective similarity of the objects, suggesting that high-level object representations are shaped by temporal schema learning. Furthermore, we found that temporal schemas also affected reasoning about non-temporal properties; participants were more likely to infer that objects in the same temporal community were associated with the same environment. We contrasted different models of schema-mediated reasoning behavior and found that reasoning is influenced by both abstract knowledge of temporal schemas (i.e., whether two objects were associated with the same community or a different community) and detailed knowledge of temporal statistics, as simulated based on a successor representation model of statistical learning. We found that the fidelity of temporal schema representations in hippocampus and precuenus predicted the degree to which temporal schemas affected reasoning behavior. Our results suggest that temporal schemas are represented at multiple levels of abstraction, and that hippocampus and precuneus may support reasoning based on these temporal schemas.

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Poster

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Topic: H.08. Learning and Memory

Support: R21MH120798

Title: Quantifying individual differences in latent-cause inference

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Abstract: Every day, humans are subject to a combination of new and familiar experiences, in the face of which we need to behave appropriately. To do this, we must continuously trade off learning new things with generalizing from prior knowledge. This problem can be solved optimally through inferring the latent causal structure of the environment, so that we can generalize appropriately across experiences that we infer to originate from the same cause. Failure in this process could underlie psychopathological deficits in generalization, such as the tendency to form new, idiosyncratic beliefs based on little evidence, characteristic of schizotypy. Latent-cause inference has been shown to support a wide array of cognitive processes, from fundamental learning and memory to social judgements. Computationally, this process can be parametrized in a formal Bayesian model with three parameters: how likely it is that a new cause occurs (concentration), how variable are the events that a cause tends to create (size prior), and how long each cause is active (decay rate). Designing a task that allows confidently estimating these parameters at the individual level is crucial for mapping psychopathology dimensions such as schizotypy onto the latent-cause inference process. Here, we developed such a task, in which participants are shown ambiguous stimuli resembling microbes, which they need to cluster according to two perceptual features (the length and number of spikes on the microbe). Across three studies conducted online (N = 187 after quality filtering), we found that participants vary widely in their clustering behavior, forming anywhere between 2 and 22 clusters spanning variable portions of the perceptual space. We estimated model parameters using hierarchical fitting, and saw that these correlate in a meaningful way to task behavior - for example, a higher decay rate was associated with fewer assignments to old clusters, suggesting a higher turnover of latent causes ($r_s < -0.6$, $p < 0.001$ in all studies). In addition, we performed parameter recovery, by simulating behavior using the estimated parameter values and fitting the model to this simulated data, and found strong correlations between actual and recovered values ($r_s > 0.9$, $p < 0.001$ for all parameters). Lastly, we found that latent-cause inference models provide a superior fit to the task behavior compared to other classes of models such as reinforcement learning. Overall, our task successfully captures the latent-cause inference process and allows quantifying individual differences in

model parameters, being therefore well-suited for both computational psychiatry and neuroimaging studies of latent-cause inference.

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Poster

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Topic: H.08. Learning and Memory

Support: R01DA042065
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NSF REU #1757554

Title: Towards examining event segmentation in mental disorders

Authors: *N. WOLF[1], L. BEUGELSDYK[2], D.-M. MIREA[3], Y. NIV[4], O. BEIN[3];
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Abstract: Event segmentation theories posit that continuous experience is segmented into discrete events when changes in context occur. These changes, termed event boundaries, lead to ending one event representation in our mind and starting a new one. Event segmentation seems to be a fundamental process in perception and cognition, underlying our ability to make sense of our experiences. Chunking our experiences inappropriately can lead to incoherent representations of our external world and impair everyday functioning, and is potentially at the heart of some mental disorders. We therefore adapted an event-segmentation paradigm to examine event segmentation in mental disorders. Previous research has shown that response times are slower at event boundaries, and can be interpreted as a marker of event segmentation. For example, when reading naturalistic stories, reading times are longer for sentences that include an event boundary compared to sentences that do not include a boundary (non-boundary sentences). Here, participants read stories of everyday life events online while their reading times were recorded. In Study 1 (N=25), we replicated the boundary effect: reading times were longer for boundary compared to non-boundary sentences. Next, to understand individual differences, we estimated the relative boundary effect per participant, and examined its stability. Split-half reliability analysis found that, across participants, the magnitude of the boundary effect in the first half of the experiment significantly correlated with the magnitude in the second half, indicating that the boundary effect was stable across the two halves of the study. This suggests that individual differences in the magnitude of the boundary effect are meaningful. In Study 2, we used a novel approach: rather than comparing between separate boundary and non-boundary sentences, we used identical boundary and non-boundary sentences, counterbalanced across groups of participants, as well as structurally similar boundary and non-boundary sentences within participants. The goal was to ensure that differences in the magnitude of the boundary effect across individuals would reflect differences in event segmentation rather than differences in processing of the sentences themselves. Analyses focused on validating this set of stories, as well as

correlating the boundary effect with self-report measures of mental disorder symptoms. Together, these studies aim to examine implicit event segmentation in populations with clinical and subclinical mental health impairments such as anxiety, depression, schizotypy, and ADHD.

Disclosures: N. Wolf: None. **L. Beugelsdyk:** None. **D. Mirea:** None. **Y. Niv:** None. **O. Bein:** None.

Poster

P858. Timing and Temporal Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P858.07

Topic: H.08. Learning and Memory

Title: What happens next: Complementary time-resolved neural signal of temporal expectations in hippocampus and cortex

Authors: *V. VAN DE VEN, B. LI, P. DE WEERD;
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Abstract: Using functional magnetic resonance imaging study, we provide evidence for complementary spatiotemporal neural representations in hippocampal and visual cortical areas that are associated with when visual events are expected to appear. The human brain learns temporal structure from experiences to predict what will happen when. We investigated the evolution of neural representations of audio-visual temporal expectations across different multi-second delays. During 3 Tesla fMRI, participants (N=20) learned to uniquely associate each of three different auditory cues with one of three delays (3s, 6s or 9s) and subsequent visual outcomes (faces, scenes or objects). For audio-visual pairs with 3s and 6s delays, participants also saw "catch trials" in which the expected visual class was never shown over a 9s delay (for which the 9s audio-visual pairs acted as baseline condition). Using time-resolved support vector machine (SVM) multivariate pattern analyses (MVPA), we analysed at which moment during the delay the hippocampus and visual cortex represented the cue-dependent expected visual classes during catch trials. We found that MVPA classification accuracy (3s vs. 9s; 6s vs. 9s) of catch trials in hippocampal CA1 and visual cortex was highest ($p<0.001$, permutation test) across the delay at the moment that the visual classes were expected to appear. Further, spatiotemporal patterns for visual classes could be classified in CA1 (3s vs. 6s; $p < 0.01$) but not in visual cortex. Higher CA1 classification accuracy correlated with faster task response times, suggesting behavioral relevance of the spatiotemporal hippocampal representations in temporal expectancy. Finally, we aimed to describe the spatiotemporal nature of the representations in CA1 and visual cortex, for which we developed new MVPA approaches. We found that CA1 representations included a sequence of non-overlapping voxel sets with peak classification accuracy for different moments during the delay, while visual cortical patterns became more similar to the expected visual classes as delay time progressed (prospective coding). Our findings reveal that temporal expectancy of "what will happen when" includes the time-resolved integration of complementary representations in hippocampus and cortex.

Disclosures: V. van de Ven: None. **B. Li:** None. **P. De Weerd:** None.

Poster

P858. Timing and Temporal Processing II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P858.08

Topic: H.08. Learning and Memory

Title: Multimodal Temporal Pattern Discrimination in Awake-Behaving Mice

Authors: *S. POST[1], C. CARLAN[1], O. ABU-WISHAH[2], S. ALI[3], A. GOEL[4];
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Abstract: Multimodal Temporal Pattern Discrimination in Awake-Behaving Mice
Sam Post, Craig Carlan, Anubhuti Goel
Timing is a critical ability across species, enabling judgment of whether to stop or go through a yellow light or when best to feint a predator. Timing behaviors involve perception and discrimination of intervals, prediction, and enaction of timed movements, all of which likely necessitate complex interactions between primary sensory cortices and downstream higher order areas. Here, we investigate discrimination of temporal intervals using a multimodal sensory guided task in which mice learn to discriminate between sequences of 4 synchronous visual and auditory stimuli. Each stimulus's duration within the set is either 200 ms (preferred) or 900 ms (nonpreferred). A water reward, associated with the preferred condition, is dispensed at 1.2 to 1.4 s, and a time out period of 6.5 s is given if the mouse incorrectly responds. Following learning, we then test the mice on a unimodal paradigm to determine if there is transference of learning between stimulus modalities.
Using a discriminability index to determine performance, we find that there is robust learning in the multimodal task and moderate transference of learning to a visual-only version of the task. We find that with improved performance across sessions, mice's lick rates and the variability of their lick rates immediately preceding reward and punish windows correlate with correct and incorrect responses. Prior to learning, there is little difference in lick rates classified by response type. With learning however, correct rejection lick rates slightly depress prior to the reward window and substantially depress prior to the punishment window; false alarm lick rates do not consistently depress at either interval and display less variability across the trial period.
These licking trends are reliably observed in the multimodal and unimodal paradigms and indicate that mice indeed learn to time reward and punishment windows in dependence on stimuli and discrimination of them. We hypothesize that mice discriminate the two conditions via intrinsic mechanisms in which neural networks encode temporal information locally. At present we are using in-vivo 2 photon calcium imaging in primary visual cortex (V1) layer 2/3 to test this hypothesis. Our previous in-vitro work shows that cortical networks are capable of 'learning' to time by broadly disinhibiting the network at learned intervals. We expect to find similar mechanisms in V1 in mice in which an increased excitation-inhibition ratio is temporally coordinated with reward and punishment windows following learning.

Disclosures: S. Post: None. **C. Carlan:** None. **A. Goel:** None.

Poster

P858. Timing and Temporal Processing II

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Program #/Poster #: P858.09

Topic: H.08. Learning and Memory

Support: NIH Grant 3R01NS114405-01S2
NIH Grant T32-NS007421

Title: Neural circuitry of time orientation: a lesion study

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Abstract: What time is it? We are frequently called upon to compare our internal representation of time against a common reference. Assessing orientation to time is a cornerstone of neurological and psychiatric mental status exams. Focal brain damage can disrupt this ability, but the underlying circuitry supporting time orientation is unclear. In this study, we sought to localize the most critical neuroanatomical substrates of time orientation based on impairments following focal, acquired brain damage. We used behavioral and neuroimaging data from the Iowa Neurological Patient Registry. Registry patients are screened for premorbid psychopathlogy, significant medical history, and neurodegenerative disease prior to enrollment. We used the Benton Temporal Orientation Scale (BTOS) to assess time orientation in N=132 ($n_{impaired}$=33) neurological patients with focal, stable brain lesions from the Iowa Neurological Patient Registry. Assessments were performed 3 months or more after lesion onset. We used proportional subtraction to compare the relative frequency of lesions at each voxel in patients with time disorientation and in brain damage comparisons who are temporally oriented. Scores of 5 or more were considered impaired for time orientation, which corresponds with errors in identifying the year, the month, and/or multiple durations of time including the day of the month, day of the week, and/or time of day. We found that damage to the hippocampus bilaterally, left fusiform gyrus, left parahippocampal gyrus, and right ventromedial prefrontal cortex was associated with impaired performance. Then, we created 5mm spherical regions of interest (ROIs) around peak clusters in the proportional subtraction statistical map to seed a structural lesion network mapping (sLNM) analysis. sLNM uses white matter tractography data from healthy adults to identify tracts connecting lesion-derived seeds with other brain areas. This analysis implicated lesions of the left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, forceps minor, right cingulum, and right anterior thalamic tract in association with time disorientation. Taken together, we conclude that impaired time orientation is associated with damage to the temporal lobe and ventromedial prefrontal cortex, regions in the default mode network (DMN). This evidence derived from patients with focal, acquired brain lesions supports prior literature implicating the hippocampus and DMN in time orientation and extends this literature by showing that patients with DMN lesions are at a higher risk of time disorientation following brain injury.

Disclosures: J.D. Skye: None. **A.D. Boes:** None. **D. Tranel:** None.

Poster

P867. Place Cells II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P867.01

Topic: H.09. Spatial Navigation

Support: NSF Grant 1703340

Title: Spatial Navigation to Unrewarded and Unmarked Goal Locations

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Abstract: The CA1 region of the hippocampus encodes locations and rewards using place cells and reward cells. We studied the roles of auditory and visual cues on the rats' ability to learn unmarked (no marked boundary) positive and unmarked (no boundary, small mark on the floor) negative zones on an open field arena. When the rat entered the positive zone, it was rewarded at a random feeder along the circumference of the arena, away from the zone. For negative zones, rather than actively punishing the rat, we used reward withdrawal to avoid fear and stress which are known to significantly depend on non-hippocampal structures such as the amygdala. When the rat entered the negative zone, the feeder that was cued was de-activated and a 10-second delay was initiated before another reward location became active. When auditory cues were used, distinctive sounds were played when the rat entered the positive or negative zone. The experiments consisted of four conditions: positive zone only; negative zone only; positive zone then halfway through the experiment, the area switched to becoming a negative zone; and simultaneous positive and negative areas at different locations on the maze. When visual cues were used, each experimental session was divided into two halves; learning and manipulation. During learning, a local cue on the arena wall and a distal cue on the curtain surrounding the arena were on the side closest to the zone. Three manipulations were tested: the cues and the zone moved together to a new location in the arena, the cues moved but the zone remained unchanged, or the zone moved and the cues remained unchanged.
Behaviorally, we found that the rats quickly learned to enter the positive zone and receive a subsequent reward elsewhere on the maze. They also learned to avoid the negative zone by adjusting their trajectories. In the visually cued experiments, rats were able to navigate more accurately into the positive zone and avoid the negative zone when the cues and zone moved together, but less so when the cues and zone were moved separately. These results show that pairing the zone and distal cues had a significant effect on the rats' behavior. Pilot tetrode recordings in CA1 of the dorsal hippocampus during the auditory cue experiment showed place fields accumulation around the reward locations and near the positive and negative zones. We also observed place field remapping in response to manipulations, and significant changes in their firing rate, especially in the consecutive positive-negative conditions.

Disclosures: J.R. Wieland: None. **B. Gerken:** None. **J. Fellous:** None.

Poster

P867. Place Cells II

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Program #/Poster #: P867.02

Topic: H.09. Spatial Navigation

Support: #DGE1746891
R01 NS039456

Title: Place Field Repetition in Hippocampal CA1 in a Novel City-block Maze

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Abstract: The mammalian brain solves the problem of navigation via a distributed network of regions centered on the medial temporal lobe, supported by the spatially selective firing properties of place cells of the hippocampus. Place field firing activity is known to be affected by variables related to movement and trajectory (Markus et al., 1995; Wood et al., 2000; Frank et al., 2000; Ferbinteanu et al., 2003) as well as the border configuration around the place field (Skaggs and McNaughton, 1998; Barry and Burgess et al., 2007). Further, in environments with repeating structural motifs, place cells have been observed with repeating fields at many or all of the analogous regions (Spiers et al., 2015; Grieves et al., 2016; Cowan and Nitz, 2014). However, many of these apparatuses featured a limited number of repeated regions and restricted behavior to access such regions. To explore whether and how place fields exhibit repetition in a more complicated environment, tetrode recordings were taken from CA1 as rats navigated a city-block maze consisting of rectilinear passageways arranged in a grid. Place fields with single fields were observed, as expected, as well as cells with repeating fields. Across 11 days of recording from four animals, an average of 41.9% of cells (+/- 20.1%) exhibited place field repetition, defined has having two or more fields in geometrically similar locations. Within six of these days, the number of repeating cells was significant (6/11 days with significant amount of repetition, $p < 5.8*10^{-6}$). Repeating place fields were typically observed in alleys sharing a common orientation, consistent with earlier findings on the role of head direction on repeating firing fields (Harland et al., 2017). Further, repetition within each cell was not observed in all maze locations that shared a common geometry, but was gated by a particular region of the maze, suggesting a role for global, allocentric inputs on the firing. These data show that place field repetition can be observed in complex environments in which the animal can take a variety of routes through each field.

Disclosures: W. Hockeimer: None. **R. Lai:** None. **J.J. Knierim:** None.

Poster

P867. Place Cells II

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Topic: H.09. Spatial Navigation

Support: NIH grant R01 MH083809

Title: A comparison of spatial and contextual coding in the hippocampus and retrosplenial cortex.

Authors: *D. SUBRAMANIAN, Z. HE, A. M. P. MILLER, D. M. SMITH;
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Abstract: The hippocampus (HPC) and retrosplenial cortex (RSC) are involved in spatial navigation and context coding, but they appear to encode this information differently. For example, CA1 neurons exhibit compact place fields while RSC neurons fire reliably at higher rates across wide areas of the environment. Recently, we discovered that RSC neurons exhibit a rate code for the context, even without spatial specificity (Miller et al, 2021, Cerebral Cortex, 31). We examined the mechanisms of spatial/contextual coding by analysing individual neuronal responses and population level activity patterns of neurons in dorsal CA1 and the granular b subregion of RSC while the rats (n=7) foraged in two different contexts - black and white square boxes. To characterize the spatial encoding of the context, we computed pixel-by-pixel spatial correlation for each neuron as a measure of the similarity of spatial firing patterns across trials. The spatial firing patterns were more similar for visits to the same context than for visits to different contexts in both regions. However, this difference was greater in the HPC than in the RSC. Specifically, the spatial firing patterns were more similar for visits to the same context and more distinct across visits to different contexts in the HPC as compared to RSC. We also used a decoding approach in which we predicted the rat's location based on population level spatial firing patterns and found that decoding success was greater in the HPC. Thus, spatial firing patterns in the HPC distinguished the contexts better than spatial firing patterns in the RSC. In contrast, the RSC was better at differentiating contexts via rate coding. We used a population level decoding approach where we repeatedly sampled the firing rates of all the neurons (250 msec bins) and classified which context they were drawn from. Again, firing rates in both regions clearly distinguished the two contexts. However, classification accuracy was higher in the RSC as compared to HPC. We also compared various firing characteristics in both regions and found that HPC firing was sparse while RSC firing was more distributed. We also used a Linear-Nonlinear (LN) model (Hardcastle et al, 2017, Neuron, 94) to examine which variables were encoded by the neurons. Both regions encoded several navigation-related and contextual variables simultaneously (multiplexing), but head direction was more prominently encoded in the RSC. These results suggest that in an open field, the HPC preferentially employs a sparse spatial coding mechanism for distinguishing contexts while the RSC preferentially employs a more distributed rate coding mechanism which includes egocentric head direction information.

Disclosures: D. Subramanian: None. **Z. He:** None. **A.M.P. Miller:** None. **D.M. Smith:** None.

Poster

P867. Place Cells II

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Program #/Poster #: P867.04

Topic: H.09. Spatial Navigation

Support: NSF STC award CCF-1231216

Title: Animal-to-animal variability in hippocampal context identification

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Abstract: Hippocampal place cells represent an animals' environment. When animals are moved to a different context, hippocampal place cells change their spatial response patterns, known as hippocampal remapping. However, there is variability in the extent of hippocampal response change across animals when presented with the same experiences. In this work, we analyzed electrophysiological recordings from Alme et al., 2014, in which five rats were exposed to 11 different environments. To compare the hippocampal maps in two rooms, we computed average rate map correlation coefficients. We found that many place cells remap in repeated rooms. Furthermore, we discovered that the heterogeneity in animals' remapping behavior is structured: some animals consistently remap to a greater extent in response to a variety of contextual changes, whereas other animals consistently remap to a lesser extent. In summary, our findings emphasize the role that animal-specific factors play in hippocampal context identification.

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Poster

P867. Place Cells II

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Topic: H.09. Spatial Navigation

Support: NIH Grant R01 NS102537
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JHU Kavli Postdoctoral Distinguished Fellowship

Title: Neural closed-loop manipulation of place cell firing in rodents using optic flow cues

Authors: *B. LI[1], M. S. MADHAV[6,7], R. P. JAYAKUMAR[2,3,4], F. SAVELLI[8], K. WRIGHT[3], J. J. KNIERIM[3,5], N. J. COWAN[4,2];
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Abstract: Place cells are neurons in the mammalian hippocampus that fire when the animal is in a particular location in the environment. This activity involves integrating self-motion information over time (path integration), combined with landmark information. Optic flow is often proposed to be an important idiothetic cue for path integration (Sharp et al, 1995; Wiener et al, 2013; Mao et al, 2020), but the ability of optic flow to control the firing locations of hippocampal place cells has not been directly demonstrated. Previous work in our lab (Jayakumar et al, 2019) has shown that place fields in rats remain locked to a set of reliable landmarks even when the landmarks are moved as a function (experimental gain) of the rat's velocity. Here we show that place cell activity can be similarly controlled using optic-flow cues.
We trained rats to run on a circular track placed in the center of a virtual reality dome. During running, we

projected a set of 80 uniformly spaced, vertical stripes onto the interior of the dome. These stripes were designed to create a non-polarizing optic-flow cue. We moved the stripes at an experimental gain either >1 or <1, creating the illusion of running faster or slower, respectively, relative to the optic flow pattern. We recorded place cells from CA1 during each session. In 5 rats, the experimental gain manipulation was predetermined (open-loop trials). We found that the place fields drifted around the circular track with respect to the laboratory even when the stripes were stationary, likely due to accumulated error from path integration in the absence of landmarks. In the majority of experiments, the rate of drift increased or decreased in response to >1 or <1 experimental gain values, respectively, showing that optic flow influences path integration and the firing locations of place cells.
To further demonstrate the strength of this influence, we placed 4 of the rats under neural closed-loop control, modifying the speed of the stripe pattern in real time based on CA1 place cell activity. Using a decoding algorithm, we estimated the rate of place field drift in real time and fed this into a novel feedback control system that adjusted the experimental gain of the stripes so as to drive the hippocampal drift rate towards a desired setpoint. Using this feedback control loop, we achieved more robust control over the activity of place fields, successfully maintaining the desired drift rate over extended periods of time with only optic flow manipulations in a majority of sessions. These results demonstrate that optic flow can exert powerful control over the hippocampal cognitive map and confirm its hypothesized role as a major idiothetic cue for path integration in mammals.

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Poster

P867. Place Cells II

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Program #/Poster #: P867.06

Topic: H.08. Learning and Memory

Support: NICDS grant P01HD080679

Title: Dorsal hippocampus retrieves category representations in rats

Authors: *M. BROSCHARD[1], J. KIM[2], B. C. LOVE[3], J. H. FREEMAN[2];
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Abstract: Categorization is an essential process that organizes experiences according to perceptual similarity. Recent neuroimaging experiments suggest that the hippocampus plays a central role in category learning by building and storing category representations. This is supported by *in vivo* studies demonstrating that single units in the hippocampus track changes along non-spatial feature spaces. In the current experiment, we assessed the role of the rat dorsal hippocampus in storing category representations through inhibitory DREADDs and computational modeling. Using a touchscreen apparatus, rats were trained to categorize distributions of artificial stimuli containing black and white gratings that varied along two continuous dimensions (i.e., spatial frequency and orientation). For some rats, categorizing the

stimuli required selective attention to a single stimulus dimension (i.e., 1D task). For other rats, categorizing the stimuli required attention to both dimensions (i.e., 2D tasks). Inactivating the hippocampus impaired learning for both 1D and 2D tasks but had no effect on a control discrimination task with the same trial structure as the categorization tasks. We then fit the neural network model SUSTAIN (Supervised and Unsupervised STratified Adaptive Incremental Network) to the learning data to examine the role of the hippocampus in storing category representations. Model simulations suggest that the hippocampus uses pattern completion mechanisms to retrieve relevant category representations to make category decisions.

Disclosures: M. Broschard: None. **J. Kim:** None. **B.C. Love:** None. **J.H. Freeman:** None.

Poster

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Topic: H.09. Spatial Navigation

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NIMH award 1R56MH125655-01
Nudelman Foundation Women in Neuroscience Summer Fellowships

Title: Testing for Odor Discrimination and Habituation in a rat model of Fragile X Syndrome

Authors: *D. OKWUBODU[1,2], D. ASHADE[1,2], E. ROBSON[1,2], U. SALEEM[1,2], S. KIM[1,2], L. L. COLGIN[1,2,3];
[1]Ctr. for Learning and Memory, [2]Dept. of Neurosci., [3]Inst. for Neurosci., The Univ. of Texas at Austin, Austin, TX

Abstract: Fragile X Syndrome is the most common monogenetic cause of autism spectrum disorders. A common symptom of autism spectrum disorders is impaired social interactions, and CA2 is a subregion of the hippocampus that is thought to play a key role in social cognition. The principal neurons of the hippocampus are place cells, neurons that have receptive fields for particular locations in space. Previously published research showed that place cell firing patterns in CA2, a hippocampal subregion hypothesized to be important for social memory, changed in response to social experiences (Alexander et al., *Nature Communications* 2016). Our preliminary data indicate that CA2 place cells responded specifically to the olfactory component of social stimuli (Mably et al., *SfN abstracts* 2018). Preliminary data also suggest that CA2 place cell responses to social odors were absent in a rat model of Fragile X syndrome (Fmr1 knockout rats, or "FXS rats") (Robson et al. *SfN abstracts* 2019). Here, we aimed to determine whether the lack of CA2 place cell responses to social odors in FXS rats was due to dysfunctional olfaction. Olfactory habituation and dishabituation tests were performed to determine whether FXS rats detected and discriminated odors as well as age-matched wildtype control rats. Preliminary results suggest that FXS rats habituated to social and non-social odors presented across sessions and were able to discriminate between different social and non-social odors. However, preliminary results suggest that FXS rats explored social stimuli, but not non-social stimuli, less than

wildtype rats. This pattern of results suggests that deficient CA2 place cell responses to social odors in FXS rats are not explained by deficits in basic olfactory function but may be related to impaired social behaviors.

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Poster

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Program #/Poster #: P867.08

Topic: H.09. Spatial Navigation

Support: DOD CDMRP award W81XWH1810314
NIMH award 1R56MH125655-01

Title: Investigating awake replay in a rat model of Fragile X Syndrome

Authors: *M. M. DONAHUE[1,2], E. ROBSON[1,3], L. L. COLGIN[1,2,3];
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Abstract: Fragile X Syndrome (FXS) is a neurodevelopmental disorder that can cause impairments in spatial cognition. The hippocampus is thought to support spatial cognitive functions through the activity of place cells, neurons that fire selectively in particular regions of space. The reactivation or "replay" of previously active place cell sequences during sharp wave-ripples (SWRs) is believed to be important for spatial memory-guided planning and spatial memory consolidation. Previous research has shown that SWRs are abnormal in a mouse model of FXS (Boone et al. 2018), but to our knowledge the replay of place cell sequences during SWRs has not been examined in a rodent model of FXS. Here, we examined whether SWR-associated replay was impaired in preliminary data from a rat model of FXS (*Fmr1* knock-out rats or "FXS rats"). We recorded CA1 place cells in FXS rats and wildtype (WT) control rats during unidirectional running on a circular track and subsequent waking rest periods. We then used a Bayesian decoding algorithm to estimate angular positions on the circle track represented by ensembles of CA1 place cells during replay events. Our preliminary results suggest that replay fidelity was similar between WT and FXS rats. However, the temporal compression of sequences of locations represented during replay events was observed to be lower in preliminary data from FXS rats. Additionally, preliminary results suggest that FXS rats had a higher proportion of reverse replay events than WT rats. These results raise the possibility that impairments in SWR-associated replay contribute to aberrant spatial cognitive functions in FXS.

Disclosures: M.M. Donahue: None. **E. Robson:** None. **L.L. Colgin:** None.

Poster

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NIMH award 1R56MH125655-01

Title: The effects of social and neutral odors on hippocampal place cell activity

Authors: E. ROBSON[1,2], A. J. MABLY[1,2], L. T. HEWITT[1,3], P. DEMETROVICH[1,3], M. M. DONAHUE[1,3], L. L. COLGIN[1,2,3];
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Abstract: The hippocampus is important for spatial learning and memory. Hippocampal place cells receive sensory information from internal and external sources to form a representation of space by localizing their firing to specific locations of an environment ("place fields"). We and our colleagues previously reported that place cells in the CA2 region of the rat hippocampus change their firing patterns ("remap") after a social interaction with a familiar conspecific (Alexander et al., *Nature Communications* 2016). Further experiments have suggested that CA2 place cells remap specifically to the olfactory content of the social experience (Mably et al., *SfN abstract* 2018). Here, our preliminary data show that while CA2 place cells respond to social odors they do not respond to non-social, or neutral, odors. A differential pattern of results was observed for preliminary data from CA3, with CA3 place cells responding to neutral, but not social, odors. Moreover, CA1 place cell activity seemed unaffected by both neutral and social odors. These data suggest that social and non-social olfactory stimuli are processed differently by different hippocampal subregions. Insights gained from our ongoing studies may aid the understanding of disorders associated with specific sensory processing and integration deficits, and impaired social behaviors, such as Fragile X syndrome.

Disclosures: E. Robson: None. **A.J. Mably:** None. **L.T. Hewitt:** None. **P. Demetrovich:** None. **M.M. Donahue:** None. **L.L. Colgin:** None.

Poster

P867. Place Cells II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P867.10

Topic: H.09. Spatial Navigation

Support: Mrs Anne Uren and the Michael Uren Foundation
Alzheimer's Research UK ARUK-NC2019-IMP
BBSRC BB/R022437/1

China Scholarship Council (No.201906100047)

Title: Hippocampal neuronal firing in the air-lifted T-maze alternation task

Authors: *Y. LI, M. A. GO, S. V. PRADO, S. R. SCHULTZ;
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Abstract: The hippocampus is essential for spatial working memory. The continuous T-maze alternation task is widely used for assessing short-term spatial working memory in rodents. Behavioral performance and recording of hippocampal neuronal firing under head-fixation during the T-maze alternation task in the real-world environment has however not been demonstrated to date. Here we present the assessment of spatial working memory while imaging hippocampal CA1 neurons by two-photon calcium imaging in an air-lifted T maze in head-fixed mice. Methods: We injected AAV-jGCaMP7s into hippocampal CA1 subregion (pyramidal layer) in the mouse (Chat-ires-Cre, male, 3-4 months, N=4), then implanted a glass craniotomy imaging window by aspirating cortex above the injection site. A metal head-plate was glued to the skull. Animals were allowed to recover for at least one week after surgeries. Water restriction was used to motivate animals navigation and learning in the maze. Animals were trained under head-fixation in the air-lifted T maze cage for 2 sessions daily on 8-12 consecutive days. Animals were started running from the stem arm and allowed to choose one of reward arms for the first trial. In subsequent trials, rewards were only given when animals entered the goal arm opposite to the arm visited on the previous trial. After the mouse was well trained (the percentage of alternation is above 70% in consecutive 3 training sessions), we employed two-photon microscopy to record hippocampal CA1 neurons activities via calcium imaging when the head-fixed mouse was been testing in the floating T-maze. Calcium imaging videos were processed by motion correction and ROI segmentation via CalmAn. Results: Head-fixed mice can be well-trained in the floating T maze for continuous alternation tasks after 15 sessions. We observed both hippocampal place cells encoding the reward location and the return arm. In addition, we analysed the alternation navigation into two trial types (right-left turn trials and left-right turn trials), finding trial type-specific firing hippocampal neurons (“splitter cells”) that were selectively active on the stem arm and strongly predicted the future path. Our results provide the first demonstration of hippocampal place cells and splitter cells representations in head-fixed mice performing alternation in the air-lifted T maze by combining two-photon calcium imaging.

Disclosures: Y. Li: None. **M.A. Go:** None. **S.V. Prado:** None. **S.R. Schultz:** None.

Poster

P867. Place Cells II

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P867.11

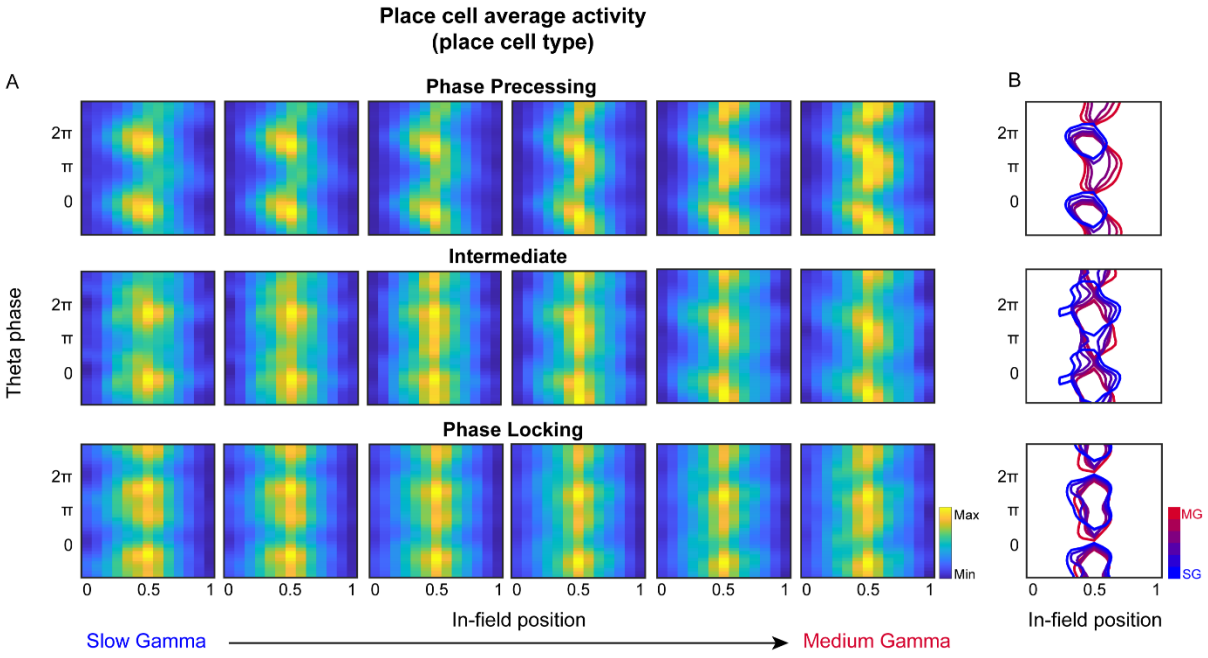
Topic: H.09. Spatial Navigation

Support: EU - ITN 62002873
EU - H2020 840704

Title: Time-varying gamma balance in CA1 distinguishes between differential spatial coding regimes

Authors: *M. GUARDAMAGNA, F. STELLA, F. P. BATTAGLIA;
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Abstract: In the CA1 subfield of the hippocampus, converging inputs at different layers provide complementary streams of information and independently shape the activity of local pyramidal cells (Colgin et al., 2009; Schomburg et al., 2014, Fernandez-Ruiz et al., 2016). Fine scale spike timing phenomena within this circuitry are found both at the single cell (phase precession) and population levels (theta sequences). To which extent these processes are related to each other and influenced by the same or different set of converging inputs remains still unknown.
Here we investigate the association of oscillations at distinct gamma frequency ranges with the appearance of phase precession and theta sequences in the CA1 place cells population. To this purpose, we take advantage of a new chronic implant device (the Hybrid Drive) combining linear silicon probe recordings with high density tetrode arrays in freely moving mice. We describe for the first time how phase precession selectively appears in a sub-population of CA1 place cells in association with dominant medium gamma (60-90 Hz) power from the stratum lacunosum moleculare (SLM) - Figure A-B. Conversely, theta sequences are increasingly present as the slow gamma (20-45 Hz) from the stratum radiatum (SR) becomes more dominant.
Our findings, indicating a substantial complementarity between phase precession and non-local coding in the hippocampus, point to the existence of functionally distinct collective-activity states in CA1. As CA1 pyramidal cells receive two anatomically segregated, excitatory inputs: the Schaffer collaterals, tagging the SR from CA3, and the perforant path tagging the SLM from the entorhinal cortex (EC Layer 3), we hypothesize that such states depend on the competition between these two inputs. Gamma oscillations, rooted in the layer-specificity of these inputs, would then reflect their instantaneous balance.



Disclosures: M. Guardamagna: None. **F. Stella:** None. **F.P. Battaglia:** None.

Poster

P867. Place Cells II

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Program #/Poster #: P867.12

Topic: H.09. Spatial Navigation

Support: NSF NeuroNex #1707408

Title: Hippocampal neural dynamics of spatial navigation in the Morris water maze

Authors: *R. RESHEF, M. SHAHI, D. AHARONI, P. GOLSHANI;
UCLA, Los Angeles, CA

Abstract: Learning and memory enables the organism to acquire, store, retrieve, and update knowledge of the world through experience as well as to use this knowledge to navigate through a myriad of stimuli to facilitate survival. Lesions or inactivation of the hippocampus impair the encoding and retrieval of spatial memories. Hippocampal place and head direction (HD) cells activity has long been proposed to be related to the representation of one's location in space and the heading direction in that space. Yet, how place and HD neuronal population dynamics change with spatial learning and how this activity drives navigation to a learned goal is poorly understood. To address these questions, using wire-free miniaturized microscopy of genetically encoded calcium indicator GCAMP7f**,** we imaged the activity of CA1 neurons during spatial learning of a target oriented two-dimensional navigational task, the Morris Water Maze - a gold standard task for spatial navigation. Using generalized linear models (GLM) we were able to disentangle the activity of place cells and HD cells in CA1 as animals navigate in the maze. Our results demonstrate that the tuning of space and HD cells becomes more selective as animals learn to navigate to the goal. As we were able to track the activity of cells across days, we also found that tuning selectivity of individual neurons increases. Thus, cells become more tuned to location and heading direction as learning continues. Future work will determine whether this increased selectivity in tuning is essential for learning.

Disclosures: R. Reshef: None. **M. Shahi:** None. **D. Aharoni:** None. **P. Golshani:** None.

Poster

P867. Place Cells II

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Program #/Poster #: P867.13

Topic: H.08. Learning and Memory

Title: Recognition and approximate reconstruction of exponentially many arbitrary patterns leading to a Content-Addressable Memory Continuum.

Authors: *S. SHARMA, S. CHANDRA, I. FIETE;
MIT, CAMBRIDGE, MA

Abstract: How does the hippocampus, vastly outnumbered by the number of potential patterns in cortical neurons, store memories of experiences encoded by cortex? It is assumed to act as an associative memory, but classical models such as the Hopfield network store and robustly recall only up to N arbitrary patterns in a network of size N. Recently proposed associative memory architectures enable robust reconstruction of an exponential number of patterns (Hillar & Tran, 2018; Chaudhuri & Fiete, 2019; Krotov & Hopfield, 2016); however, these networks involve biologically implausible assumptions about synapses (Krotov & Hopfield, 2016) or the amount of information recalled per pattern is small because they are highly structured (Hillar & Tran,2018; Chaudhuri & Fiete, 2019).
We construct an entorhinal-hippocampal (EC-HC) attractor network using the theme of modular input structures with random feedforward EC-HC projections and associatively learned return weights that exhibits exponentially many robust (large-basin) fixed points. Training the HC to EC weights (hebbian learning) over only a small subset of contiguous grid cell states results in the formation of a large number of additional HC fixed points with large basins that can be reconstructed robustly from unseen grid cell states. In other words, these untrained hippocampal patterns can be robustly reconstructed in the presence of large amounts of noise from grid inputs. Further, the addition of hetero-associative recurrent synapses within HC leads to learning of the grid state transition matrix and the potential for high-capacity sequence memory.
Because place cells construct conjunctions between sensory experience and abstract spatial coordinates (Manns & Eichenbaum, 2006), we add a sensory input stream to HC. The combination of structured and unstructured inputs enables storage and robust recollection of a large number of arbitrary sensory patterns from partial cues. This allows us to span a content-addressable memory continuum with varying degrees of recovered information that depends on the number of stored patterns, with complete recovery of a small number of patterns (recall) and partial recovery (recognition) for an exponentially large number of patterns. Thus, our proposed model supports high-capacity associative memory, essential for interference-free episodic memory and spatial learning across time.

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Poster

P935. Probe Design and Engineering: New Recording Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P935.01

Topic: I.04. Physiological Methods

Title: Atomically thin platinum ditelluride cortical neural probes

Authors: *D. KIREEV[1], G. JEANPIERRE[1], R. T. JAYANTH[1], S. HAN[5], Y. JUNG[5,6,7], S. R. SANTACRUZ[1,2,3], D. AKINWANDE[1,4];
[1]Dept. of Electrical and Computer Engin., [2]Dept. of Biomed. Engin., [3]Inst. for Neurosci., [4]Texas Materials Inst., The Univ. of Texas at Austin, Austin, TX; [5]NanoScience Technol. Ctr., [6]Dept. of Materials Sci. and Engin., [7]Dept. of Electrical and Computer Engin., Univ. of Central Florida, Orlando, FL

Abstract: Based on the decades of research progress in implantable electrodes, we recognize that three features make an effective implantable electrode material: high conductivity, low interface impedance,

and small thickness or softcore. Atomically thin two-dimensional (2D) materials are unique constructs that fit the application explicitly due to their intrinsic flexibility and tissue imperceptible thinness. In this work, we report on platinum ditelluride ($PtTe_2$) as the active material of choice. Unlike graphene and most other transition metal dichalcogenides, $PtTe_2$ is a highly metallic 2D material with superior conductivity properties and attractively low (~400°C) synthesis temperature. *In vitro* studies show that $PtTe_2$ exhibits superior interface capacitance and area-normalized impedance compared to gold and platinum. An ultrathin ~10 µm polyimide is used as a supporter for the $PtTe_2$ cortical probe where the $PtTe_2$ is thermally converted from the thin (~5 nm) Pt film pre-deposited on the polyimide. This $PtTe_2$ growth is performed at a low temperature of 400°C directly on the polyimide, making the probe fabrication easy and attractive. The resulting $PtTe_2$ is confirmed to be ~20 nm thick in a 2D multi-layered structure. the probe is passivated with another layer of a thin (~5 µm) polyimide yielding a stack of polyimide/$PtTe_2$/polyimide with 32 measurement sites with 200 µm pitch and 400 μm^2 electrode opening. *In vivo* studies are performed by acutely implanting the $PtTe_2$ cortical probe into the frontal eye fields (FEFs) in the left hemisphere of a rhesus macaque monkey using a guide tube and polyethylene glycol to acutely increase stiffness during penetration into neural tissue. We examine signal stability and signal-to-noise ratio (SNR) of the recorded local field potentials and single unit spiking activity across daily sessions. Recordings are compared with signals from standard metal (tungsten) microwire electrodes. The $PtTe_2$ cortical probe's conductive properties, low impedance, and thinness make it a desirable invasive electrode that will contribute to the next generation of soft, biocompatible electrodes.

Disclosures: D. Kireev: None. **G. Jeanpierre:** None. **R.T. Jayanth:** None. **S. Han:** None. **Y. Jung:** None. **S.R. Santacruz:** None. **D. Akinwande:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P935.02

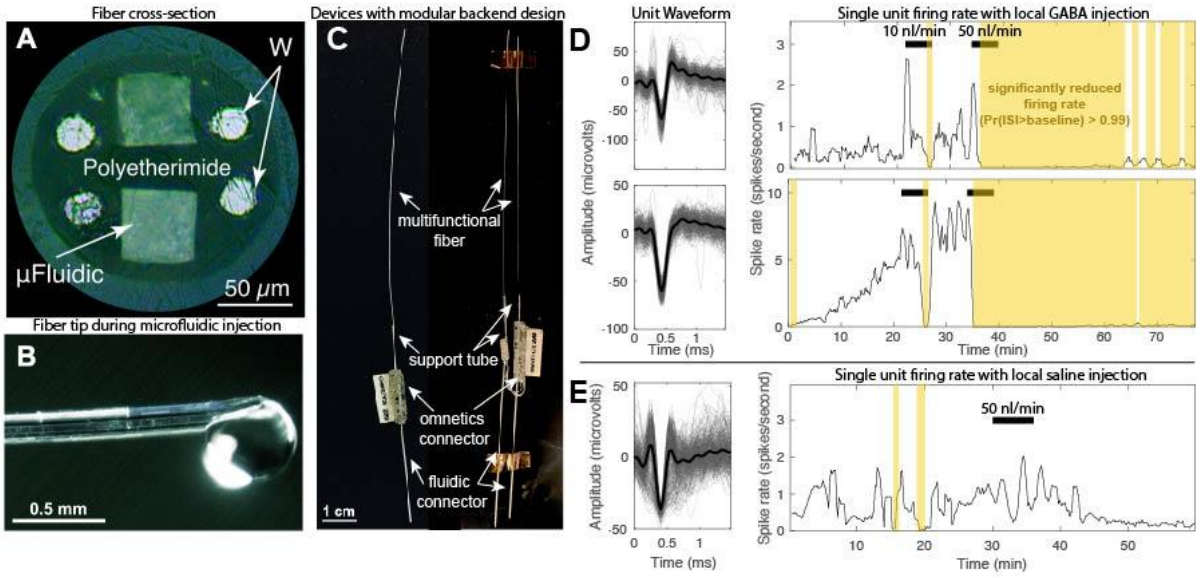
Topic: I.04. Physiological Methods

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McGovern Institute for Brain Research (PA)
NIMH R37MH087027
ONR MURI N00014-16-1-2832

Title: Multifunctional fiber-based neurotechnology enables cortical neuromodulation in non-human primates

Authors: *I. C. GARWOOD[1], A. J. MAJOR[2], M.-J. ANTONINI[1], J. CORREA[3], M. K. MAHNKE[2], E. K. MILLER[2], E. N. BROWN[1], P. ANIKEEVA[4];
[1]HST, [2]PILM, [3]Brain and Cognitive Sci., [4]MSE, MIT, Cambridge, MA

Abstract: Local modulation of cortical neural receptors in-vivo provides important insight into cortical circuit dynamics. In recent years, there has been significant innovation in multifunctional neural interfaces for rodents, enabling direct receptor modulation with simultaneous electrophysiology monitoring. Microscale flexible devices have enabled intracranial neuromodulation while reducing damage to delicate neural tissues. We translated multifunctional fiber-based neurotechnology for use in non-human primate (NHP) studies for the first time. The intracranial portion of the device, the fiber, is 150-200 um in diameter and contains four electrodes and two microfluidic channels in polyetherimide cladding. The devices are smaller and more flexible than commercial multifunctional devices used in NHP research. The backend connectors of the device are highly modular and compatible with common NHP setups (see fig below). We implanted these fibers in the premotor cortex and recorded single unit and local field potential activity. We demonstrated that a local 5-minute infusion of muscimol, a $GABA_A$ receptor agonist, reduced firing rates. The distribution of interspike intervals (ISIs) prior to injections were estimated with an inverse gaussian model. We compared post-injection ISI distributions with baseline ISI distributions. At infusion rates of 10 nl/min, there was a significant decrease in firing rate 3.8-4.1 min (Pr(ISI > baseline) > 0.99) after the injection, which recovered 0.3 min after the injection was stopped. At 50 nl/min, there was a significant decrease in firing rate 0.64-1.29 min after the injection began, which partially recovered over 20 minutes after the injection stopped. An infusion of saline at 50 nl/min did not reduce the firing rate. In summary, we translated and validated multifunctional fiber-based devices in NHPs.



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Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P935.03

Topic: I.04. Physiological Methods

Support: N66001-17-2-4010 (DARPA)

Title: Characterization of Recording Electrodes to Measure Evoked Compound Action Potentials (ECAPs)

Authors: *N. VERMA, B. KNUDSEN, A. SKUBAL, J. FRANK, K. LUDWIG;
Univ. of Wisconsin - Madison, Madison, WI

Abstract: Appropriately designed electrodes to make *in vivo* recordings of neural activity have been essential to the understanding of the nervous system. Recording electrode design has been extensively explored for use in measurement of naturally occurring neural activity in the brain. Recently, recording of evoked compound action potentials (ECAPs) in the periphery has garnered interest due to their relevance in neuromodulation therapies for determining target engagement and enabling closed-loop operation. Here, we compare several types of recording electrodes - microelectrodes, cuff electrodes, and longitudinal interfascicular electrodes (LIFE) - and their ability to make *in vivo* recordings of spontaneously occurring, sensory evoked, and electrically evoked neural activity in the peripheral nerves of a large animal.

The great auricular nerve, innervating the auricle, and cervical vagus nerve of domestic pigs were instrumented with several recording electrodes. Spontaneous neural activity, sensory evoked neural activity induced by gentle brushing of the skin, and electrically ECAPs delivered through non-invasive and implanted electrodes were recorded. A finite element model (FEM), implemented in COMSOL, was used to further explore the parameter space for the design and performance of these recording electrodes. We show that the recording cuff has superior performance in measuring implanted stimulation cuff ECAPs while the tungsten microelectrodes, routinely used for microneurography in humans, have superior performance in measuring naturally occurring action potentials and transcutaneous electrical stimulation (TES) ECAPs. Further, we show how choice of reference electrode position may be optimized depending on target fiber type to be recorded. Additionally, we show that TES paired with microneurography recordings can be used to functionally map sensory innervation areas of the auricle for individual subjects, allowing individualized placement of stimulation electrodes in non-invasive neuromodulation therapies, such as auricular vagus nerve stimulation (aVNS), to achieve on-target neural fiber activation.

We present *in vivo* recordings from the peripheral nerves of domestic pigs paired with finite element models to explore recording electrode design for recording of peripheral neural activity, particularly ECAPs. These findings provide a basis to optimize recording electrode design and configuration for measurement of *in vivo* ECAPs in the development and deployment of neuromodulation therapies.

Disclosures: N. Verma: None. **B. Knudsen:** None. **A. Skubal:** None. **J. Frank:** None. **K. Ludwig:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.04

Topic: I.04. Physiological Methods

Support: NIH NINDS R01NS089688
U01NS113279

Title: Polysaccharide-based bioactive coating for intracortical recording microelectrodes

Authors: *V. DHAWAN[1], T. CUI[2];
[2]Dept. of Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Invasive neural electrodes offer high spatial selectivity in recording neural activity, stimulating neurons, and sensing neuroactive species. However, their implantation in the brain initiates a foreign body response (FBR) which hinders device function for chronic applications. Bioactive coatings are promising in camouflaging electrode surfaces and promote seamless integration with nearby tissue while maintaining device performance. Existing protein-based coatings are susceptible to denaturation during processing and are not active players in reducing FBR, despite their neurite growth-promoting properties. Chondroitin sulfate (CS) is a naturally occurring polysaccharide in the brain, is commercially available, and offers a more stable, hydrophilic alternative with specific bioactivity for novel neural electrode interface application. Negatively charged sulfate groups in CS are implicated in neurite growth-promoting properties, shown by many *in vitro* studies. Immobilized CS was also shown to bind to key player MCP-1 chemokine. As a surface coating, CS can be utilized to sequester MCP-1 and dampen the downstream inflammatory cascade. The abundant hydroxyl groups in CS impart hydrophilicity to the surface, which is critical for preventing non-specific protein adsorption, the first step in FBR. CS was immobilized on SiO_2 glass coverslips for *in vitro* testing via divinyl sulfone linker. Preliminary surface characterization with Fourier-transform infrared spectroscopy confirmed successful CS immobilization indicated by the addition of S=O, C-O/C=O, and O-H groups. The CS-coated surface also showed reduced non-specific protein adsorption, compared to uncoated control. Primary cortical neurons were grown on CS and control samples (n = 3 cultures) and total neurite outgrowth (υm) was normalized to control. The CS samples had significantly higher mean neurite growth (145%±51, Welch's t-test, $p<0.0001$) compared to control (85%±36). Additionally, a significantly higher mean cell count was observed in the CS samples (119±36, Welch's t-test, $p<0.0001$) than the control (29±11). Primary microglia had smaller morphology with drastically reduced cellular extensions when grown on CS samples compared to controls which promoted normal growth with branching. Future work will investigate the interaction between activated microglia and CS using lipopolysaccharide and phorbol 12-myristate 13-ester simulation models. This work utilizes the untapped potential of polysaccharide-based coatings which can aid seamless integration of neural electrodes for optimal device performance with applications for neuroscience and clinical translation.

Disclosures: V. Dhawan: None. **T. Cui:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.05

Topic: I.04. Physiological Methods

Support: NIH Grant RF1NS113303-01

Title: Steeltrode: a microfabricated stainless steel neural interface for high spatio-temporal resolution recording in non-human primates

Authors: *Z. AHMED[1], I. KIMUKIN[1], J. REDDY[1], V. JAIN[1], T. TEICHERT[2], M. CHAMANZAR[1]; [1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Dept of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Translational neuroscience research can greatly benefit from tools for high-resolution neural recording from deep structures within the non-human primate (NHP) brain. While high-density neural probes have been devised for rodents, mainly leveraging well-established nanofabrication techniques for silicon-based devices, the inherent brittleness of silicon renders such devices vulnerable to fracture as the aspect ratio is made larger to investigate deep brain regions of larger non-human primate brains. As a result, the silicon-based microfabrication processes for rodent probes cannot be directly translated to realize implantable NHP neural interfaces meant for deep brain interrogation. To address this outstanding issue and the unmet demand for such tools in primate electrophysiology, we have developed a novel neural probe platform in flexible polymers and stainless steel. Stainless steel has great mechanical robustness and biocompatibility making it suitable for ultra-high aspect ratio NHP neural devices. Our new hybrid flex/rigid device architecture, called steeltrode, uses a stainless steel shank to allow robust insertion, while benefiting from a flexible polymer cable to relieve tethering forces and leave the device freely floating in the brain after implantation. We have optimized a novel microfabrication process to implement high-density electrical interconnects on stainless steel platform to fabricate devices with upto 102 channels. The long aspect ratio stainless steel probes feature 8-cm long shanks with a small cross section of 250 um x 150 um with densely packed microelectrodes with customizable diameters (15-50um) and arrangements of electrodes. We have conducted benchtop experiments to characterize the probe functionality using artificial action potential signals to measure the yield, crosstalk and SNR and also test chronic viability with accelerated lifetime testing. We have also recently validated the functionality of the probes in both macaque and rodent models. Isolated single units and multi-unit activities from different depths of the cortical laminae were recorded from the macaque motor cortex. With a shorter variant (~1 cm shank length) of the stainless steel probe, we have recorded multi-channel single unit data from Hippocampus (~2 mm depth) of wild-type mice, which demonstrates the versatility of our neural probe platform. Robustness and customizability of our microfabricated steeltrodes can facilitate distributed simultaneous volumetric recording from different depths across cortical regions in large animals and enable development of novel tools for translational research.

Disclosures: Z. Ahmed: None. **I. Kimukin:** None. **J. Reddy:** None. **V. Jain:** None. **T. Teichert:** None. **M. Chamanzar:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.06

Topic: I.04. Physiological Methods

Support: NIH NINDS R01NS104344

Title: Multi-layer Metallization in Ultra-Microelectrode Arrays for Neural Interfaces

Authors: *N. GERAMIFARD, S. COGAN;
The Univ. of Texas at Dallas, Richardson, TX

Abstract: Microelectrode arrays (MEAs) are used in the neural recording and modulation of neural activity. Ultra-microelectrodes may improve the selectivity of stimuli by enabling the stimulation of small tissue volumes. Ideally, to achieve the desired performance, higher electrode densities, large channel counts with effective encapsulation and small array footprints are required. However, increasing the electrode density and scaling down the interconnects may lead to high capacitive coupling between channels, hence increase in signal crosstalk and interference in the stimulation or signal recording. Here, we introduce amorphous silicon carbide (a-SiC) based UMEAs featuring two layers of patterned metallization sandwiched between a-SiC dielectric layers suitable for neural interface devices and provide electrical and electrochemical characterization. UMEAs with a total of 4 shanks with a cross-sectional area of less than 120 μm^2 and 4 to 8 electrodes on each shank were developed for densely packed electrodes. Some electrodes were fabricated with high capacitance and low impedance sputtered iridium oxide film (SIROF) with 200 μm^2 area whereas other channels were left encapsulated for electrical characterization. Voltage transient, electrochemical impedance spectroscopy and DC current measurements were used to evaluate leakage current and capacitive coupling between the adjacent channels. Scanning electron microscope images of cross-sectional cuts made by focused ion beam (FIB) milling of fabricated devices suggest that the two-metal-layer interconnects have a good structural integrity with a 2 μm traces interspacing and a 2 μm a-SiC interlayer encapsulation. Leakage currents between metal traces was measured as a function of steady state voltage bias between -1 and 1 V using a Keithley acquisation system and were found to be approximately $1x\ 10^{-13}$ A, both in air and PBS. Parasitic capacitance between parallel traces was calculated from voltage transient measurements in response to 1-10 μA current pulses with a pulse width of 50-200 μs and was found to be an order of magnitude smaller than the charge injection capacity of the SIROF electrodes. These results indicate that parasitic capacitive coupling is unlikley to substantively affect stimulation current pulse. Using the a-SiC as a base and interlayer insulator enables the development of ultramicroelectrode arrays with multi-layer metallization that permits an increase in the number of electrode sites with a desirably low shank cross-sectional area.

Disclosures: N. Geramifard: None. **S. Cogan:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.07

Topic: I.04. Physiological Methods

Support: H2020-MSCA-IF-2019 grant 896996

IIT – NetS3 laboratory

Title: Chromos probes: toward the development of minimally invasive high-channel count si cmos probes

Authors: *J. F. RIBEIRO, A. PERNA, L. GIANTOMASI, G. ORBAN, F. BOI, G. N. ANGOTZI, L. BERDONDINI;
Italian Inst. of Technol., Genova, Italy

Abstract: The chronic stability and the signal quality of intracortical implantable multielectrode array probes is tightly linked to the level of the brain tissue inflammatory response to the implant. To improve performances, free-floating devices assembled on flexible connectors, probes integrated on flexible polymeric substrates approaching the stiffness of the brain tissue and advances in implantation methods were demonstrated. More recently, it was shown that the reduction of the cross-sectional size of probes realized by rigid materials, such as silicon, plays a major role to improve the recording performances after weeks from the implant. However, downscaling the cross-sectional shank size of conventional Si-probes implies a drastic reduction of the number of integrated microelectrodes due to spatial constraints in electrically wiring each microelectrode to individually contact pads for external connection. Active dense implantable neural probes based on CMOS technology, such as Neuropixels, Neuroseeker or, more recently, the SiNAPS-probes developed in our lab, might allow to overcome this limitation in the number of integrated electrodes over small cross-sectional shank sizes. Indeed, although realized with different circuit's architectures and functionalities, such devices introduced the combined use of standard CMOS and MEMS technologies to realize monolithic active probes that integrate into the same substrate hundreds of closely spaced microelectrodes together with electronic circuits required for recording extracellular neural signals. In particular, the solution introduced by SiNAPS uses in-pixel amplifiers integrated beneath each microelectrode and on-probe multiplexing circuits to reduce the number of output lines. Differently than other CMOS neural probes that integrate low noise neural amplifiers in the probe base, the SiNAPS technology allows to avoid most of the connection lines in the shanks. By leveraging the high modularity nature of this technology, here we report the first results toward the realization and characterization of implantable probes, named ChroMOS probes, with 64 electrodes-pixels integrated in a 23 µm wide shank. We will present and discuss preliminary results obtained from passive silicon neural probes with shank cross-sections from 23 to 83 µm wide, 15 to 20 µm thick and 3 to 5 mm long. These passive neural probes were used to study the mechanical stability, materials resilience, tissue inflammation and the insertion protocol. Also, this passive neural probes allowed to develop and optimize the necessary CMOS compatible microstructuring process to realize ChroMOS probes.

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Poster

P935. Probe Design and Engineering: New Recording Methodologies

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P935.08

Topic: I.04. Physiological Methods

Support: 1R21EY026365- 01

Title: Neuroroots, minimally invasive, bioinspired probes for long term recordings

Authors: *V. SHAUTSOVA[1], E. ZHAO[2], M. D. FERRO[2], S. JAYABAL[4], J. L. RAYMOND[5], N. MELOSH[3];
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Abstract: Chronic neural technologies have enormous potential for clinical neuroprosthetic and neuromodulation devices and for fundamental neuroscience enabling research on how the computations performed by a neural circuit change over time, during development, experience-dependent learning and memory, aging, or disease progression. Recent research efforts have identified several key aspects for chronic devices to establish a reliable and glial scar-free neural-probe interface: (i) neural probes dimensions on the cellular scale (10µm) to minimize their perturbation to the host biological matrix, (ii) high probe flexibility to ensure complete compliance with the host tissue, (iii) minimal surgical damage (100µm shuttle size) to allow efficient tissue recovery and destruction of local circuits and (iv) mechanical and electrical stability during long-term operation under physiological conditions. To address these stringent conditions, we developed bio-inspired flexible neural probes, NeuroRoots, mimicking natural axons. The individual dimensions of the neural probes are cellular size, while the probes are centimeter long and organized in axon-like tendrils. This enables seamless device integration with brain tissues by matching the neural probe physical properties, in particular the dimensions and the mechanical flexibility, with that of the cellular networks in living brain. A significant aspect of this design is its internal potential for easy scalability coming from mechanical separation of individual probes. The probes are delivered in the brain using a microwire shuttle making it compatible with existent surgical instruments. Our results demonstrate high quality of the signal and long-term stability of the electrodes being chronically implanted in rats to record the neural activity during 7 weeks. A key goal of the current study is to create miniaturized probes with even smaller dimensions that can be used in parts of the nervous system that are difficult to access with existing technologies including the spinal cord, parts of the brain stem, and the cerebellum.

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Poster

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Program #/Poster #: P935.09

Topic: I.04. Physiological Methods

Support: NINDS 1UF1NS107659-01
Phi Sigma Biological Honor Society, Beta Lambda Chapter

Title: Characterization of silicon-supported carbon-fiber microelectrode arrays for dopamine measurements with flow injection analysis

Authors: *B. M. SMITH[1], J. D. GILES[1], P. R. PATEL[2], J. M. RICHIE[2], C. A. CHESTEK[2], P. A. GARRIS[1];
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Abstract: The challenging demands of investigating dopamine (DA) neurotransmission in the brain have led to numerous advancements, including the development of multi-site sensors capable of monitoring the highly complex nature of DA signaling. University of Michigan engineers have recently focused on developing minimally invasive carbon-fiber multielectrode arrays (CF-MEAs) for the purpose of multisite electrical and chemical recording. The latest iteration of CF-MEAs utilizes individuated silicon support shanks with the goal of insertion into deep subcortical structures of the rodent brain without the need for a shuttle such as polyethylene glycol or guide cannula. These novel devices feature sixteen Parylene C-insulated carbon fibers (d=8.4 μm) with a 100-μm pitch, an overall width of 1.5 mm, and a shank length of 6.0 mm. The silicon support structure for each fiber decreases in size stepwise from 55.5 to 15.5-μm with a ~20-μm depth. A 300-μm length of fiber extends beyond the silicon support, and laser ablation of insulation at the tip yields a 50-μm length of bare carbon fiber (d= 7.0-μm) as the sensing region. Here we evaluate these CF-MEAs for the purpose of measuring the neurotransmitter dopamine (DA) using fast-scan cyclic voltammetry (FSCV), a state-of-the-art electroanalytical technique for measuring neurochemicals that provides a voltammogram (i.e., a plot of measured current versus applied potential) at each 100-ms measurement for chemically identifying the analyte. We utilize flow injection analysis (FIA), an automated “beaker” technique that directs a timed bolus of analyte to the sensing surface, to characterize CF-MEAs for DA measurements. Through statistical analysis of sensor performance metrics, including speed of response, sensitivity, signal-to-noise ratio, total background current, and electrochemical variation, we show that performance of CF-MEAs compares favorably with the single carbon-fiber microelectrode, the longstanding gold-standard sensor for FSCV. Moreover, we demonstrate that CF-MEAs are amenable to chemometrics analysis using principle component regression in order to resolve individual analytes from a mixed signal. The favorable DA-sensing metrics of CF-MEAs coupled with the ability to effectively separate and quantify interfering signals suggests that CF-MEAs are well-suited for spatially resolved neurotransmitter analysis across a broad mediolateral span of the brain.

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Poster

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Topic: I.04. Physiological Methods

Support: NSF Grant IOS1754869
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Title: Carbon fiber electrodes for intracellular recording and stimulation

Authors: *Y. HUAN[1], J. P. GILL[1], J. B. FRITZINGER[1], P. R. PATEL[2], E. DELLA VALLE[2], J. D. WEILAND[2], C. A. CHESTEK[2], H. J. CHIEL[1];
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Abstract: To understand neural circuit dynamics, it is critical to manipulate and record from many neurons, ideally at the single neuron level. Traditional recording methods, such as glass microelectrodes, can only control a small number of neurons. More recently, devices with high electrode density have been developed, but few of them can be used for intracellular recording or stimulation. Carbon fiber electrodes (CFEs) are 8 micron-diameter electrodes that can be organized into arrays with pitches ranging from 100 to 200 microns. They have been shown to have good signal-to-noise ratios (SNRs) and are capable of stable extracellular recording during both acute and chronic implantation in vivo in neural tissue such as rat motor cortex. Given the small fiber size, it is possible that they could be used for intracellular arrays. We tested this using the large identified and electrically compact neurons of the marine mollusk *Aplysia californica*. The cell bodies of neurons in *Aplysia* range in size from 30 to over 250 microns. We compared the efficacy of CFEs to glass microelectrodes by impaling the same neuron's cell body with both electrodes and connecting them to a DC coupled amplifier. We observed that intracellular waveforms were essentially identical, but the amplitude and SNR in the CFE was lower than in the glass microelectrode. CFE arrays could record from 3 to 8 neurons simultaneously for many hours, and many of these recordings were intracellular as shown by recording from the same neuron using a glass microelectrode. Stimulations through CFEs coated with platinum-iridium had stable impedances over many hours. CFEs not within neurons could record local extracellular activity. Despite the lower SNR, the CFEs could record synaptic potentials. Thus, the stability for multi-channel recording and the ability to stimulate and record intracellularly make CFEs a powerful new technology for studying neural circuit dynamics.

Disclosures: Y. Huan: None. **J.P. Gill:** None. **J.B. Fritzinger:** None. **P.R. Patel:** None. **E. della Valle:** None. **J.D. Weiland:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epic Medical, Inc. **C.A. Chestek:** None. **H.J. Chiel:** None.

Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.11

Topic: I.04. Physiological Methods

Support: NINDS 1UF1NS107659-01
Phi Sigma Biological Honor Society, Beta Lambda Chapter

Title: Characterization of silicon-supported carbon-fiber microelectrode arrays for dopamine measurements in vivo

Authors: *R. L. CHICOSKY[1], B. M. SMITH[1], P. R. PATEL[2], J. M. RICHIE[2], C. A. CHESTEK[2], P. A. GARRIS[1];
[1]Sch. of Biol. Sci., Illinois State Univ., Normal, IL; [2]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: The ability to monitor brain neurotransmitters with high fidelity is critical for establishing the neural underpinnings of behavior and pathology. New carbon-fiber microelectrode arrays (CF-MEAs), with individuated silicon supports designed to insert into sub-cortical structures in the rat brain, have compared favorably to the gold standard carbon-fiber microelectrode (CFM) for fast-scan cyclic voltammetry (FSCV) dopamine (DA) measurements with flow injection analysis (see companion abstract). Here we evaluate these new CF-MEAs for DA recordings in the striatum of the urethane anesthetized rat. DA is a neurotransmitter critical for locomotion, motivation, and cognition that also plays a role in the pathologies of Parkinson's disease, substance use disorder, and schizophrenia, and the striatum is a brain region strongly implicated in reward learning. Striatal DA levels are readily measured by conventional CFMs coupled to FSCV. Electrically evoked DA measured in the striatum by a CF-MEA were both stable over time and pulse number dependent, indicating a broad dynamic [DA] measurement range. Moreover, DA signals collected from a 1.5-mm by 1.0-mm grid (100-μm mediolateral and dorsoventral resolution) suggest striatal heterogeneity in terms of both DA signal amplitude ([DA]max) and dynamics. Striatal DA signals were categorized into fast and slow, with fast DA signals further subdivided into four different types based on temporal profile (Types 1-4). The effects of amphetamine (AMPH), a potent inhibitor of the DA transporter combining high abuse potential and clinical efficacy in treating attention deficit hyperactivity disorder, were assessed using a three-parameter (DA release or [*Rp*], DA uptake or [*kU*], and DA diffusion or [*kT*]) restricted diffusion kinetic model. Post-AMPH electrically evoked DA signals, while kinetically heterogeneous, showed an increase in both [DA]max and *Rp*, and a decrease in both *kU* and *kT* in all channels of the CF-MEA. AMPH-induced non-electrically evoked DA transients, sub-second to second increases in extracellular DA resulting from burst firing of DA neurons, were observed both synchronously across all channels of the CF-MEA and asynchronously across just four channels of the CF-MEA in a time-dependent fashion. Our results demonstrate that CF-MEAs afford a similar utility as CFMs for monitoring brain DA signals in a temporally, chemically, and spatially resolved manner while providing the transformative advantage of substantively expanded spatial coverage for superior characterization of kinetically heterogeneous DA signal types that have previously been underexplored.

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Poster

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Program #/Poster #: P935.12

Topic: I.04. Physiological Methods

Support: NIH U01NS094375
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NIH OT2OD024907

NSF 1707316

Title: Carbon Fiber Electrode Arrays: Past, Present, and Future

Authors: *P. R. PATEL[1], J. G. LETNER[1], E. DELLA VALLE[1], Y. HUAN[2], B. M. SMITH[3], J. M. RICHIE[1], J. P. GILL[2], P. A. GARRIS[3], H. J. CHIEL[2], D. CAI[1], J. D. WEILAND[1], C. A. CHESTEK[1]; [1]Univ. of Michigan, Ann Arbor, MI; [2]Case Western Reserve Univ., Cleveland, OH; [3]Illinois State Univ., Normal, IL

Abstract: Our group has developed multiple platforms and processes that have enabled minimally invasive carbon fiber electrodes to detect electrical or chemical activity in various animal models and target regions. Our most widely used platform centers around a flexible polyimide board with 16 carbon fibers in a compact 2x8 configuration. With this device, we have acutely recorded neural activity from rat cervical vagus nerve (blowtorched tips with a poly(3,4-ethylene-dioxythiophene) (PEDOT) coating) and *Aplysia* (blowtorched or laser cut tips with PEDOT). In addition, we have ablated the insulation at the tips and chronically implanted this device into rat nucleus accumbens to record extracellular dopamine levels using fast scan cyclic voltammetry. We are currently ramping up production and distribution of an improved 16-channel array that utilizes thin, individuated silicon shanks as supports for the carbon fibers. The devices come in various lengths, useful for targeting a variety of brain regions. We have used longer devices to map the heterogeneity of both electrically evoked and amphetamine-induced phasic dopamine signals in rat striatum. The shorter devices have recorded chronic neural activity in rat motor cortex with a tip plating of either PEDOT or platinum iridium (PtIr). Additionally, the device tips can be localized within the tissue either by slicing through them *in situ* or by localizing their tract after explant. Our chronic results show that these newest devices still have little to no detriment to the surrounding tissue. We are also exploring the use of these arrays for stimulating and recording in *Aplysia*, by blowtorching and plating the tips with PtIr. The previous arrays have been adapted for acute use in targets outside of the rat brain; however, they are not suitable for chronic use in those targets. To alleviate this we have developed a silicone encased carbon fiber array with small form factor and recorded acute unit activity from feline dorsal root ganglion. Our goal is to build on this design to create chronically implantable variants for other models such as octopus and *Aplysia*. Lastly, we have begun preliminary work on transitioning towards a wireless package that can record or stimulate via carbon fiber electrodes. This would enable us to interface with new targets, such as the retina, along with those previously mentioned, but with no tethering forces and maximum flexibility in electrode placement.

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Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.13

Topic: I.04. Physiological Methods

Support: NINDS (UF1NS107659)
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Title: Subcellular Resolution Localization of Carbon Fiber Electrodes in Rat Motor Cortex

Authors: *J. G. LETNER[1], P. R. PATEL[1], L. A. WALKER[2], D. CAI[3], C. A. CHESTEK[1];
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Abstract: Brain machine interfaces (BMIs) can restore motor function to individuals with neurological deficits such as spinal cord injury and are commonly enabled by the implantation of neural electrodes in motor cortex. Chronic implantation of carbon fiber electrodes has shown to elicit a minimal foreign body response due to their subcellular diameter (8.4 µm) (Patel *et al.*, 2016; Welle *et al.*, 2020), making the electrodes possible candidates for clinical BMIs and characterizing nearly healthy tissue with electrophysiology and histology. However, the "slice-in-place" protocol that we developed to retroactively localize the tip recording sites with micrometer resolution (Patel *et al.*, 2020) proved not applicable to implants in cortical regions because cryosectioning was prohibited by the remaining headcap mounting screws. Recent changes in electrode design and protocol enabled us to localize the recording sites after explant to analyze the surrounding tissue with subcellular resolution. We implanted one male Long-Evans rat with a 16-channel high density carbon fiber array in layer V motor cortex for 3 months and recorded electrophysiology throughout the implant's lifetime. We stained the implant and contralateral control sites for neurons, astrocytes, and microglia, then imaged the sites with a confocal microscope in 3D. Using histological biomarkers, we located the tips with subcellular accuracy, typically in the absence of glial accumulation at the tips. 3D scaffolds of somae were reconstructed to measure neural morphologies, derive neural locations relative to the electrodes, and measure neuronal densities. We found that the distance of the closest neuron to the tip is 16 ± 5 µm (mean ± SD) and that of the second closest is 22 ± 5 µm; both were not different from control via two sample t-tests. Compared to control with two sample t-tests, neuron density was significantly reduced at 20-30 µm ($p=0.004$) and 30-40 µm ($p=0.01$) radial bins from the fibers, but was not significantly different at the 40-50 µm bin. Neuron density within 50 µm was 84% ± 20% that of control, a small but significant change ($p=0.004$, two sample t-test). Elliptical fitting to neurons (Du *et al.*, 2017) suggests they were stretched compared to control via a Kolmogorov-Smirnov test ($p=1.1 \times 10^{-67}$). N=16 fibers from 1 device. Overall, we found that these high-resolution analyses elucidated effects of carbon fiber electrode implantation that were previously obfuscated from array-scale analyses. These effects render carbon fibers biocompatible with further room for design improvements. Also, high resolution scaffolds of the surrounding neurons may prove useful in electrophysiological modelling.

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Poster

P935. Probe Design and Engineering: New Recording Methodologies

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Program #/Poster #: P935.14

Topic: I.07. Data Analysis and Statistics

Title: Event detection is a main determinant of spike sorting in human intracranial single unit recordings

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NeurTex Brain Res. Inst., Dallas, TX

Abstract: Four different spike sorting techniques have largely been used to identify the firing activity of single neurons in human intracranial microwire recordings. As previously shown, these 4 techniques have a low level of agreement between them (AMIall ranging from 0.041 - 0.16 on a 0-1 scale) and lead to different estimates of the fraction of neurons responsive to different stimuli (0.08 - 0.31).
Spike sorting requires two distinct steps: detecting periods of time which may contain an action potential waveform (events) and subsequently grouping these events into clusters of similar waveform shape. While prior studies have examined the effects of different clustering techniques on a fixed set of waveform events, this study measures agreement for both event detection and clustering using adjusted mutual information (AMI). Use of AMI allows the joint computation of agreement in events detected (AMIevent), agreement when sorting common events (AMImatch), and agreement in sorting overall (AMIall). These 3 measures were computed for 2752 channels of recording previously performed at the Barrow Neurological Institute.
There are six possible pairs of four sorting techniques. The distribution of AMIevent had grossly different patterns depending on the pair of spike sorting techniques considered. The Brain Modeling Laboratory (BML) techique was the most different from the OSort or Combinato techniques, while agreeing more closely with the WaveClus technique.
The values of AMIevent and AMImatch for each channel were used in a linear model to predict AMIall. AMIevent was a significant predictor (p<0.05) for all 6 of the possible pairs of spike sorting, while AMImatch was a significant predictor for 4 of the 6 pairs. While one might expect that increasing noise in the passband (300-3000 Hz) would decrease AMIall, noise was significantly negatively correlated for only the BML-Combinato pair. AMImatch was not significantly correlated with noise level for any pair. Overall these results suggest that different spike sorting techniques identify different aspects of the underlying signal which reflect a common responsiveness to experimental stimuli. They also show that further work is needed to understand the relationship of these signals to single neuron firing.

Disclosures: P.N. Steinmetz: None.

Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.01

Topic: I.06. Computation, Modeling, and Simulation

Title: Exploring disease similarities and dissimilarities using structural attributes of genes and proteins

Authors: *R. MOUSSA[1], S. CHANDRASENA[2], M. ELADAWI[2], X. ZHANG[2], R. E. MCCULLUMSMITH[2], R. SHUKLA[2];
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Abstract: Similarities and dissimilarities between disorders are not well understood. High-throughput omics technologies have revealed multifactorial associations between different diseases. However, these studies are limited to studying a few diseases at a time. Furthermore, the selection of disorders is limited by the biased selection of comparable disorders, datasets/cohort availability, and challenges with data normalization. Recently, we showed that disease specific gene-sets (aka disease-signatures) can be leveraged to mitigate these issues and can be used to understand disease similarities and dissimilarities at a functional level using biological pathways, cell-types, and drug targets. In our present work, we are now extending this approach to understanding disease similarities and dissimilarities at a structural level, involving several gene attributes, such as length, GC content, and IRES, as well as protein attributes such as amino acid composition, conserved domains, and prosite patterns. Disease signatures were obtained from DisGeNET and structural attributes from Ensembl BioMart. Different machine learning models (decision trees, logistic regression, random forest, and lasso methods) were evaluated for their ability to reveal associations between diseases and structural attributes. Different coefficients of structural attributes for a given disease were revealed. The coefficients will be further used to generate a penalty matrix which will be used to fine-tune a disease-disease interaction network. Our approach provides a promising lead to compare different diseases and to explore novel pharmacological interventions based on structural attributes.

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Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.02

Topic: I.06. Computation, Modeling, and Simulation

Title: Understanding Cortical Function with Novel Modeling Approaches of C. elegans Neuronal Activity

Authors: *W. G. RYAN, V[1], A. S. IMAMI[2], S. M. O'DONOVAN[3], R. SHUKLA[4], B. BAMBER[5], R. E. MCCULLUMSMITH[1];
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Abstract: Cortical function comprises the gestalt of sensory interpretation mechanisms in the brain that form the foundation of consciousness. Traditional feed-forward theories of cortical function to date have failed to fully capture the complexity between interactions in the neural connectome. Recent work challenging this paradigm posits recurrent and generative theories better model the architecture of the neocortex. The *C. elegans* model permits assessment of neuronal activity across all 302 neurons simultaneously, as well as temporal kinetics of neuronal activation in response to external stimuli. It follows that this is an ideal system to facilitate learning about neuronal networks and to test our assumptions about the theories of cortical function. To that end, we performed whole-brain neuronal activity recordings of behaving *C. elegans* in response to an aversive stimulus that elicits backward

locomotion. Data from neuronal Ca^{2+} imaging profiles were processed and normalized to generate activity pattern heatmaps. Activity patterns revealed highly dynamic neurons wherein the feed-forward model does not drive all neuronal activity in response to stimuli. To better assess the complexity of neuronal network dynamics and sensory plasticity within *C. elegans*, we sought to apply recent approaches in deep learning systems neuroscience able to better model non-linear interactions within these activity patterns. We demonstrated successful deconvolution of activity within *C. elegans* neuronal activity using OASIS. Re-convolved calcium imaging traces were generated with fidelity to the ground truth data for our proposed novel generative model, permitting the detection of the most statistically functionally relevant temporospatial features within neuronal activity patterns. Work is ongoing to optimize the generative model in order to generate importance maps. Importance maps express the effect of simulated temporal perturbations to infer these features. Ultimately, we propose these novel approaches as an ideal avenue to better our understanding of the underlying mechanisms of cortical function and how they could give rise to sentient systems.

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Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.03

Topic: I.06. Computation, Modeling, and Simulation

Title: Incorporating single cell transcriptomic data into a hippocampal computer model to understand epilepsy pathophysiology

Authors: *V. REDDY[1], M. A. SHERIF[2], R. MCCULLUMSMITH[1], R. SHUKLA[1];
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Abstract: Temporal Lobe Epilepsy (TLE) is one of the most common neurological disorders and is characterized by recurrent seizures. Although TLE genetic and electrophysiological markers such as gamma oscillations are well characterized, alteration of the interactions between neurons predisposing a cortical region to seizures are not fully understood. To study these non-linear interactions, we incorporated RNA expression changes into a microcircuit computer model of the hippocampus, an area strongly implicated in TLE. Cellular deconvolution of bulk RNAseq data with single cell transcriptomic data from pilocarpine-induced temporal lobe epilepsy mouse model hippocampus revealed three distinct cell clusters characterized as pyramidal (PYR) cells, oriens-lacunosum moleculare (OLM) interneurons, and parvalbumin-positive (PV) interneurons. We used the differential expression (log fold change) of genes coding for the AMPA, NMDA, and $GABA_A$ receptor subunits in the control and epileptic conditions for each cell cluster to guide scaling of receptor density in the model. The model was composed of 800 PYR, 200 PV and 200 OLM neurons. PYR cells of the model activate PV, OLM, and other pyramidal cells via NMDA and AMPA receptors; in return, the PV and OLM interneurons inhibit PYR cells by acting on their $GABA_A$ receptors. Guided by the RNA expression data, we ran simulations

where we increased the density of both PYR AMPAR and PV $GABA_AR$. Increasing pyramidal AMPAR density increased gamma power generated by the model, suggesting increased seizure susceptibility. However, the magnitude of increase was modulated by the PV $GABA_AR$ density scaling. Our work illustrate how microcircuit computer modeling can maximize information gained from single-cell and bulk RNAseq experiments. Single-cell transcriptomics provides cellular and molecular characteristics of brain changes in great detail, but this information is merely a snapshot of cell states. To more accurately estimate the molecular contribution of neurons in disease phenotypes, we propose the integration of single-cell transcriptomic data with biophysically-realistic microcircuit models. Applying this integrative approach to a penetrant phenotype such as epilepsy will aid our understanding of the non-linear interactions between different cell types resulting in seizure onset.

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Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.04

Topic: I.06. Computation, Modeling, and Simulation

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Title: Topographically detailed computational model of the motor and somatosensory thalamic circuits

Authors: *J. V. S. MOREIRA[1], F. S. BORGES[1], D. DOHERTY[1], W. W. LYTTON[1], S. DURA-BERNAL[1,2];
[1]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., BROOKLYN, NY; [2]Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: The thalamus is a key router of information going in and out of the cerebral cortex, and has been widely studied at the cellular and circuit levels. However, in recent years, computing power enabled large-scale simulations of these circuits. In this study, we developed a large-scale model of the motor and somatosensory thalamus, with ~2250 neurons, incorporating recent data on projection targets and circuit architecture. Our objective was to reconcile the single cell dynamics of thalamic relay and reticular nuclei cells with circuit-level observations. The model was built using the NetPyNE tool and the NEURON simulator. It is composed of four first-order excitatory nuclei: the motor cortex projecting ventral anterior/ventrolateral and ventromedial nuclei; and the somatosensory cortex projecting ventral posterolateral and ventral posteromedial nuclei. It also includes a higher-order excitatory posterior medial nucleus with separate motor and somatosensory projecting sectors. First-order nuclei present topographical connectivity, whereas higher-order nuclei are connected via divergence rule, as literature shows. All excitatory nuclei are interconnected within the thalamus through projections to the reticular nucleus, represented here by a single-layered motor sector and a three-layered somatosensory sector. We

used single compartment cell models based on Destexhe (1996) with adjusted parameters. Both cell types feature Hodgkin-Huxley-type mechanisms, including Na+ and K+, low-threshold transient Ca2+, and K+ leak currents, and relay cells also have a hyperpolarization-activated cationic current and a rapidly-inactivating and transient K+ current. The connectivity rules were based on data of axonal and dendritic footprints for each nuclei, and probability and weight of connections were tuned within biological constraints to match dynamics observed experimentally. The results show our model reproduces the key features, such as tonic- and burst-firing behavior at single-cell level; rhythmic bursting and spindle oscillations at circuit level; stable self-sustained rhythmic activity; and responsiveness to driver inputs, shifting its dynamics and being susceptible to external modulation. We are currently integrating this model with existing models of motor cortex and somatosensory cortex. This will provide a framework to study neural coding, information flow and learning mechanisms in the cortico-thalamo-cortical circuits of the sensorimotor pathway with an unprecedented level of detail, allowing us to make predictions about the mechanisms underlying physiological and pathological sensorimotor dynamics in the brain.

Disclosures: J.V.S. Moreira: None. **F.S. Borges:** None. **D. Doherty:** None. **W.W. Lytton:** None. **S. Dura-Bernal:** None.

Poster

P955. Network Models: Experimentation II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P955.05

Topic: I.06. Computation, Modeling, and Simulation

Support: AOARD/AFOSR Grant 17IOA006
NIH/NIMH R01MH110514
NSF BCS #1932619

Title: Convergent Cross Sorting for Estimating Dynamic Coupling

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Abstract: Natural systems exhibit diverse behavior generated by complex interactions between their constituent parts. To characterize these interactions, we introduce Convergent Cross Sorting (CCS), a novel algorithm based on convergent cross mapping (CCM) for estimating dynamic coupling from time series data. CCS extends CCM by using the relative ranking of distances within state-space reconstructions to improve the prior methods' performance at identifying the existence, relative strength, and directionality of coupling across a wide range of signal and noise characteristics. In particular, relative to CCM, CCS has a large performance advantage when analyzing very short time series data and data from continuous dynamical systems with synchronous behavior. This advantage allows CCS to better uncover the temporal and directional relationships within systems that undergo frequent and short-

lived switches in dynamics, such as neural systems. In this paper, we validate CCS on simulated data and demonstrate its applicability to electrophysiological recordings from interacting brain regions.

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Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.06

Topic: I.06. Computation, Modeling, and Simulation

Support: EU Grant Agreement No. 945539
Specific Grant Agreement No. 800858
CSCS Grant under project ID ich002 and ich011

Title: Spiking neural network based on hippocampal circuitry

Authors: *S. COPPOLINO, M. MIGLIORE;
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Abstract: Learning to navigate a complex environment is, in general, not a difficult task for humans. Finding the correct path to follow to exit from a maze does not require a long training session; in most cases, just a single exploration of the environment is sufficient to recall the correct trail to the exit. This ability is in contrast with the performances of any deep learning algorithm in learning a trajectory through an arbitrary sequence of objects or places. Although artificial network architectures such as Long Short-Term Memory or Bidirectional Recurrent neural networks have reached impressive practical results, they require an exponentially long time for an appropriate learning phase. This suggests that something is missing in the artificial reproduction of basic cognitive functions.
In this work we present a model based on cell types and circuitry observed in the hippocampus, a brain region well known to integrate space, time, and memory to solve a spatial navigation task. Place-cells, head-direction cells, and other neurons types are wired together with plastic synapses to form a self-organizing network able to learn, in a single learning trial, the correct sequence of objects to follow toward an exit. The learning process is controlled by a spike-time-dependent plasticity rule, with excitatory and inhibitory neurons modulating the learning/forgetting cycle during the exploration of the environment. This allows the spiking neurons network, implemented in PyNN, to control the navigation of a virtual robot connected through a set a python-ROS transfer functions. The results suggest a new generation of explainable artificial intelligence algorithms for spatial navigation.
[1] S. Coppolino, G. Giacopelli and M. Migliore, "Sequence Learning in a Single Trial: A Spiking Neurons Model Based on Hippocampal Circuitry," in *IEEE Transactions on Neural Networks and Learning Systems*, doi: 10.1109/TNNLS.2021.3049281.

Disclosures: S. Coppolino: None. **M. Migliore:** None.

Poster

P955. Network Models: Experimentation II

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Program #/Poster #: P955.07

Topic: I.06. Computation, Modeling, and Simulation

Support: French national research agency grant No ANR-20-CE45-0005-01 (Brain-Net)

Title: Development of an unsupervised Spiking Neural Network for vocal and speech patterns classification

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Abstract: One of the fundamental tasks that human beings do on a daily basis is pattern recognition and the human brain performs this very efficiently. Taking inspiration from the human brain, Artificial Neural Networks (ANNs), or Deep Neural Networks (DNNs), to be specific, are making significant progress in reproducing this ability and are successfully used for various static and sequential pattern recognition applications today such as Natural Language Processing (NLP), Image Recognition and Automatic Speech Recognition (ASR), just to name a few. However, they come with their limitations - they usually require rigorous training on very large datasets and heavy computations. An alternative, aimed at addressing these issues, are Spiking Neural Networks (SNNs) which are more biologically plausible and need fewer data to train. Moreover, developing new SNN architectures dedicated for complex pattern recognition tasks is crucial as they could be implemented in energy-efficient neuromorphic hardware. In this context, we developed a potentially energy-efficient SNN with Spike-Timing-Dependent-Plasticity (STDP) for unsupervised classification of audio patterns. We built a simple network using Low Threshold Spiking (LTS) neurons. The input audio is converted into spike trains across several frequency bands using 'time-to-first-spike' encoding method and these spike trains modulate the membrane potentials of the LTS neurons in the output layer causing them to spike. We assessed the performance of our network on synthetic spectrotemporal patterns mimicking vocal spectrograms which allowed us to evaluate the network's output with respect to the known ground truth. Such a network could perfectly classify 8 different patterns (f-score = 1) and remained very robust when noise was added to alter the patterns (f-score of 0.75 for 25% perturbation of the encoding spike trains). The next step will be to evaluate the network on vocal and speech datasets. The ability to classify vocal patterns in a completely unsupervised manner with a rather simple network architecture is interesting and opens new avenues for more complicated pattern detection with SNNs.

Disclosures: S. Pokala: None. **B. Yvert:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

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Program #/Poster #: P984.01

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS120832
NSF Grant NeuroNex 1707352
NIH Grant U01NS099709
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Title: Investigation of synaptic communication through Interluminescence by patch-clamp recordings from cultured neurons

Authors: *M. PRAKASH[1], A. BJOREFELDT[3], M. TREE[1], N. C. SHANER[5], C. I. MOORE[4], D. LIPSCOMBE[4], U. HOCHGESCHWENDER[2];
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Abstract: In BioLuminescent OptoGenetics (BL-OG) a genetically encoded light source, a luciferase, activates a light-sensing optogenetic element, a channelrhodopsin or a pump. When light emitter and light sensor are tethered, as in luciferase-opsin fusion proteins (luminopsins, LMO), application of the luciferin coelenterazine (CTZ) and subsequent light production will change the membrane potential of the cell expressing the LMO. Here, we leverage this coupling strategy across the synapse by placing the luciferase in the presynaptic neuron and the opsin in the postsynaptic neuron. In the presence of CTZ, light emitted from the luciferase activates the opsin of synaptically connected neurons. We previously demonstrated the effects of this 'Interluminescence' on synapse-specific circuit control in multi electrode array recordings of cortical and striatal neuron co-cultures. Here we tested BL-OG effects across the synapse by patch clamp recordings from individual postsynaptic neurons. E18 rat cortex and striatum neurons were nucleofected with a luciferase-dTomato construct and an excitatory opsin-EYFP construct, respectively, and were plated on glass coverslips as a mixed culture. At DIVs 28-40, synaptic pairs were located by visualizing the reporter expression for the luciferase (red) on presynaptic cortical neurons and for the opsin (yellow) on postsynaptic striatal neurons. Whole cell patch configuration was achieved on the opsin-expressing postsynaptic neuron and synapse-specific modulation of the postsynaptic neuron was recorded in current clamp mode. Generation of action potentials was compared in the presence of CTZ and vehicle. Depolarization in postsynaptic neurons was robustly elicited with bioluminescence from presynaptic partners and was likely due to trans-synaptic communication. Such biological light activation across genetically determined synaptic partners offers the potential to optogenetically dissect synaptic communication non-invasively.

Disclosures: M. Prakash: None. **A. Bjorefeldt:** None. **M. Tree:** None. **N.C. Shaner:** None. **C.I. Moore:** None. **D. Lipscombe:** None. **U. Hochgeschwender:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P984.02

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF NeuroNex 1707352

Title: A bioluminescent optogenetic synapse drives robust, dynamic changes in mouse thalamocortical circuits in vivo

Authors: *J. MURPHY[1], N. FRIEDMAN[1], M. PRAKASH[2], R. ST. LAURENT[1], D. LIPSCOMBE[1], N. SHANER[3], U. HOCHGESCHWENDER[2], C. I. MOORE[1];
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Abstract: Current opto- and chemogenetic tools generically modify cellular excitability, or require gene expression to target specific synaptic junctions. The ability to selectively regulate the impact of afferents on a specific subset of their synaptic targets, and only when these afferents are active, would be a powerful asset to understanding dynamic neural circuits. Here we present a bioluminescent optogenetic tool that provides a high degree of synaptic selectivity and is capable of regulating circuits based on their intrinsic activity. This intersectional dynamic goal is achieved by packaging bioluminescent enzymes in dense core vesicles within presynaptic neurons and expressing optogenetic channels on their postsynaptic targets. When the bioluminescent substrate coelenterazine (CTZ) is introduced, bioluminescent light is generated at synaptic clefts that recently released enzyme, activating the optogenetic channels in neurons postsynaptic to a presynaptically-active input. Our group has tested this molecular tool extensively in vitro. Here we present data employing this molecule in vivo in the anesthetized mouse.
We targeted thalamocortical synaptic projections of the mouse vibrissal system from the posterior medial and ventral posteromedial (VPM) thalamic nuclei onto parvalbumin positive (PV) neurons in primary somatosensory cortex (SI). Thalamic neurons were virally targeted to express bioluminescent enzymes in dense core vesicles. In mice receiving vibrissal stimulation, application of CTZ directly onto the cortical surface of SI elicited strong bioluminescent light output, indicating that thalamic neurons were indeed releasing bioluminescent enzymes at their axonal terminals in SI. Next, we recorded laminar multi-unit activity in SI before and after application of CTZ to the SI surface. Upon CTZ administration and emission of bioluminescent light, a marked increase in multiunit firing was observed spanning a wide swath of SI laminae. In a second cohort of animals we virally targeted only VPM, which projects densely to PV cells in deeper layers while avoiding those in superficial layers. In this cohort of animals we observed a laminar shift to the middle layers of bioluminescence driven MUA activity in agreement with VPM termination patterns.
These data provide strong preliminary evidence that a synapse- and activity-dependent optogenetic construct driven by bioluminescent light is a viable and potentially powerful tool for dynamic neural circuit dissection.

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Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

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Program #/Poster #: P984.03

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant NeuroNex 1707352
NIH Grant U01NS099709
Grant W.M. Keck Foundation
Swedish Research Council Grant 2016-06760

Title: A new excitatory luminopsin for combined optochemical manipulation of neuronal activity

Authors: *A. BJOREFELDT[1,2,5], J. W. MURPHY[5], E. L. CRESPO[3], N. G. FRIEDMAN[5], G. G. LAMBERT[6], T. M. BROWN[3], M. KNOBLOCK[3], N. J. COON[3], G. FOLKERT[3], C. I. MOORE[5], U. HOCHGESCHWENDER[4], N. C. SHANER[6];
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Abstract: Experimental manipulation of neural activity in genetically defined populations is currently largely centered around optogenetic or chemogenetic techniques, each featuring unique strengths and limitations. To increase user flexibility, and facilitate designs where advantages of each above approach can be leveraged at distinct experimental stages, we have developed bioluminescent optogenetics (BL-OG) which provides combined opto- and chemogenetic control in a single molecule (a luminopsin, or LMO). The LMO features a bioluminescent light emitter fused to an optogenetic actuator, enabling both direct activation of the opsin using an LED (for temporally precise control) and chemogenetic manipulation of neuronal populations distributed throughout the brain via systemic administration of the bioluminescent substrate coelenterazine (CTZ). To expand the utility of BL-OG, we here sought to further increase the efficacy of chemogenetic (bioluminescent) activation of LMOs. Through engineering of novel Förster resonance energy transfer (FRET)-based bioluminescent emitters featuring superior brightness and emission spectra matched to *Volvox* channelrhodopsin 1 (VChR1), we develop and thoroughly benchmark a new excitatory LMO (LMO7) that will improve the efficacy of chemogenetic activation in targeted neuronal populations.

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Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

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Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant NeuroNex 1707352
NIH Grant U01NS099709
Grant W.M. Keck Foundation
NIH Grant R21EY030716

Title: Precise and sustained manipulation of selected cell ensembles through photoswitchable bioluminescent-optogenetics (PS BL-OG)

Authors: *A. I. MORE[1,2], J. W. MURPHY[1,2], G. G. LAMBERT[3], C. A. DEISTER[1,2], T. M. BROWN[1,2], O. MCKISSICK[1,2], A. TORREBLANCA ZANCA[3], D. B. GREGORY[3], U. HOCHGESCHWENDER[4], N. C. SHANER[3], C. I. MOORE[1];
[1]Brown Univ., Providence, RI; [2]Carney Inst. for Brain Sci., Providence, RI; [3]UCSD, La Jolla, CA; [4]Central Michigan Univ., Mount Pleasant, MI

Abstract: BioLuminescent-OptoGenetics (BL-OG) is a combined strategy that allows chemogenetic and/or optogenetic cellular manipulation and regulation. Luminopsins are BL-OG fusion proteins, connecting bioluminescent luciferases with optogenetic actuators that can stimulate or inhibit neural circuits through administration of a small-molecule luciferin. Luminopsins drive robust fluctuations in MUA activity in neocortex with a response that is sensitive and proportional to luciferin availability [Gomez-Ramirez, et al., 2019].
Because they will provide several distinct benefits, we are creating an array of photoswitchable (PS) Luminopsins that enable brighter and color-shifted luciferase light production after activation. First, this strategy allows selection of specific cells (e.g., members of a neural ensemble sharing similar tuning) to achieve sustained chemogenetic control lasting up to several hours. To our knowledge, this construct is the first to provide such selectivity in chemogenetics. Second, because BL-OG cellular control is directly proportional to BL light production, photon emission allows real-time tracking of the duration and magnitude of PS-activated chemogenetic control: Relating the strength of ensemble manipulation to behavioral variables, re-energizing ensemble control, or choosing alternative ensembles can therefore be conducted optimally. Third, in contrast to holographic optogenetics, PS does not require maximal light delivery in a discrete millisecond-specific window, and can therefore be applied to deeper targets and a much larger array of cells, providing a more robust option for many experimental goals.
To date, we have developed multiple Luminopsin constructs that are effectively photo-switched ‘on’ through activated availability for bioluminescent FRET (BRET). We have now confirmed robust PS BL-OG activation can be achieved in mouse neocortical neurons in vivo, showing substantially brighter and color-shifted output when activated. Further, these constructs show robust two-photon (2P)-driven PS, providing a high degree of precision in choosing cells or processes to modulate. We are currently testing the magnitude of electrophysiological effects following PS BL-OG activation in neurons and the impact this molecule has on well-controlled psychophysical behavior.

Disclosures: A.I. More: None. **J.W. Murphy:** None. **G.G. Lambert:** None. **C.A. Deister:** None. **T.M. Brown:** None. **O. McKissick:** None. **A. Torreblanca Zanca:** None. **D.B. Gregory:** None. **U. Hochgeschwender:** None. **N.C. Shaner:** None. **C.I. Moore:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P984.05

Topic: I.08. Methods to Modulate Neural Activity

Title: Bl-og related perceptual modulations in awake-behaving animals

Authors: *L. GRUEL BUDET, E. F. MURPHY, H. BAEZ, M. GOMEZ-RAMIREZ;
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Abstract: Optogenetics enable selective control of genetically-tagged cell ensembles with high temporal precision and single-cell resolution. A major limitation of optogenetics is the use of invasive external light devices to drive cell activity. A recent method, termed Bioluminescent OptoGenetics (BL-OG), circumvents this limitation by fusing a photo-enzyme to an optogenetic element. The optogenetic element is driven by bioluminescent light emitted by injecting a chemical substrate (e.g., Coelenterazine; *CTZ*)that is catalyzed by the photo-enzyme (e.g., slow-burn Gaussia Luciferase; *sb-GLuc)*. An unresolved question is whether the BL-OG technique is a reliable and viable method to modulate sensory processing and perception in behaving animals. Here, we trained mice to perform a speed-reaction time task with auditory and/or visual stimuli. Treatment mice were injected with the novel luminopsin-7 (LMO7)construct, a BRET-based BL-OG molecule, in the antero-lateral secondary visual cortex (AL-Vis). A control group underwent the same surgical procedure as the LMO7 mice, but were not injected with the virus. Preliminary data show that mice were able to detect unisensory and multisensory stimuli, with multisensory stimuli detected much faster and at a lower threshold level than unisensory stimuli. We expect to find that injection of h-CTZ will lead to enhanced detection in the LMO7 mice but not the control group. We further expect that BL-OG effects will lead to enhanced perception of multisensory stimuli as compared to unisensory stimuli. Our study will further our understanding of the BL-OG technique by providing an estimate of its effects on sensory processing and behavior.

Disclosures: L. Gruel Budet: None. **E.F. Murphy:** None. **H. Baez:** None. **M. Gomez-Ramirez:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

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Program #/Poster #: P984.06

Topic: I.08. Methods to Modulate Neural Activity

Title: Non-invasive injections of h-Coelenterazine elicit proportional responses in mouse cortex

Authors: *E. F. MURPHY, H. BAEZ, L. GRUEL BUDET, M. GOMEZ-RAMIREZ;
Univ. of Rochester, Rochester, NY

Abstract: BioLuminescent OptoGenetics (“BL-OG”) is a chemogenetic method that enables optogenetic reactions without the use of an external light device. In BL-OG, a photo-enzyme (e.g., slow-burn Gaussia Luciferase; *sbGLuc*) is tethered to an optogenetic element (e.g., Volvox-Channelrhodopsin-1; *VCHR1*) that is activated via bioluminescent light. Bioluminescence is generated by injecting a chemical substrate (*luciferin*, e.g., Coelenterazine; *CTZ*) that is catalyzed by the photo-enzyme neighboring the opsin. In a

previous study, we showed proportional increases in neural firing and bioluminescence in response to higher doses of CTZ. However, these BL-OG effects were observed during invasive injections of the luciferin directly into the brain. Thus, to demonstrate that BL-OG is a viable method for modulating neural activity non-invasively, it is key to determine dose response curves when the substrate is injected systemically. Here, we injected different dosages of h-CTZ via the tail vein of mice expressing the BL-OG construct LMO7, a novel and more photo-efficient BRET-based molecule that tethers the bioluminescent and fluorescent protein NCS2 to VCHR1. Bioluminescence was imaged using an EMCCD camera while animals ran on a wheel, and different concentration dosages of h-CTZ were injected. Pilot data reveal proportional increases in bioluminescence in response to increasing dosages of h-CTZ. Our study furthers our understanding of the BL-OG technique by providing a map between BL-OG effects and systemic injections of h-CTZ via the tail vein.

Disclosures: E.F. Murphy: None. **H. Baez:** None. **L. Gruel Budet:** None. **M. Gomez-Ramirez:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

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Program #/Poster #: P984.07

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant NeuroNex 1707352
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Title: Red-shifted luminopsins

Authors: E. IKEFUAMA[1], J. W. SIMKINS[1], M. O. TREE[1], L. M. BARNETT[3], G. G. LAMBERT[4], D. LIPSCOMBE[5], C. I. MOORE[6], N. C. SHANER[4], *U. HOCHGESCHWENDER[2];
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Abstract: BioLuminescent-OptoGenetics (BL-OG) is a bimodal approach for controlling the activity of optogenetic elements. Opsins can be activated by light from a physical source or by applying a small chemical, a luciferin, that is oxidized by a luciferase enzyme thereby emitting bioluminescent light. Various luciferases have been tethered to opsins in blue light utilizing luminopsins (LMOs), and these have been applied for excitation and inhibition of targeted neuronal populations in vivo[1-4]. To expand the utility of BL-OG we generated red-shifted LMOs by combining a Renilla luciferase variant that emits light above 500 nm with red fluorescent proteins based on mCherry, mOrange, and mScarlet to leverage Förster resonance energy transfer (FRET) for bright and red light emitters. We used structure-guided design and directed evolution to optimize FRET efficiency between luciferase and fluorescent proteins, resulting in three LMOs with emission peaks between 560 - 592 nm. We tethered these red light emitters to excitatory (VChR1, ChrimsonR) and inhibitory (Halo, hGtACR1) red-shifted opsins and tested their efficacy in neurons in vitro and in vivo. This set of red LMOs expands the toolset for recording and controlling neural activities in the brain by allowing multiplexing with blue-shifted LMOs, opsins, and sensors.

[1]Berglund et al., Proc Natl Acad Sci USA 113: E358-67, 2016 [2]Gomez-Ramirez et al., J Neurosci Res. Sep 23, 2019 [3]Celinskis et al., Annu Int Conf IEEE Eng Med Biol Soc. 2020:4385-4389, 2020 [4]Medendorp et al., iScience 24:102157, 2021

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Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

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Topic: I.08. Methods to Modulate Neural Activity

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Title: Imaging the cortex and spinal cord using bioluminescent calcium indicators and miniaturized microscopy

Authors: *D. CELINSKIS[1,2], J. MURPHY[1,2], N. C. SHANER[3], U. HOCHGESCHWENDER[4], D. LIPSCOMBE[1,2], C. Y. SAAB[5], C. MOORE[1,2], D. BORTON[1,2];
[1]Brown Univ., Providence, RI; [2]Carney Inst. for Brain Sci., Providence, RI; [3]Univ. of California, San Diego, CA; [4]Neurosci., Central Michigan Univ., Mt Pleasant, MI; [5]Dept. of Biomed. Engin. and Neurolog. Inst., Cleveland Clin. Lerner Res. Inst., Cleveland, OH

Abstract: Optical imaging is a transformative tool for neuroscience, enabling the elucidation of biological circuits that generate behavior. State-of-the-art imaging tools rely on a restrained preparation, limiting natural behavior while measuring cellular activity via fluorescence (FL). Recently, advances in wearable miniature microscopy expanded the range of accessible behaviors by allowing imaging in freely behaving animals. However, miniature microscopes (miniscopes) are currently used for brain imaging using FL. Miniscopes have not been adopted for imaging bioluminescence (BL) and/or other parts of the body. However, unfavorable attributes of FL indicators constrain the extent of imaging experiments. These attributes include photobleaching, autofluorescence and excitation light scattering noise, especially in the parts of the body like the spinal cord due to myelination. All 3 issues can be eliminated, and an increase in imaging depth achieved, by using BL instead of the FL. BL does not require an external light source and offers a lower biological noise floor, often creating higher signal-to-noise ratio. However, the overall lower BL light intensity presents a challenge for imaging using low-cost low-sensitivity miniscopes.
The objective of our work is to improve the quality of cortical and spinal imaging using BL and miniature microscopy tools. To this end, we (i) present an expansion of the miniscope use towards neurovascular imaging in the spinal cord. Spinal neurovascular imaging is accomplished by integrating a custom 3D-

printed vertebral implant with miniscope hardware that ensures mechanical and optical stability over time up to 5 months post-implantation. Such implants allow interchangeable imaging of the brain or spinal cord in free or restrained mice. (ii) We demonstrate our ability of imaging BL calcium indicators using EM-CCD camera at rates up to 2 frames-per-second (FPS) through a cranial window in behaving animals following the systemic administration of BL substrate (luciferase), and as fast as 10 FPS with the topical administration of luciferase. With intracortical administration of luciferase BL calcium signals can be imaged using redesigned FL miniscopes (the 'BLmini') at rates as fast as 5 FPS (Celinskis et al., 2020). Altogether, our work presents significant progress towards BL calcium imaging with experimenter-friendly peripheral routes of substrate administration using low-cost wearable miniature microscopes across multiple sites throughout the nervous system.

Disclosures: D. Celinskis: None. **J. Murphy:** None. **N.C. Shaner:** None. **U. Hochgeschwender:** None. **D. Lipscombe:** None. **C.Y. Saab:** None. **C. Moore:** None. **D. Borton:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P984.09

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF grant 2027113
Perkin Elmer Postdoctoal fellowship
NSF Grant NeuroNex 1707352
NIH Grant U01NS099709

Title: Bioluminescent Genetically Encoded Indicators for Molecular Imaging of Neuronal Activity

Authors: E. D. PETERSEN[1], E. L. CRESPO[2], G. G. LAMBERT[3], A. T. TORREBLANCA[3], R. ORCUTT[3], U. HOCHGESCHWENDER[2], N. C. SHANER[3], A. GILAD[1];
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Abstract: Genetically encoded optical sensors and advancements in microscopy instrumentation and techniques have revolutionized the scientific toolbox available for probing complex biological processes such as release of specific neurotransmitters. Most genetically encoded optical sensors currently used are based on fluorescence and have been highly successful tools for single-cell imaging in superficial brain regions. However, there remains a need to develop new tools for reporting neuronal activity *in vivo* within deeper structures without the need for hardware such as lenses or fibers to be implanted within the brain. Our approach to this problem is to replace the fluorescent elements of the existing biosensors with bioluminescent elements. This eliminates the need of external light sources to illuminate the sensor and overcomes several drawbacks of fluorescence imaging such as limited light penetration depth, excitation scattering, and tissue heating that are all associated with the external light needed for fluorescence imaging.We have bioengineered the first genetically encoded bioluminescent neurotransmitter indicators using a multistep screening approach. First rational design using a variety of split luciferases and linker

variants to fuse the luciferases to a sensing protein. Then an automated workflow to screen for improved variants in mammalian cells, using automation for mini preps and transfection of mammalian cell cultures. As a result, we created a BioLuminescent Indicator of the Neurotransmitter Glutamate (BLING). Using our protein evolution approach in mammalian cells, we were able to improve our BLINGs response by 2.5x. Our improved glutamate indicator demonstrated a 255% +/-50 increase in response to neurotransmitter presentation when expressed in mammalian cells, can report changes in extracellular glutamate when used in a plate reader and outperforms various fluorescent sensors in plate reader assays. Finally, to test the feasibility of imaging BLING we used real-time microscopy which demonstrated up to a 310% increase in light emission detectable at the single cell level. We expect this new approach to neurotransmitter indicator design to enable the engineering of bioluminescent probes for multiple additional neurotransmitters, ultimately allowing neuroscientists to monitor activity associated with a specific neurotransmitter as it relates to behavior in a variety of psychiatric disorders, among many other applications.

Disclosures: E.D. Petersen: None. **E.L. Crespo:** None. **G.G. Lambert:** None. **A.T. Torreblanca:** None. **R. Orcutt:** None. **U. Hochgeschwender:** None. **N.C. Shaner:** None. **A. Gilad:** None.

Poster

P984. Bioluminescent Activators and Indicators in Neuroscience

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:15 AM - 11:15 AM

Program #/Poster #: P984.10

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant NeuroNex 1707352
NIH Grant R01GM121944
NIH Grant U01NS113294
NIH Grant R01GM121944

Title: Bright and high-contrast bioluminescent calcium indicators

Authors: G. G. LAMBERT[1], E. L. CRESPO[2], A. TORREBLANCA ZANCA[1], D. HEYDARI[1], R. ORCUTT[1], D. B. GREGORY[1], S. VENN[2], M. O. TREE[2], D. LIPSCOMBE[3], C. I. MOORE[3], U. HOCHGESCHWENDER[2], ***N. C. SHANER**[1];
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Abstract: Calcium is the ubiquitous cellular second messenger and calcium signals are proxy for biologically significant events including neuronal action potentials. Genetically encoded fluorescent calcium sensors are well established tools in neuroscience, but they have a number of limitations for use in biological tissue, such as tissue heating from illumination, other off-target biological effects of high-intensity excitation, and scattering of excitation light that confines imaging to small volumes of the brain. Previous generations of bioluminescent calcium indicators have insufficient brightness and relatively small calcium-dependent changes in signal magnitudes, and these properties have limited their widespread adoption in the neuroscience research community. Here, we present “Calcium

BioLuminescence-Activity Meters" (CaBLAMs), a family of bioluminescent calcium indicators engineered from a novel luciferase and calcium sensor domain topology. By optimizing each component of these indicators, including the luciferase domain, split site, calmodulin and RS20 peptide, and linker length and composition, we have achieved extremely low baseline emission at cytosolic resting calcium concentrations, a high Hill coefficient, and a very high signal change (delta-L/L) at physiologically relevant elevated cytosolic calcium concentrations. Further optimization of the luciferin (substrate) used for imaging the CaBLAMs generates signals large enough to observe glutamate-induced calcium events originating in dendrites and propagating to the soma in individual neurons ex vivo. These new sensors have the potential to enable imaging of calcium activity in deep brain regions in behaving mice for the first time without the need for an excitation light source.

Disclosures: G.G. Lambert: None. **E.L. Crespo:** None. **A. Torreblanca Zanca:** None. **D. Heydari:** None. **R. Orcutt:** None. **D.B. Gregory:** None. **S. Venn:** None. **M.O. Tree:** None. **D. Lipscombe:** None. **C.I. Moore:** None. **U. Hochgeschwender:** None. **N.C. Shaner:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.01

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: 1R15 AG060461-(01)

Title: Effects of forebrain expression of chimeric GluN2 subunits on NMDAR synaptic pool at hippocampal excitatory synapses

Authors: *R. E. KEITH[1], T. C. DUMAS[2];
[2]Psychology, [1]George Mason Univ., Fairfax, VA

Abstract: N-methyl-D-aspartate receptors (NMDARs) are voltage-gated glutamatergic receptors which engage in both ionotropic and non-ionotropic signaling. In the hippocampus, NMDARs consist of two obligatory GluN1 subunits and two auxiliary GluN2 subunits (predominantly GluN2A and GluN2B) (Wyllie et al., 2011). During postnatal development, NMDARs undergo a GluN2 subunit switch from predominantly GluN2B prior to the third postnatal week to mostly GluN2A and triheteromeric NMDARs following the third postnatal week. However, this subunit switch is not accompanied by a change in the total NMDAR pool, despite the fact that GluN2 subunit composition of the NMDAR influences the trafficking of the receptor to the synapse. Indeed, it remains unknown how GluN2 functional domains (the N-terminus, transmembrane domains and C-terminus) may separately and independently affect the available pool of synaptic NMDARs. As the channel kinetics and protein-binding partners conferred by GluN2 subunits are unique, it is possible to separate the effects of GluN2 functional domains by determining the GluN2 expression of the NMDARs present at the synapse. The developmentally regulated expression of these subunits also permits dissociation of the influence of GluN2A and GluN2B functional domains at different stages of postnatal development. Thus, using transgenic mice which express the N-terminus and TM regions of GluN2A (ABc) or GluN2B (BAc) fused to the opposite

subunit type C-terminus, we examined the GluN1 content of hippocampal and neocortical postsynaptic density fractions prior to (P17-P19) and after (P22-P24) forebrain maturation, and in young adulthood (P30-P60). As GluN1 subunits are required for NMDAR assembly and the formation of functional channels, expression of GluN1 acts as a proxy for measuring NMDAR expression. Our findings demonstrate no differences in total NMDARs at the synapse between transgenic mice and wildtypes, suggesting that the expression of the ABc or BAc subunits alone does not increase the size of the NMDAR synaptic pool. Results from immunoprecipitation experiments demonstrate an approximate 30% transformation of NMDARs from native to transgenic. These results suggest that total NMDAR synaptic content is not affected by the functional domains of GluN2 subunits. Thus, it is likely the synaptic pool of NMDARs is more strongly regulated by patterned synaptic activity of NMDARs, rather than purely the structural composition of GluN2 subunit functional domains.

Disclosures: R.E. Keith: None. **T.C. Dumas:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.02

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: HIMH Grant 084989

Title: RNA-binding FMRP and Staufen sequentially regulate the Coracle scaffold to control synaptic glutamate receptor and bouton development

Authors: *C. SONG[1], S. N. LEAHY[1], K. BROADIE[1,2,3];
[1]Biol. Sci., [2]Kennedy Ctr. for Res. on Human Develop., [3]Brain Inst., Vanderbilt Univ., Nashville, TN

Abstract: Fragile X Syndrome (FXS) caused by loss of the Fragile X Mental Retardation Protein (FMRP) is the leading heritable cause of both intellectual disability and autism spectrum disorders. Previously, we have established that FMRP plays important roles in modulating synaptic bouton formation and glutamate receptor (GluR) levels at the *Drosophila* neuromuscular junction (NMJ). However, the underlying molecular mechanism was entirely unknown. FMRP is primarily shown to act as an mRNA-binding translational regulator, with a number of known transcript targets. Here, we focus on FMRP-interacting mRNA-binding protein (RBP) Staufen and its downstream mRNA target, the actin-binding GluRIIA anchor Coracle. We tested FMRP, Staufen and Coracle interactions at the third instar NMJ, measuring synaptic bouton numbers and protein levels based on antibody labeling with fluorescent confocal imaging. Bouton numbers were counted blind to genotypes, and protein levels were quantified in sum-slice-projected images without including background fluorescent signals. We discovered that both *dfmr1* and *staufen* mutants, as well as trans-heterozygous double mutants, display increased synaptic bouton formation and GluRIIA levels, suggesting a common mechanism. To test protein-mRNA interactions, tagged FMRP and Staufen were transgenically expressed, followed by immunoprecipitation (IP) with anti-tag antibody-coated beads. By assaying IP'd RNAs, we found FMRP binds *staufen* mRNA and Staufen binds *coracle* mRNA, suggesting a FMRP-Staufen-Coracle pathway. With antibody labeling,

we found FMRP and Staufen both limit postsynaptic Coracle expression at the NMJ. We found that coracle mutants, as well as muscle-targeted coracle RNAi and overexpression, increase synaptic bouton formation and GluRIIA expression. Loss-of-function/gain-of-function phenotype convergence is consistent with Coracle functions in other contexts. Consistent with GluRIIA accumulation from disruption of the FMRP-Staufen-Coracle pathway, *dfmr1*, *staufen* and *coracle* mutants all elevate neurotransmission strength. FMRP, Staufen and Coracle also all suppress bone morphogenetic protein (BMP) trans-synaptic signaling mediating postsynaptic GluRIIA control of presynaptic bouton formation. These findings suggest that FMRP regulates Staufen to inhibit Coracle control of GluRIIA in the postsynaptic domain, and that postsynaptic GluRIIA in turn signals presynaptic bouton development. This work provides insights into the molecular mechanism of FMRP regulation of synaptic development, identifying potential new FXS treatment targets.

Disclosures: C. Song: None. **S.N. Leahy:** None. **K. Broadie:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH R00 MH106757
Pilot Discovery Award from CTSI-CN
Young Investigator Award from the Brain and Behavior Research Foundation
Margaret Q. Landenberger Research Foundation

Title: Maturation of glutamatergic transmission onto dorsal raphe serotonergic neurons

Authors: *A. KISNER, A. POLTER;
The George Washington Univ., Washington, DC

Abstract: Serotonin (5-HT) is a developmentally regulated neuromodulator/neurotransmitter that plays a critical role in brain development and influences a wide range of physiological processes as well as susceptibility to psychiatric illnesses. Over the course of development, ongoing maturation of synaptic inputs from upstream brain areas critically regulate serotonergic circuit function. Previous studies demonstrated that in early postnatal development functional excitatory synaptic activity onto dorsal raphe (DR) 5-HT neurons progressively increases and undergoes significant changes during the first 21 days of life (Rood et al.). However, little is known about developmental adaptations of convergent glutamatergic and GABAergic synapses onto DR 5-HTergic neurons or expression and function of postsynaptic receptors that regulate synaptic strength of these cells. Here, we used acute slice electrophysiology to systematically study the maturation of synaptic function onto DR 5-HT neurons from the neonatal period through adulthood. We found that during early postnatal day (PND) 6 the ratio of excitatory:inhibitory synaptic transmission onto 5-HT neurons is nearly proportional (mean excitation-inhibition ratio of spontaneous synaptic current amplitude 0.87 ± 0.13 and frequency 0.92 ± 0.22). While inhibition remained relatively stable over development, the strength of glutamatergic transmission increased

throughout adolescence and adulthood (one-way ANOVA, $F_{(5,55)} = 4.975$, $p = 0.0057$). We next examined the developmental adaptation of glutamatergic receptors by measuring the AMPAR/NMDAR ratio. We found that the AMPAR/NMDAR ratio also gradually increases and peaks during adolescence (one-way ANOVA, $F_{(5,46)} = 3.245$, $p = 0.0047$) and remains relatively stable throughout adulthood. The contribution of the AMPAR-mediated component to the evoked-synaptic currents in 5-HT neurons was significantly higher than the NMDAR-mediated component and was stable across the entire developmental period. Lastly, we examined whether there are shifts in the composition of AMPARs in these synapses along development. The peak of current-voltage relationship of the AMPAR-component over the course of development showed that in a subset of 5-HT neurons these receptors are inwardly rectifying, indicating that they are permeable to calcium even into adulthood. We anticipate that our findings will be a starting point to understand how the maturation of synapses on 5-HT neurons contributes to the integration of information from upstream brain areas and reciprocal modulation of forebrain circuits by 5-HTergic neurons.

Disclosures: A. Kisner: None. **A. Polter:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.04

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant 5R01NS098804-04
NIH Grant 5F31NS113394-02

Title: Developmental regulation of H3K27me3 drives synapse maturation and social behavior

Authors: *U. CHAN[1], V. RAMESH[1], R. LI[1], M. MINTO[1], K. GE[2], A. E. WEST[1];
[1]Neurobio., Duke Univ. Sch. of Med., Durham, NC; [2]Natl. Inst. of Diabetes and Digestive and Kidney Dis., NIH, Bethesda, MD

Abstract: The deposition and removal of H3K27me3 by methyltransferases EZH1 and -2 and demethylases KDM6A and -B are tightly regulated throughout development to control transcription. This repressive mark is lost at specific loci during differentiation to mediate specific gene activation necessary for each developmental stage, thereby providing a mechanism underlying the induction of cell-specific and temporally specific gene expression programming. However, this raises the question as to what the role of H3K27me3 in non-dividing cells like neurons may be and whether there are mechanisms governing its dynamicity throughout neuronal development. We have previously identified a novel role for KDM6B in post-mitotic cerebellar granule neurons (CGNs) in mediating the induction of a mature gene expression program that includes many synaptic genes. Consistent with this, there is a gradual loss of H3K27me3 along specific loci of KDM6B target genes like *Grin2c* at different time points post-differentiation. Therefore, we hypothesize that dynamic regulation of H3K27me3 by KDM6B is required during CGN maturation for proper synaptic development. To do this, we conditionally knock out *Kdm6b* by electroporating CRE recombinase into the developing cerebellum of $Kdm6b^{fl/fl}$ mice. Neurons without

Kdm6b have smaller and less complex dendritic claws, which are the sites that contain a majority of the synaptic inputs onto CGNs. Furthermore, we have shown that proper claw formation is dependent on KDM6B's enzymatic activity. KO CGNs also have an increased distribution of VGLUT2-positive synapses on their smaller claws, suggesting that under normal conditions, KDM6B works to develop these claws in order for the cells to properly distribute synapses. Interestingly, mice lacking KDM6B's demethylase activity show deficits in social novelty and discrimination, highlighting a possible behavioral consequence linked to chromatin misregulation. Whether this aberrant phenotype is specifically due to synaptic defects associated with loss of KDM6B's enzymatic activity remains to be resolved. That being said, these experiments elucidated a novel role for KDM6B in regulating synapse development and expanded our knowledge on how chromatin regulation contributes to neuronal maturation and ultimately, social behavior.

Disclosures: U. Chan: None. **V. Ramesh:** None. **R. Li:** None. **M. Minto:** None. **K. Ge:** None. **A.E. West:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.05

Topic: B.06. Synaptic Transmission

Support: NIH R01 AG061865

Title: Protein Quality Control Machinery In The Postsynaptic Compartment

Authors: *A. UPADHYAY, J. N. SAVAS;
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Abstract: Protein Quality Control Machinery in the PostsynapticCompartment
Arun Upadhyay, Jeffrey N. Savas
Department of Neurology, Northwestern University Feinberg School of Medicine Chicago 60611
Background: Synapse formation is a tightly regulated developmental process controlled by multiple transcriptional factors, axon guidance cues, signaling pathways, and synaptic adhesion proteins. To maintain the synaptic structures, cells continuously replace old proteins with newly synthesized copies. However, the mechanisms involved in regulating the turnover of synaptic proteins are unknown.**Objective:** Identify the synaptic protein quality control (PQC) machinery. Determine if presynaptic or postsynaptic compartments selectively harbor different PQC factors.**Methods:** We isolated the synaptic membranes from P21 rat brains using classical sucrose-density gradient methods and purified the PSD fraction. We analyzed different fractions isolated from the brain and compared the proteomic profiles using sample multiplexing by isobaric TMTlabeling of peptides followed by MS3 mass spectrometry. Further bioinformatic analysis was performed to identify crucial PQC players in presynaptic and postsynaptic fractions. Immunoblots and other biochemical assays verified the results obtained.**Results:** Gene ontology (GO) enrichment analysis of the TMT experiment data sets revealed the abundance of numerous chaperones and components of the protein degradation machinery. While

chaperones were abundant in the synaptosome fraction, postsynaptic density (PSD)fractions were selectively enriched with UPS components, including ubiquitin-activating (E1), conjugating (E2), E3 ligase, and deubiquitinase enzymes. Among all these proteins, WW domain-containing HECT E3 ubiquitin ligases are most significantly enriched at postsynaptic locations. Notably, our results indicate that proteasome-mediated protein degradation actively regulates the turnover of proteins in postsynaptic compartments.**Conclusions.** Ubiquitin proteasomal system (UPS) synchronizes cellular processes in the postsynaptic compartment by regulating the turnover of critical protein components involved in signaling and metabolic processes. Our results suggest that HECT domain E3 ubiquitin ligases are essential components of postsynaptic proteostasis machinery required for neuronal development and protection from neurodegeneration.
Presenting Author: Arun Upadhyay, Ph.D. (arun.upadhyay@northwestern.edu)Corresponding Author: Jeffrey Savas, Ph.D. (jeffrey.savas@northwestern.edu)

Disclosures: A. Upadhyay: None. **J.N. Savas:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

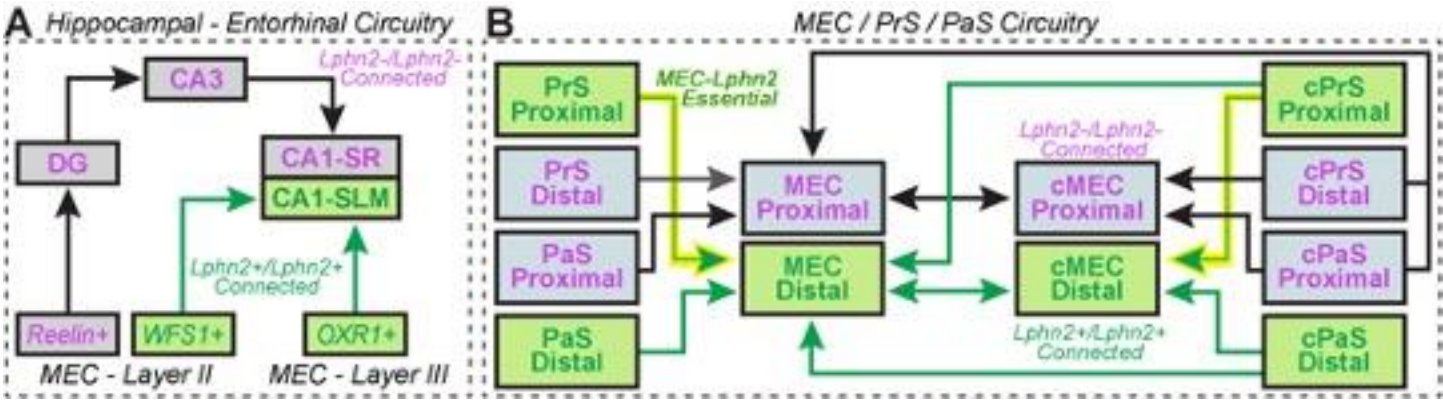
Support: Whitehall Foundation 2018-08-01
Initial Complement Funds from the University of California, Riverside to G.R.A.

Title: Latrophilin-2 controls topographic synaptic assembly of entorhinal inputs

Authors: *J. D. DONOHUE, T. R. MURPHY, G. R. ANDERSON;
Neurosci., Univ. of California, Riverside, RIVERSIDE, CA

Abstract: Brain circuits are comprised of distinct interconnected neurons that are assembled according to synaptic recognition molecules presented on defined pre- and post-synaptic sites. This cell-cell recognition process is mediated by varying cellular adhesion molecules, including the latrophilin family of adhesion G-protein coupled receptors (Lphn1-3; gene symbols *ADGRL1-3*). Recently, latrophilins have been shown to mediate excitatory synaptogenesis through trans-synaptic interactions with extracellular binding partners teneurins and FLRTs. Of the three latrophilin genes, Lphn2 demonstrates the most stringent expression patterning, and is the focus of this study. Here we sought to define cell type specific expression and Lphn2 protein localization within the parahippocampal circuit of interconnected subregions of the medial entorhinal cortex (MEC), presubiculum (PrS), and parasubiculum (PaS). In doing so, we find notable topographical expression patterning at both the protein and RNA level in all three of these interconnected regions. To study the role of Lphn2 in controlling the connectivity between these regions, we utilized a retrograde labeling approach. Performing dual-retrograde viral tracing from the Lphn2 deficient versus enriched compartments of the MEC reveals unique topographical patterning of inputs arising from the PrS and PaS which mirrors Lphn2 expression. We find that Lphn2 enriched compartments of these regions show strong connectivity, whereas Lphn2 deficient compartments of these

regions show similarly enriched connectivity. Using this retrograde viral labeling method coupled with a Lphn2 conditional knock-out mouse model, we find that deletion of Lphn2 expression in the MEC selectively impairs labeling of inputs arising from the ipsilateral PrS. Combined with analysis of Lphn2 expression within the MEC, these data reveal Lphn2 as a molecule that is expressed by defined cell types, and selectively controls circuit development between interconnected regions.



Disclosures: J.D. Donohue: None. **T.R. Murphy:** None. **G.R. Anderson:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.07

Topic: B.06. Synaptic Transmission

Support: NIMH grant MH052804
Stanford Interdisciplinary Graduate Fellowship

Title: Mechanism of Self-Avoidance in Synaptic Neurexin Complexes

Authors: *C. WANG[1], J. H. TROTTER[1], K. LIAKATH-ALI[1], S. LEE[1], X. LIU[2], T. C. SUDHOF[1,3]; [1]Mol. and Cell. Physiol., Stanford Univ., Stanford, CA; [2]Cell Biol., Yale Univ., New Haven, CT; [3]Howard Hughs Med. Inst., Stanford, CA

Abstract: Synapses are thought to be organized by interactions of presynaptic neurexins with postsynaptic ligands, such as neuroligins and cerebellins. However, when a neuron forms adjacent pre- and postsynaptic specializations, such as observed in dendro-dendritic or axo-axonic synapses, *cis*-neurexin/ligand interactions would be energetically favored but functionally inactive. Here, we reveal an organizational principle for preventing synaptic *cis*-interactions ('self-avoidance'). Using dendro-dendritic synapses between mitral and granule cells in the olfactory bulb as a paradigm, we show that, owing to its higher binding affinity, cerebellin-1 blocks the *cis*-interaction of neurexins with neuroligins, thereby enabling *trans*-interaction of neurexins with their ligands. In mitral cells, ablating either cerebellin-1 or neuroligins severely impaired granule cell->mitral cell synapses, as did overexpression of wild-type neurexins but not of mutant neurexins unable to bind to neuroligins. Our data uncover a

molecular interaction network that organizes the self-avoidance of non-functional neurexin *cis*-complexes, thus allowing assembly of functional *trans*-synaptic neurexin complexes.

Disclosures: C. Wang: None. **J.H. Trotter:** None. **K. Liakath-Ali:** None. **S. Lee:** None. **X. Liu:** None. **T.C. Sudhof:** None.

Poster

P027. Synapse Formation

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P027.08

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: 1 F31 NS118799-01A1
Training Grant 5 T32 MH 19929-25

Title: Exploring the mechanisms of Semaphorin/Plexin-mediated synapse formation in the intact hippocampus

Authors: *S. ADEL[1], T. KOWALSKI[2], M. BUCK[4], S. PARADIS[3];
[1]Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; [3]Biol., [2]Brandeis Univ., Waltham, MA; [4]Case Western Reserve Univ., Cleveland, OH

Abstract: In the mammalian brain, two main types of chemical synapses - glutamatergic and GABAergic - play opposing roles in exciting or inhibiting the postsynaptic cell. While it is critical that upon cell-cell contact, new synapses form the correct postsynaptic specialization (excitatory or inhibitory), it remains a fundamental mystery in developmental neurobiology which molecular pathways specify this identity. We previously reported that in mammalian hippocampus, semaphorin-4D (Sema4D) and sempahorin-4A (Sema4A) promote formation of inhibitory synapses by signaling to their receptor Plexin-B1, while Sema4A also promotes formation of excitatory synapses by signaling to another Plexin-B family member, Plexin-B2. We sought to identify specific cellular signaling mechanisms downstream of Plexin-Bs that differentially specify formation of inhibitory or excitatory synapses. To accomplish this goal, we developed four chimeric versions of Plexin-B receptors with domain swaps between Plexin-B1 and Plexin-B2. We verified their expression and surface localization in COS7 cells. Currently, we are expressing the chimeric Plexin-B receptors in hippocampal slices from *Plxnb1; Plxnb2* double knockout mice to assay which domains are necessary and/or sufficient to promote excitatory or inhibitory synapse formation upon treatment with Sema4D or Sema4A. The results of these experiments will elucidate how different class 4 Semaphorins initiate distinct, Plexin-B signaling mechanisms to promote excitatory or inhibitory synapse formation.

Disclosures: S. Adel: None. **T. Kowalski:** None. **M. Buck:** None. **S. Paradis:** None.

Poster

P029. Neural Circuit Maturation and Remodelling II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P029.01

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: CIHR/EraNet

Title: Role of p75 neurotrophin receptor in cortical parvalbumin-positive GABAergic interneurons plasticity and cognitive flexibility

Authors: *P. CHEHRAZI[1,2], B. CHATTOPADHYAYA[2], M. LAVERTUJOLIN[2], G. DI CRISTO[2]; [1]universite de montreal, Montreal, QC, Canada; [2]CHU St. Justine, Montreal, QC, Canada

Abstract: Parvalbumin (PV)-positive GABAergic interneurons constitute the majority of interneurons in the cortex and play a key role in the function and synchronization of cortical networks. Alterations in PV-interneuron connectivity, especially in the medial prefrontal cortex (mPFC), has been found in different psychiatric disorders. We have previously shown that the expression of the p75 neurotrophin receptor (p75NTR) regulates the time course of PV cell synapse maturation in a cell-autonomous fashion. Here, we show that p75NTR removal in postnatal PV cells affects the connectivity and plasticity of PV interneurons and mPFC function in adult PvCre dependent conditional knockout (cKO) mice. We first analyze the effect of p75NTR removal on the efferent and afferent connectivity of PV cells in the perisomatic region. We quantified putative synapses formed by PV cells, identified by the juxtaposition of PV and gephyrin, a post synaptic scaffolding protein of GABAergic synapses. We further used Synaptotagmin 2 immunolabeling to identify PV cell pre-synaptic sites Both the density of PV+gephyrin+ puncta and the percentage of perisomatic PV puncta showing juxtaposed gephyrin were significantly increased in mPFC but not in visual cortex (VC) of cKO mice. Similarly, Synaptotagmin+ puncta were significantly increased around pyramidal cell somata in mPFC of cKO mice. Further analysis of prefrontal PV cells showed higher density of putative excitatory synapse density on PV cell somata. An important indication of PV cell maturation is the appearance of specialized extracellular matrix structures called perineural nets (PNNs) around the soma and primary dendrites of mature cortical PV cells. p75 cKO mouse showed a significant increase in the number of PV cells encircled by PNN, as revealed by WFA staining, in mPFC but not VC. These mice also showed deficits in attentional set-shifting task, a measure of attention and cognitive flexibility, and in extinction of fear memories, both of which rely on mPFC function.We are currently investigating whether the observed structural remodeling lead to PV cell activity alterations as revealed by measuring expression levels of the neuronal activity marker c-Fos in PV cells following tail-pinch stimulation. In addition, we are investigating whether AAV-mediated reintroduction of P75NTR in PV cells can rescue their structural alteration in cKO mice. These findings suggest that P75NTR is a critical regulator of PV cell plasticity, thus modulating cognitive functions, in adult mPFC.

Disclosures: P. Chehrazi: None.

Poster

P029. Neural Circuit Maturation and Remodelling II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P029.02

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant K99DC018779

Title: Hormonally-regulated maturation of spontaneous neural activity and associative learning

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Abstract: Adult behavior is the product of neural circuits that have been sculpted during development by genetic programs and experience in the form of neural activity. Despite the fundamental role of spontaneous neural activity in circuit refinement, the mechanisms underlying neural activity state transitions and their behavioral function remain poorly understood. The *Drosophila* mushroom body, with its well characterized anatomy, powerful genetic tools and well-established role in learned behaviors, is an ideal system for investigating the developmental maturation of higher order neural circuits and behavior. Here, we identify and characterize a hormonally-triggered age-dependent reduction of spontaneous activity in Kenyon cells, the principal neurons of the mushroom body, which is required for enhanced associative learning, thereby gaining insight into fundamental neurodevelopmental processes. By monitoring neural activity *in vivo*, we identified spontaneous, asynchronous activity in the mushroom body learning center of very young adult flies. This activity declines significantly over the first week of adulthood. Moreover, this activity is generated cell-autonomously via Cacophony voltage-gated calcium channels in a single cell-type, α'/β' Kenyon cells. We identified juvenile hormone, a crucial regulator of developmental timing similar to mammalian thyroid hormones, as the trigger for the transition from the young high activity state to the mature low activity state. Animals with juvenile hormone signaling transiently inhibited specifically in α'/β' Kenyon cells in a young sensitive period failed to transition to the mature low activity state. Our findings suggest that JH signaling directly orchestrates changes in ion channel and transcriptional activator gene expression that modify the output of Kenyon cell circuits. Fascinatingly, we observed a significant enhancement in aversive associative learning performance over the first week of adulthood, the same time course as the decrease in spontaneous activity. α'/β' activity in a young animal sensitive period was required for subsequent robust learned behavior in mature animals. Transient hormonal signaling in young animals was also required to enhance subsequent learned behavior. Thus, we identified a hormone-triggered neural activity state transition in young animals required for the maturation of associative learning. Taken together, these studies improve our understanding of fundamental mechanisms for brain development and suggest that hormone signaling in young animals coordinates the maturation of neural activity, enabling the emergence of mature adult behaviors.

Disclosures: S.G. Leinwand: None. **K. Scott:** None.

Poster

P029. Neural Circuit Maturation and Remodelling II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P029.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: German Research foundation (CRC1080, project number 221828878)

Title: Single-nucleus RNA-sequencing of reprogrammed neurons reveals transcriptional dynamics in response to neural network activity modulation

Authors: *N. SHARIF[1,2], F. CALZOLARI[1], B. BERNINGER[3,1];
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Abstract: Cortical astrocytes can be reprogrammed into glutamatergic forebrain neurons through overexpression of the basic-helix-loop-helix transcription factor Neurog2 (Berninger et al., 2007). Over a period of 2-6 weeks *in vitro*, the reprogramming process stably induces properties such as acquisition of complex neuronal morphology, expression of neuron-specific proteins and the gain of functional neuronal properties such as action potential firing and establishment of synaptic connections. However, little is known regarding the extent to which induced neurons (iNs) can undergo lasting and hence functional transcriptional adaptations in response to changing network activity. Here, we assessed the transcriptional response of iNs to global network activity modulation and compared it to the response elicited in endogenous cortical neurons (eNs). To this end, we co-cultured iNs with eNs and pharmacologically inhibited network activity for 2 days. By performing single-nucleus RNA-seq analysis we demonstrate that iNs can undergo changes in known activity-dependent, synapse-related gene expression. Interestingly, however, iNs and eNs modulate mostly distinct sets of genes that possibly reflect differences in cell identity as well as maturation level. By inferring gene regulatory network dynamics, we are beginning to identify shared and unique transcriptional programs underlying responses to changes in neuronal network activity in endogenous and reprogrammed neurons.

Disclosures: N. Sharif: None. **F. Calzolari:** None. **B. Berninger:** None.

Poster

P029. Neural Circuit Maturation and Remodelling II

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Program #/Poster #: P029.04

Topic: A.06. Synaptogenesis and Activity-Dependent Development

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Title: Mature parvalbumin interneuron function in prefrontal cortex requires activity during a postnatal sensitive period

Authors: *S. CANETTA[1], E. S. HOLT[2], L. J. BENOIT[1], E. TEBOUL[2], R. T. OGDEN[1], A. HARRIS[1], C. KELLENDONK[1];
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Abstract: In their seminal findings, Hubel and Wiesel identified sensitive periods in which experience can exert lasting effects on adult visual cortical functioning and behavior via transient changes in neuronal activity during development. Whether comparable sensitive periods exist for non-sensory cortices, such as the prefrontal cortex (PFC), in which decreased activity can lead to persistent changes in adult circuit function and behavior, remains unknown.
In sensory cortices, experimental manipulations of activity are elicited by directly manipulating the primary sensory organ. This approach is not feasible in the PFC as it receives no direct sensory information. To overcome this challenge, we have developed a system that allows modulation of prefrontal activity during distinct developmental windows using viral expression of the DREADD receptor, hM4DG$_i$. Here, we specifically modulated the activity of prefrontal parvalbumin-expressing (PV) interneurons, as this cell population is known to sculpt the output of excitatory cortical pyramidal neurons and to undergo a protracted period of physiological maturation and integration into cortical circuitry during peripuberty and adolescence.
Using this system, we investigated whether peripuberty and adolescence is a sensitive period in which transiently altering the activity of PV interneurons can persistently impact adult PFC function and behavior. We expressed hM4DG$_i$, or the control protein mCherry, in developing PV interneurons, administered the agonist for hM4DG$_i$, clozapine-N-oxide, from postnatal day P14 to P50, and examined attentional set-shifting behavior and underlying prefrontal cortical activity using stereotrodes in adulthood (P90). We also assessed the connectivity of PFC PV cells onto pyramidal neurons in adulthood using optogenetics combined with slice electrophysiology. Sample sizes range from 4 to 17 and both sexes were included.
We now demonstrate that inhibition of prefrontal PV interneurons during peripuberty and adolescence results in *persistent* impairments in adult prefrontal circuit connectivity, *in vivo* network function and behavioral flexibility that can be ameliorated by targeted activation of PV interneurons using a stabilized step function opsin in the adult animal. In contrast, transient suppression of PV interneuron activity in adulthood produces no lasting effects. These findings identify an activity-dependent sensitive period for prefrontal circuit maturation and highlight how abnormal PV interneuron activity during development can persistently alter adult prefrontal circuit function and cognitive behavior.

Disclosures: S. Canetta: None. **E.S. Holt:** None. **L.J. Benoit:** None. **E. Teboul:** None. **R.T. Ogden:** None. **A. Harris:** None. **C. Kellendonk:** None.

Poster

P029. Neural Circuit Maturation and Remodelling II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P029.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Role of GABAergic synaptic maturation in the anterior piriform cortex in the home-nest odor discrimination of infant rats. A behavioral and computational study

Authors: G. E. PARDO[1], C. MEDINA-SALDIVAR[1], C. BECERRA[1], L. F. PACHECO-OTALORA[1], *E. M. ORURO[2];
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Abstract: Background: During the first two weeks of postnatal life, infant rodents exhibit social preferences guided by odors of the mother, other conspecifics, or other nest-typical scents. In mice pups, home odor preference is present as early as five days of age; however, the ability to discriminate home nest odors from other, closely related nests appears on the postnatal day (PND) 10. In the present work, we also report this phenomenon in infant rats. One possible explanation at the neuronal level for why PND 10 pups discriminate their nest odor from another very similar nest odor but not younger pups is the differential rewarding action of the maternal care profile (nest entries/exists) in the olfactory circuit involved in this behavior. Another possible explanation is the developmental change of GABAergic synaptic transmission in the olfactory cortex. **Methods**: To test the first hypothesis, we use our previous olfactory bulb (OB)- anterior piriform cortex (aPC) computational circuit model for PND 5-8 rat pups built with our own experimental data and conditioned to home odor as the conditioned stimulus (CS) paired with norepinephrine (NE) release. The CS-NE pairing was simulated according to the maternal care profile experimental data corresponding for PND 5 and PND 10 and then evaluated for the response of the OB-aPC circuit to the CS and other nest odor, 60% similar to the home odor. To test the second hypothesis, we included experimental data from PND 5 and PND 10 aPC GABA synaptic input profile to OB-aPC computational circuits and then simulated the home-odor processing in the presence of NE release. This configuration attempts to represent active odor processing of the pups inside the nest while receiving maternal care. The response of the OB-aPC circuit to the home odor and other nest odor, 60% similar to the home odor, was evaluated before and after the odor-NE exposition. **Results**: The results show that the number of active neurons and evoked spikes for the home-odor and other nest odor were similar for both ages in the maternal profile conditioning simulation. On the other hand, the number of active neurons and evoked spikes in response to home odor were higher than for the other nest in the PND 10 circuit, but this comparison was similar in the PND 5 circuit. **Conclusions**: Our results support the idea that the ability to discriminate between closely associated nest odors in PND 10 rat pups can be, at least partially, attributed to the developmental changes of GABA synaptic transmission in the odor processing circuits of the rats rather than to a change in rewarding stimulation of the maternal care profile.

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Poster

P029. Neural Circuit Maturation and Remodelling II

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Program #/Poster #: P029.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01HD100607-01A1

Title: Spontaneous neuronal activity is reduced during the 'vulnerable' period of nascent neural circuit formation in the hippocampus of Ts65Dn mice, a genetic model of Down syndrome

Authors: F. MADAMBA, B. K. LE, ***A. M. KLESCHEVNIKOV**;
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Abstract: Down syndrome (DS), a developmental disorder due to triplication of chromosome 21, is characterized by developmental delays and profound cognitive impairment. Most of the changes leading to the abnormalities become apparent during the "vulnerable" early period of brain development when neonatal neural circuits are formed and developed. Spontaneous neuronal activity plays a pivotal role in the establishment of appropriate synaptic connections and the maturation of the neural circuits. Here we compared spontaneous neuronal activity in the CA3 region of littermate Ts65Dn and normosomic control (2N) pups during the first three weeks of postnatal development. The measurements were performed using microelectrode recordings of spontaneous multi-unit activity (MUA) in acute hippocampal slices. We observed that, on average, the MUA frequency was significantly reduced in slices of Ts65Dn *vs*. 2N pups at the age of p8 - p12 (2N: 100 ± 12.6%, Ts65Dn: 66.1 ± 6.9%, $p = 0.011$). In older animals (p14 - p25), the averaged MUA frequency was not different in Ts65Dn *vs*. 2N pups (2N: 100 ± 8.8%, Ts65Dn: 103.9 ± 8.8%, $p = 0.37$). One of the factors contributing to the decrease in spontaneous neuronal activity is the increased expression of Kir3.2 subunits of G-protein-coupled inwardly rectifying potassium channels, which gene (*Kcnj6*) is triplicated in DS and Ts65Dn DS model. The decrease in spontaneous neuronal activity likely affects synaptogenesis and contributes to the formation of malfunctioning neural circuits, which serve as the neural basis for cognitive abnormalities in DS. Correcting spontaneous neuronal activity during this 'vulnerable' period of brain development by genetic or pharmacological means might correct the formation of neural circuits and improve cognition in DS models.

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Poster

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

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Title: Emergence of complex network topology from the self-organization of cultured neural circuits

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Abstract: In the last two decades the study of neural elements, such as neurons and brain areas, and their interactions in a network perspective has been an area of active research. The discovery of the small-world and scale-free properties in these networks has been helping to uncover their complex dynamics. However, little is known about how these complex frameworks emerge during neurodevelopment and how they are changed by sensory stimuli. Regarding small-world architecture, some hypotheses were raised in the computation models research field. Watts and Strogatz (1998) proposed a random rewiring scenario of a lattice network for generating small-world networks, while Kwok et al. (2007) suggested a Hebbian-like rewiring scenario of random neuronal networks. Nonetheless, the biological rewiring process is not efficient, especially when considering structural networks. To investigate how the self-organization of *in vitro* neural circuits drives to complex neuronal network topology we applied effective connectivity techniques to electrophysiological signals from rat dissociated hippocampal neuron cultures during their maturation process (29 days *in vitro*, freely available data set: 10.6080/K0PC308P). Bivariate Transfer Entropy, an information-theoretic quantity used to measure time-dependent interactions, was computed using binarized spike rasters derived from the neural recordings to construct weighted and directed networks. Topological properties were measured using graph-theoretic metrics and compared during different stages of network development (min: 9, max: 18, mean: 15 per day *in vitro*). As the number of edges in the network increased over time neurons formed clusters and the small-world topology emerged. Further, we detected the subdivision of the networks into communities where modules of few highly connected neurons were integrated mostly by high firing rate neurons. These findings suggest an important role of silent synapses activation during neurodevelopment. We hypothesized that the organization of the developing network topology in these complex frameworks is due to plasticity and homeostatic mechanisms that reinforce synchronized spontaneous activity by activating silent synapses and scaling active ones. Once such a mechanism might establish effective connections, clustering together and linking within modules synchronized neurons as well as favoring connections between high firing rate neurons. This empirical study allowed the formulation of a new hypothesis regarding small-world architecture and other complex network properties, instead of considering a rewiring of connections we suggest a selection of silent ones.

Disclosures: P. Correia Antoneli: None. **T.F. Varley:** None. **M. Porcionatto:** None. **O. Sporns:** None. **J. Faber:** None.

Poster

P029. Neural Circuit Maturation and Remodelling II

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P029.08

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Grant to Thomas Biederer by Mead Johnson Nutrition/Reckitt Benckiser

Title: The human milk component myo-inositol promotes the postnatal maturation of neuronal connectivity in offspring

Authors: *S. VOGEL[1], M. ABOULEISH[1], B. E. CARBONE[1], S. D. MARIA[2], B. LABHART[2], S. C. PHILLIPS[2], A. L. MORROW[3,4], C. KUANG[5,6], D. HONDMANN[5,6], T. BIEDERER[1,7,8];
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Abstract: Rationale: Brain development is guided by an interplay of genetic and environmental factors. Dietary contributions, including bioactive compounds in human milk, are incompletely understood. We investigated human milk samples collected across global populations and found that the sugar alcohol *myo*-inositol is most abundant in the first postnatal weeks when synapses form rapidly in the infant brain. We analyzed effects of *myo*-inositol on brain development in the visual system due to its well-defined postnatal maturation. Methods: We supplemented the diet of male and female C57B6J mice with 50 mg/kg body weight *myo*-inositol or vehicle control daily from the day after birth to postnatal day 8 to 35 (P8-P35). We measured visual acuity by recording visually evoked potentials from the visual cortex (V1) of adult animals. Furthermore, we measured thalamic eye input segregation by labeling of retinal ganglion cells using cholera toxin (CTB) bound fluorescent dyes. Microglial pruning of retinogeniculate synapses was measured with immunohistochemistry (IHC) staining for a marker of microglia. Reconstructions of cells were then used as 3D masks and internalized CTB-conjugated dyes were quantified. IHC was used to characterize synapse size and density in V1. Investigators were blinded to treatment allocation during image acquisition and data analysis. Results: *Myo*-inositol supplementation increased adult visual acuity from 0.38 ± 0.17 to 0.66 ± 0.30 cycles per degree (unpaired t-test; N=5/8, t=4.49, p=0.0009). At P14, *myo*-inositol significantly augmented eye input segregation in the thalamus. There was no difference in segregation at the earlier P11 timepoint. In the same region, microglia from *myo*-inositol treated P8 mice contained 28 ± 15% more CTB-labeled boutons, occupying 4.3 ± 0.42% of the cell volume compared to 3.4 ± 0.24% for control animals (unpaired t-test; N=5/6, t=1.88, p=0.046). In V1b at P35 we found a selective increase in the size but not density of Homer positive puncta, a marker of postsynaptic excitatory synapses. Size was increased from 0.129 ± 0.02 μm^2 in control animals to 0.192 ± 0.02 μm^2 for *myo*-inositol supplementation (unpaired t-test; N=5/4, t=2.764, p=0.028). Conclusions: Dietary complementation with *myo*-inositol from birth substantially increased visual acuity. This was accompanied by improved formation of neuronal connectivity, with *myo*-inositol promoting retinotopic input refinement and synaptic pruning in the visual thalamus and synapse maturation in the visual cortex. These results reveal significant effects of the human milk component *myo*-inositol on neuronal connectivity and input processing in the developing brain.

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Poster

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Program #/Poster #: P029.09

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Vi Riddell Pediatric Rehabilitation Pain Research Program Grant #1001200
NSERC Grant RT690332
CIHR Grant 10015088

Title: Dexmedetomidine: how safe is this anesthetic?

Authors: *N. JIMENEZ-TELLEZ[1], F. IQBAL[2], M. PEHAR[2], A. CASAS-ORTIZ[1], T. K. RICE[3], N. I. SYED[4];
[1]Biochem. and Mol. Biol., [2]Hotchkiss Brain Inst., [3]Anesthesiology, Perioperative and Pain Med., [4]Cell Biol. and Anat., Univ. of Calgary, Calgary, AB, Canada

Abstract: Anesthetics are an essential part of most - if not all - major clinical procedures. However, the precise mechanisms of how anesthetics exert their actions remain poorly defined. Moreover, notwithstanding their essential requirements for all surgical procedures, recent animal studies have raised alarm bells regarding anesthetic's long-term cytotoxic effects - especially on the brain. In this study, we tested dexmedetomidine (DEX), an anesthetic agent with distinctive molecular targets, to evaluate its effects on neuronal development and cognition both *in vitro* and *in vivo*. For the *in vitro* model, rat cortical neurons extracted from postnatal day 0 pups (P0) were exposed to different DEX concentrations (0.05 µM to 10 µM) and different cellular parameters were assessed, such as cellular viability, neurite outgrowth, synaptic formation, mitochondrial morphology and reactive oxygen species (ROS) production. For the *in* vivo model, rat pups were injected subcutaneously with DEX 25 µg/kg on P7 and again on P8. Open field testing was used to assess locomotor skills, anxiety and willingness to explore a new environment and hippocampal-dependent memory was evaluated on P60 using Morris Water Maze (MWM) and Novel Object Recognition tests (NORT). We show here that DEX does not cause neuronal cell death when used below 10 µM. Interestingly, DEX-exposed neurons showed an increased neuronal outgrowth, albeit with no differences in corresponding synaptic puncta formation. Furthermore, DEX resulted in a hyperfused mitochondrial network, occurring in a time-dependent manner, which also caused reduced ROS production. Subcutaneous DEX injections in rat pups did not alter the respiratory rate or oxygen saturation (SpO2). DEX did not impact locomotor skills, anxiety, or willingness to explore. Finally, DEX also did not affect spatial recognition and hippocampal-dependent memory. This study demonstrates the non-neurotoxic nature of DEX both *in vitro* and *in vivo* in an animal model providing support for its utility as a safer anesthetic agent.

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Poster

P029. Neural Circuit Maturation and Remodelling II

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Program #/Poster #: P029.10

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ZonMw TOP grant 9126021

Title: The timing of the GABA shift affects the postnatal development of inhibitory and excitatory synapses

Authors: *C. N. E. PEERBOOM, T. B. WIJNE, M. P. J. M. RIETER, N. L. JONKER, C. J. WIERENGA;
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Abstract: GABA signaling shifts from depolarizing to hyperpolarizing during the second postnatal week in rodents. The GABA shift results from a reduction in intracellular chloride concentration mediated by increased activity of the chloride exporter KCC2 relative to the chloride importer NKCC1. A delayed GABA shift has been observed in patients with autism spectrum disorder and in several mouse models for neurodevelopmental disorders. It is currently unclear whether a delayed GABA shift is cause or consequence for alterations in synaptic transmission observed in these mouse models.
Here we assessed the consequences of mistimed GABA shift on synapse development in hippocampal slice cultures. We first verified that in our slices GABA shifts between day in vitro (DIV) 2 and 22. We then set out to delay the GABA shift by blockingKCC2 with VU 0463271 or furosemide during DIV2-8 and assessed the consequences for inhibitory and excitatory postsynaptic currents (IPSCs and EPSCs) at DIV9 and DIV21. We used perforated patch clamp and the chloride indicator SuperClomeleon to assess GABA function and intracellular chloride levels. Blocking KCC2 with VU 0463271 resulted in a depolarizing GABA reversal potential at DIV8, which normalized at DIV20. Inhibitory signaling was not affected at DIV9. However, at DIV21, when chloride levels were restored, the frequency of spontaneous IPSCs was increased, while amplitudes were unaffected.
Unexpectedly, GABA became strongly hyperpolarizing at DIV 8 after DIV2-8 furosemide treatment. We observed a decrease in the frequency of spontaneous IPSCs at DIV9, which appears due to an activity dependent suppression of inhibitory transmission. We found that this was independent of BDNF or endocannabinoids. When chloride levels were restored at DIV 21, the frequency of spontaneous IPSCs and the amplitude of miniature IPSCs were increased. We are currently examining the effects of inhibiting KCC2 on excitatory transmission and spine development. Our results indicate that the timing of the GABA shift affects postnatal development and maturation of inhibitory synapses.

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Poster

P085. Opiates, Cytokines, and Other Neuropeptides

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P085.01

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Paul G Allen funding

Title: Evidence for cell type specific local neuropeptide signaling from single-cell transcriptomes of forebrain neurons from four divergent tetrapods

Authors: *S. J. SMITH;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The primary function common to all neurons is communication with other neurons. This communication can take many forms, including synaptic transmission and slow neuromodulation via secreted neuropeptides (NPs). Because neurons are very diverse in the particulars of such communication, neuron type classification schemes have proven very useful in exploring the emergence of network function, behavior and cognition from individual neuronal communication links.
To shed light on the evolution and functional relevance of peptidergic modulatory signaling within local brain regions, I have analyzed published genome-wide single cell RNA-Seq transcriptomic datasets acquired from turtle pallium (Tosches MA Science 2018 10.1126/science.aar4237), songbird HVC and RA nuclei (Colquitt B Science 2021 10.1126/science.abd9704), mouse motor cortex (Yao Z Cell 2021 10.1016/j.cell.2021.04.021) and human motor cortex (Bakken T E bioRxiv 2020 10.1101/2020.03.31.016972). Samples in each dataset were similarly annotated by hierarchical neuron-type classification.
Quantitative analysis of these single-cell transcriptomes reveals that the vast majority of neurons sampled from each tetrapod express one or more genes encoding neuropeptide precursor proteins (NPPs) at exceptionally high levels and in highly cell-type-specific combinations. Virtually all cells sampled also showed diverse cell-type-specific expression of multiple neuropeptide-selective G protein-coupled receptor (NP-GPCR) genes at high levels.
Many of the NP-GPCR genes expressed with a given brain region are cognate in their neuropeptide selectivity to NPPs expressed within that same brain region, suggesting the likelihood of local, strictly paracrine neuropeptide signaling. This prospect is particularly compelling for the GABAergic neuron types, since most such neurons are relatively sparse and lack distant axonal projections, making distant actions of GABAergic-neuron peptide release unlikely. The extraordinarily high-levels of NPP gene transcription by GABAergic neurons nonetheless argue that the NP products must be secreted and play major significant adaptive roles in local neuronal neuromodulatory communication.
This poster illustrates all findings noted above and documents both similarities and differences in NP gene expression patterns amongst the varied forebrain regions studied. The many similarities, regardless of whether they result from evolutionary conservation or convergence, add to evidence that NP signaling has long been and remains of fundamental importance to all adaptive nervous system function (Jekely G Proc Roy Soc B 2021 10.1098/rstb.2019.0761)

Disclosures: S.J. Smith: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aratome, LLC.

Poster

P085. Opiates, Cytokines, and Other Neuropeptides

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P085.02

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH R01MH117111
NIH R01NS107539
NSF CAREER Award 1846234
Beckman Young Investigator Award
Rita Allen Foundation Scholar Award
Searle Scholar Award
William and Bernice E. Bumpus Young Innovator Award

Title: Peptidergic modulation of fear responses by the Edinger-Westphal nucleus

Authors: *M. F. PRIEST, S. N. FREDA, D. BADONG, V. DUMRONGPRECHACHAN, Y. KOZOROVITSKIY;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Many neuronal populations that release fast-acting excitatory and inhibitory neurotransmitters in the brain also contain slower acting neuropeptides. These facultative peptidergic cell types are common, but it remains uncertain whether obligate peptidergic neurons, which do not release canonical fast-acting neurotransmitters, exist. Our fluorescence in situ hybridization, genetically-targeted electron microscopy, and electrophysiological characterization data strongly suggest that neurons of the non-cholinergic, centrally-projecting Edinger-Westphal nucleus in mice are fundamentally obligately peptidergic. We further show, using fiber photometry, monosynaptic retrograde tracing, anterograde projection mapping, and a battery of behavioral assays, that the peptidergic Edinger-Westphal activates in response to threatening stimuli including loss of motor control, and that it promotes fear responses and analgesia. Together, these findings elucidate an integrative, ethologically relevant function for the Edinger-Westphal nucleus and functionally align the nucleus with the periaqueductal gray, where it resides. This work advances our understanding of the peptidergic modulation of fear and provides a framework for future investigations of putative obligate peptidergic systems.

Disclosures: M.F. Priest: None. **S.N. Freda:** None. **D. Badong:** None. **V. Dumrongprechachan:** None. **Y. Kozorovitskiy:** None.

Poster

P085. Opiates, Cytokines, and Other Neuropeptides

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P085.03

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: The Scientific and Technical Research Council of Turkey (TUBITAK - Project number: 120S734

Title: Human central cervical nucleus - chemoarchitecture and involvement in pain processing

Authors: *E. CANDAR[1], I. DEMIRCUBUK[2], G. SENGUL[3];
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Abstract: Central cervical nucleus (CeCv), one of the precerebellar nuclei of the spinal cord, is located in upper cervical segments (C1-C4) and forms a column within the limits of lamina 7, adjacent to lamina 10. CeCv neurons receive afferents from neck muscles, joints of the neck, labyrinth, and project to the contralateral cerebellum via the superior cerebellar peduncle. CeCv has been shown in the cat, rat, mouse, rhesus monkey, marmoset and human. In this study, we performed an immunohistochemical analysis of neural markers for pain in the CeCv to investigate the role of this nucleus in pain processing. 10% formalin-fixed C1-C4 segments of the human spinal cord were cut on a cryostat at a thickness of 30 micrometers and stained using glutamate, GABA, substance P, calcitonin gene-related peptide, enkephalin, glycine, serotonin, acetylcholine and noradrenaline immunohistochemistry. We observed that all of these markers were found in CeCv neurons, indicating the involvement of this precerebellar nucleus in pain, in consonence with recent data building a general consensus that the cerebellum is involved in pain processing, although its specific role still remains unclear.

Disclosures: E. Candar: None. **I. Demircubuk:** None. **G. Sengul:** None.

Poster

P085. Opiates, Cytokines, and Other Neuropeptides

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Program #/Poster #: P085.04

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIAAA Grant Y1AA-3009

Title: Mu opioid receptor occupancy by intravenous naloxone in rat brain

Authors: *K. A. O'CONOR[1], Y. KANG[2], A. C. KELLEHER[1], A. BAKHODA[1], S. EISENBERG[1], J. RAMSEY[1], W. ZHAO[3], S. KIM[1], N. D. VOLKOW[3];
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Abstract: In recent years, the United States has seen a drastic rise in opioid overdose deaths that has been fueled by synthetic opioids (e.g. fentanyl, carfentanil) flooding the illicit drug market. These synthetic opioids pose a greater risk for overdose than heroin, and their reversal by naloxone (NLX) is much more challenging. Therefore, there is an urgent need to establish a reliable method for reversing opioid-induced respiratory depression. Though NLX has a high affinity for the mu opioid receptor (MOR), there have been concerns that it may be insufficient for displacing synthetic opioids or that its short half-life may result in renarcotization after a single dose administration. In this study, we assess [^{11}C]Carfentanil ([^{11}C]CFN) displacement by NLX and estimate MOR occupancy by NLX over time at clinically relevant doses using PET in rats. We show that NLX rapidly displaces [^{11}C]CFN from the brain and that MOR occupancy by NLX after 5 minutes is greater than 85% for 0.4 mg and 2.0 mg human equivalent doses (HED)). MOR occupancy by NLX decreased over time in a dose-dependent manner, with 50% occupancy

at 40 minutes for 0.4 mg HED and 80 minutes for 2.0 mg HED. Together, these results suggest that clinically relevant doses of intravenous NLX are effective for acute reversal of opioid overdose but may be insufficient in preventing renarcotization due to the abolishment of their MOR antagonism 60 minutes post-treatment which was faster at the lower 0.4 mg HED dose. Moving forward, it is necessary to establish a more reliable, long-lasting method for opioid overdose reversal.

Disclosures: K.A. O'Conor: None. **Y. Kang:** None. **A.C. Kelleher:** None. **A. Bakhoda:** None. **S. Eisenberg:** None. **J. Ramsey:** None. **W. Zhao:** None. **S. Kim:** None. **N.D. Volkow:** None.

Poster

P085. Opiates, Cytokines, and Other Neuropeptides

Location: Virtual Only

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Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: AHA Postdoctoral Fellowship POST35030003 (ADB)
NIH Grant P01HL088052 (GMT)
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Title: A novel role for the hypothalamic paraventricular nucleus in resuscitation from opioid-induced respiratory depression by fentanyl in the rat

Authors: *A. D. BRACKLEY, T. TRUONG, J. CONTRERAS, M. ANDRADE, G. M. TONEY; Cell. & Integrative Physiol., UT Hlth., San Antonio, TX

Abstract: Opioid receptor antagonists, like naloxone, are the gold standard for reversal of opioid-induced respiratory depression (OIRD). We recently found that systemic oxytocin reverses fentanyl OIRD in rats. Naloxone triggers a surge in oxytocin release from the hypothalamic paraventricular nucleus (PVN) in anesthetized rats. Given that naloxone induces PVN oxytocin release, we hypothesized that the PVN, an unrecognized brain region for opioid overdose reversal, is capable of respiratory resuscitation following fentanyl OIRD. Naloxone (5 mg/kg, i.v.) was given to conscious rats with indwelling venous catheters. Blood samples were extracted at 5 min post-naloxone to measure plasma oxytocin by ELISA. Systemic naloxone resulted in a surge in plasma oxytocin compared to vehicle in the conscious rat. Under anesthesia, phrenic nerve activity was recorded in vagotomized, paralyzed, and artificially ventilated rats to quantify inspiratory drive following fentanyl (60 nmol/kg, i.v.) and assess OIRD reversal potential following unilateral PVN nanoinjection of naloxone (3 nmol/kg, 50 nL) or vehicle (50 nL). Naloxone administration directly into the PVN both reversed and prevented OIRD by systemic fentanyl in the rat. To determine if stimulation of PVN oxytocin neurons is sufficient to counteract OIRD expired CO_2 was used to monitor rhythmic ventilation and to quantify bradypnea during OIRD in spontaneously breathing mice with channelrhodopsin expressed exclusively in oxytocin neurons. Following fentanyl OIRD, blue light (473 nm, 3.9 mW) pulses (10 ms, 20 Hz) or dummy pulses were delivered to the PVN using a 5 s On/1 s Off pattern for 3 min. Photostimulation of PVN oxytocin neurons prevented lethal effects of fentanyl OIRD, whereas dummy pulses failed to prevent lethal respiratory arrest in the mouse. Here, we

confirm that naloxone stimulates oxytocin neurons of the PVN and results in a surge of plasma oxytocin. PVN opioid receptor antagonism and photoactivation of PVN oxytocin neurons are individually capable of reversing OIRD. Findings also indicate that PVN oxytocin neurons, previously unrecognized in reversal of OIRD, are a novel target for resuscitation agents.

Disclosures: A.D. Brackley: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent. **T. Truong:** None. **J. Contreras:** None. **M. Andrade:** None. **G.M. Toney:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent.

Poster

P085. Opiates, Cytokines, and Other Neuropeptides

Location: Virtual Only

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Program #/Poster #: P085.06

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: National Institute of Mental Health Intramural Research Program
Behavior Research Foundation NARSAD Young Investigator Award
NIH Center for Compulsive Behaviors Fellowship

Title: Unique properties define subpopulations of dynorphin-containing neurons within the medial prefrontal cortex

Authors: *S. M. CASELLO, H. E. YARUR, H. WANG, Q. WANG, N. LOOMBA, H. A. TEJEDA; Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The medial prefrontal cortex (mPFC) plays an essential role in cognitive processing and regulation of emotion, sociability, and motivation. Dysfunction of the mPFC is associated with numerous neurological and psychiatric disorders including depression, anxiety disorder, schizophrenia, and addiction. These psychiatric disorders are characterized by overlapping symptom clusters, including anhedonia, cognitive deficits, and anxiety, which suggests common neurological circuitry is involved. The dynorphin (Dyn)/KOR system is highly expressed in the mPFC and is a prominent modulator of motivated behavior as well as highly implicated in stress-induced dysphoria and vulnerability to drug abuse. Although the Dyn/KOR system has been investigated in subcortical regions, our understanding of how it is embedded in mPFC networks is limited. Intricate organization of mPFC networks is crucial for proper function of these circuits, and characterizing dynorphin-containing neuron morphology and organization within in the mPFC is a necessary step to uncovering how the Dyn/KOR system shapes cortical circuits that underlie neuropsychiatric disorders. In this study, we used a combination of transgenic mice, viral tracing approaches, and ex-vivo electrophysiology to both anatomically and electrophysiologically characterize the neuronal populations that express dynorphin in the mPFC as well as elucidate their connectivity within cortical circuits. *In-situ* hybridization revealed dynorphin is predominately expressed in glutamatergic neurons and a subpopulation of GABAergic interneurons. Ex-vivo patch clamp recording confirmed that dynorphin neurons make excitatory and inhibitory

monosynaptic connections within mPFC circuitry. Investigation of excitatory dynorphin-containing neuronal long-range projections through use of both anterograde- and retrograde- viral tracing revealed outputs to the nucleus accumbens, basolateral amygdala, paraventricular nucleus of the thalamus, lateral hypothalamus, and ventral tegmental area. Further, neuronal arborization and branching patterns were investigated to identify morphological features of dynorphin-containing mPFC cell types. Uncovering the identity of mPFC dynorphin-containing neurons and the anatomical architecture of the Dyn/KOR system within the mPFC is a critical step in elucidating how dynorphin peptides shape cortical circuits that underlie neuropsychiatric disorders. Understanding this system within the mPFC may reveal therapeutic targets to treat symptoms associated with various neuropsychiatric disorders including depression, anxiety disorder, and schizophrenia.

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Poster

P085. Opiates, Cytokines, and Other Neuropeptides

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Program #/Poster #: P085.07

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: AG050431
AG069229

Title: Ace-2-interacting domain of sars-cov-2 (aids) peptide attenuates spike s1 associated behavioral and neuronal implications in mice

Authors: *R. PAIDI, K. PAHAN;
Rush Univ. Med. Ctr., Chicago, IL

Abstract: Background Coronavirus disease 2019 (COVID-19) is a serious infectious illness caused by the virus strain severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). Covid-19 patients are suffered from several brain difficulties, but the underlying mechanism is not clear. So far, there is no proper therapeutic strategy against Covid-19 and its complications on the brain. **Methods** Since SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) for entering into host cells, to target COVID-19 from a therapeutic angle, we designed a hexapeptide corresponding to the ACE2-interacting domain of SARS-CoV-2 (AIDS) that inhibits the association between receptor-binding domain-containing spike S1 and ACE-2. Recombinant spike S1 was administered Intranasally for 14 days. Wild type and mutant AIDS peptide were administered post 5 days treatment of spike S1. Post two weeks treatment, we performed several behavioral assessment and biochemical evaluation **Results** Intranasal intoxication of C57/BL6 mice with recombinant SARS-CoV-2 spike S1 led to fever, increase in IL-6 in lungs as well as in the brain, and impairment in spatial learning memory functions and motor disabilities, mimicking some of the important symptoms of COVID-19. Intranasal treatment with wtAIDS, but not mAIDS, peptide reduced fever, enhanced locomotor functions, and cognitive and memory functions in SARS-CoV-2 spike S1-intoxicated mice. Our studies show wtAIDS peptide attenuates Spike S1 inducted cytokine levels in

the brain. **Conclusion** Our results illustrated that, selective targeting of ACE2-to-SARS-CoV-2 interaction by wtAIDS may be beneficial for COVID-19 associated memory and learning deficits via maintaining the cytokine levels

Disclosures: R. Paidi: None. **K. Pahan:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

Location: Virtual Only

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Program #/Poster #: P088.01

Topic: B.02. Ligand-Gated Ion Channels

Support: CIHR MOP119298
CureGRIN Foundation
Ontario Graduate Scholarship

Title: Behavioural characterization of GRIN1 Y647S$^{+/-}$ patient variant mouse model

Authors: *M. T. SULLIVAN[1], K. INTSON[1], P. YAN[1], D. E. WATKINS-CHOW[2], S. Y. YUAN[1], D. J. STEVENS[1], V. C. RADBURN[1], W. J. PAVAN[2], A. J. RAMSEY[1];
[1]Pharmacol. & Toxicology, Univ. of Toronto, Toronto, ON, Canada; [2]Natl. Human Genome Res. Inst., Bethesda, MD

Abstract: Rationale: GRIN1 disorder is a neurodevelopmental disorder characterized by mutation to the GRIN1 gene; responsible for the genetic programming of the indispensable GluN1 subunit of NMDA receptors. Patients carrying a mutation in GRIN1 present with a large range of phenotypes of varying severity including developmental delay, intellectual disability, motor dysfunction and seizure. Cell-based assays give only partial information on the functional consequences of specific mutations and how they contribute to the individual's phenotype. Therefore, the study of mouse models carrying patient variants is necessary to fully understand the mechanisms disturbing the NMDA receptor in each mutation and to determine effective treatments for GRIN1 patients. Objectives: We aimed to characterize the behavioural profile of male and female adult mice heterozygous for the GRIN1 patient variant Y647S in domains of seizure, locomotor activity, stereotypy, social behavior, working memory and anxiety-like behaviour. Ultrasonic communication was characterized in Y647S$^{+/-}$ mice during early development.Results: Y647S$^{+/-}$ mice (n=10) displayed seizures and travelled increased distance in the open field test compared to wildtype mice (n=9). In the social interaction test, Y647S$^{+/-}$ mice spent significantly longer visiting the novel mouse compared to wildtype and while in the elevated plus maze, Y647S$^{+/-}$ mice spent a significantly larger percentage of time in the open arms. In the domains of stereotypy and working memory, Y647S$^{+/-}$ mice did not differ significantly from wildtype. Y647S$^{+/-}$ pups (post-natal day 6) displayed reduced latency to first USV call and made a greater overall number of calls compared to the wildtype pups. Conclusion: The present study demonstrates that Y647S$^{+/-}$ GRIN1 patient variant mice display a phenotype characterized by seizure, hyperlocomotion, increased sociability and reduced anxiety. These behaviours appear to closely align with the clinical symptoms of patients carrying the Y647S

variant. Ultimately, these results will provide the behavioural baseline for the investigation of treatments for GRIN1 patients harboring the Y647S variant and other individuals with GRIN1 disorder.

Disclosures: M.T. Sullivan: None. **K. Intson:** None. **P. Yan:** None. **D.E. Watkins-Chow:** None. **S.Y. Yuan:** None. **D.J. Stevens:** None. **V.C. Radburn:** None. **W.J. Pavan:** None. **A.J. Ramsey:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

Location: Virtual Only

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Topic: B.02. Ligand-Gated Ion Channels

Support: Ontario graduate scholarship- International (SV)
CIHR MOP 89825 (EKL)
CIHR MOP 119298 (AJR)

Title: Characterizing the impact of patient derived GRIN1 Y647S+/- mutation on cortical neurophysiology in a mouse model

Authors: *S. VENKATESAN[1], A. J. RAMSEY[2], E. K. LAMBE[1];
[1]Dept. of Physiol., [2]Dept. of Pharmacol. and Toxicology, Univ. of Toronto, Toronto, ON, Canada

Abstract: NMDA receptors (NMDARs) are essential for synaptic function, plasticity and enable supralinear integration of glutamatergic inputs to generate dendritic plateau potentials. *GRIN1* neurodevelopmental disorder is a rare genetic condition caused by *de novo* mutations in the *GRIN1* gene encoding the obligate GluN1 NMDAR subunit and is characterized by profound neurological deficits. The mechanisms underlying these deficits are unclear, as the consequences of various human *GRIN1* mutations on NMDAR function, dendritic integration and plasticity are unknown. Identifying the exact nature of NMDAR dysfunction can help determine the course of treatment for patients carrying the mutation. Here, we characterized the neurophysiological consequences of the patient derived *GRIN1* Y647S$^{+/-}$ mutation using transgenic mutant mice (*Grin1* Y647S$^{+/-}$) and wildtype littermate mice of both sexes. Patch clamp electrophysiology of layer 5 pyramidal neurons in the prefrontal cortex was used to examine different aspects of NMDA receptor functionality. We measured whole-cell currents evoked by bath application of NMDA as a gross measure of NMDAR activity and found them to be dramatically enhanced in the Y647S$^{+/-}$ mice. Ongoing work is examining synaptically-evoked NMDA EPSCs and NMDA dependent supralinear dendritic integration to identify synaptic and dendritic dysfunctions caused by Y647S$^{+/-}$. We are interested in how the Y647S$^{+/-}$ mutation affects integrated functioning of the NMDA receptor in close association with other synaptic ion channels and its consequences for synaptic integration and plasticity. Future work will test targeted drugs to rescue NMDAR signaling in these mice.

Disclosures: S. Venkatesan: None. **A.J. Ramsey:** None. **E.K. Lambe:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Program #/Poster #: P088.03

Topic: B.02. Ligand-Gated Ion Channels

Support: GAUK 376221

Title: Functional analysis of genetic variations in the cytosolic domain of NMDA receptors

Authors: *V. KUCHTIAK, E. TOMOVIC, L. VYKLICKY JR, A. BALIK;
Dept. of Cell. Neurophysiol., Inst. of Physiol. CAS, Prague, Czech Republic

Abstract: The function of the excitatory synapses depends on the expression and activity of ionotropic glutamate receptors, which include calcium-permeable NMDA receptors (NMDARs). NMDAR family is represented by three subunits, GluN1 (eight splice variants), GluN2 (isoforms A-D), and GluN3 (isoforms A-B). The receptor is composed of two obligatory GluN1 subunits and two subunits in different combinations of GluN2A-D and GluN3A-B. Each subunit consists of four domains: the extracellular amino-terminal, ligand-binding domains, the transmembrane domain, and the intracellular C-terminal domain (CTD). CTD has the lowest homology between NMDAR subunits and represents up to half of the entire NMDAR subunit (GluN2A/B), which indicates the functional consequences for the receptor. Indeed, CTD of the NMDAR is essential for many of its properties such as trafficking of receptor to synapses, endocytosis, and subsequent degradation of the receptor. The direct effect of CTD on the functional properties of the NMDAR ion channel has been also shown. CTD interacts with several intracellular proteins such as cytoskeletal proteins, scaffold proteins, or proteins involved in intracellular signalling. In addition to protein binding, CTD is a target of numerous post-translational modifications regulating the functional properties of the receptor. Amino acid mutations in the cytosolic part of NMDAR subunits have been found in individuals with various neurological impairments. These mutations could then contribute to the emergence and development of the disorder. We employed electrophysiological measurements and microscopy analysis to study the impact of 6 diseases associated mutations (schizophrenia, epilepsy) found in the CTD of GluN2A/B subunits. We analysed the ion channel properties, changes in the surface expression, and trafficking to synapses. Our results suggest that mutations in CTD affect ion channel properties, such as glutamate potentiation and open channel probability. The majority of the mutations we studied have decreased surface expression and receptor trafficking to the synapses. Among the mutations studied, the mutation V967L in the CTD of the GluN2A subunit led to the most significant changes, such as a 30% reduction in surface expression and synaptic localization. In summary, we showed that genetic changes in the intracellular domain of the NMDA receptor altered the functions of the receptor especially impairing its delivery to the cell surface and synaptic localization that might induce hypofunction of NMDAR signalling and thus contribute to the emergence of neurological disorders.

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Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Program #/Poster #: P088.04

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01 NS088479 (L.P.W.)

Title: Lupus auto-antibodies relieve zinc inhibition to positive modulate NMDA receptor currents

Authors: *J. GUPTA[1], L. P. WOLLMUTH[2];
[1]Stony Brook University, Stony Brook, NY, United States, Stony Brook, NY; [2]Neurobiol & Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects nearly 1.6 million Americans, primarily women and minorities. Up to 50% of patients with SLE experience neuropsychiatric symptoms such as amnesia, cognitive fatigue, and impaired concentration clinically referred to as Neuropsychiatric Lupus (NPSLE) and colloquially referred to as “brain fog”. In SLE, a subset of double stranded DNA reactive autoantibodies (DNRAbs) cross reacts with the amino terminal domain (ATD) of NMDA receptors (NMDARs), directly implicating this excitatory ion channel in SLE neuropathology. Specifically, DNRAbs interact with the DWEYS structural motif within the hinge region of the bilobed ATD. DNRAbs bind to NMDARs containing GluN2A and GluN2B subunits, but we recently demonstrated that G11, a patient derived monoclonal DNRAb, preferentially acts on GluN2A-containing NMDARs as a positive allosteric modulator (PAM). The PAM action of G11 increases NMDAR response to agonist and may impair spatial memory. However, a mechanistic understanding of the interaction between DNRAbs and GluN2A-containing NMDARs that mediates this positive allostery is unknown. We propose that the DNRAb-NMDAR interaction facilitates greater NMDAR currents by opposing the action of zinc, a negative allosteric modulator (NAM) of NMDARs that also acts at the ATD. Consistent with this idea, preliminary data indicates that positive allostery induced by DNRAbs is strongly reduced in the absence of Zn2+. We are quantitatively determining the reduction of positive allostery by DNRAbs by (i) assaying zinc response curves of GluN2A and GluN2B containing NMDARs using whole-cell electrophysiology and (ii) determining how the open or closed conformation of the ATD impacts the extent of allostery. With this data we can begin to understand the interaction between DNRAbs and zinc at the ATD binding site.

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Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Support: Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development

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Grant NS113530
Austin's Purpose
Emory Synergy Award

Title: The GluN2A Subunit of the NMDA Receptor Modulates the Rate of Functional Maturation in Parvalbumin-positive Interneurons

Authors: *C. CAMP[1], L. SHAPIRO[1], A. HANCOCK[3], A. VLACHOS[3], R. E. PERSZYK[1], N. SHARIATZADEH[1], A. ESCAYG[2], S. KOH[4], C. MCBAIN[3], K. A. PELKEY[3], S. F. TRAYNELIS[1]; [1]Pharmacol. and Chem. Biol., [2]Human Genet., Emory Univ., Atlanta, GA; [3]Section on Cell. and Synaptic Physiol., NIH, Bethesda, MD; [4]Ohama Children's Ctr., Univ. of Nebraska Med. Ctr., Ohama, NE

Abstract: N-methyl-D-aspartate receptors are glutamate-gated, calcium-permeable ion channels involved in a host of normal brain functions, including neuronal development. Traditionally, the GluN2A subunit, encoded by the *GRIN2A* gene, is thought to signal brain and circuit maturation, given its unique expression pattern where transcripts are low embryonically and then significantly increase during preadolescence. Advances in whole exome sequencing have identified mutations in the *GRIN2A* gene to be causal to several neuropathological diseases, including epilepsy and intellectual delay. More specifically, 56% of *GRIN2A* mutations are loss-of-function (LoF) , displaying diminished receptor function and/or surface expression, with *Grin2a*$^{-/-}$ mice have been reported as having signatures of epileptiform activity. However, little is understood regarding GluN2A's impact on neurodevelopmental and how its absence may impact the GABAergic interneuron network. Our data show that *Grin2a* $^{-/-}$ mice contain 33% more parvalbumin^{+} interneurons in the hippocampal CA1 region during preadolescence and adulthood. This increase in GABAergic interneuron cell density appears to be unique to parvalbumin^{+} cells, as cholecystokinin^{+} and somatostatin^{+} interneurons are unchanged across *Grin2a*$^{-/-}$ and wildtype mice. Despite an increased cell count, colocalization staining for parvalbumin^{+} synaptic densities and measures of parvalbumin cell-specific tonic inhibition remains unchanged in preadolescence and increases as the animal ages, suggesting delayed maturation. In addition, parvalbumin^{+} cells from preadolescent *Grin2a*$^{-/-}$ mice exhibit immature intrinsic and firing properties, such as an increased membrane time constant and input resistance, lower threshold for depolarization-induced block, and longer action potential half-widths than age-matched WT controls, all of which become corrected in adulthood. The sum of these data suggest that the GluN2A subunit is involved in promoting cues for interneuron apoptosis during development, as well as influencing the rate of parvalbumin^{+} cell functional maturation. The ramifications of these abnormalities are still underexplored, but likely generate a vulnerability time window during preadolescence in which an epileptiform network can manifest. Viral strategies aimed at reintroduction of the *GRIN2A* gene during this critical time window could represent a viable gene therapy option for LoF *GRIN2A* patients.

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Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Program #/Poster #: P088.06

Topic: B.02. Ligand-Gated Ion Channels

Support: NINDS R01 NS088479 (LPW)
SBU-BNL SEED Grant (LPW)

Title: Hidden intermediate states of NMDAR in synapse dynamics

Authors: *M. HE[1], L. P. WOLLMUTH[2];
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Abstract: NMDA receptors (NMDARs) are ionotropic glutamate receptors that mediate fast synaptic transmission and the synaptic plasticity underlying learning and memory. Dysfunction of NMDARs contributes to numerous neurological diseases including Alzheimer's disease, intellectual disability, epilepsy, autism spectrum disorder, and schizophrenia. NMDARs are obligate hetero-tetramers, formed by two glycine-binding GluN1 subunits and typically two glutamate-binding GluN2(A-D) subunits. A key function of NMDARs at synapses is to efficiently convert transient presynaptically released glutamate into opening of the ion channel pore, a process referred to as gating. Previously, we applied glutamate to outside-out patches containing single NMDARs. This approach is revealing since it shows underlying gating details that are not seen either with whole-cell or steady-state single channel patches. We found that glutamate applications to GluN1/GluN2A channels, which were fully saturated with agonist, resulted in either failures (no current) or successes (single channel currents) with successes occurring through two distinct intermediate pathways : rapidly after agonist binding (fast component) or with a considerable delay (slow component). These various pathways are important for synaptic transmission since they will determine how strongly the channel contributes to fast synaptic signaling. The mechanistic basis of failures and how physiological factors such as pH and Zn^{2+} affect these components is unknown. In terms of failures, one possibility is that they reflect that the channel did not recover from desensitization that arose with the prior glutamate application. However, as we increase the wait time between applications (from 4 to 10 seconds), failure rates are not decreased or eliminated. In contrast to GluN2A-containing NMDARs, which have a high open probability, diheteromeric NMDARs containing GluN2B, GluN2C, or GluN2D have a much lower open probability yet the pathways these receptors take to reach channel activation are unknown. We propose that GluN2(A-D) use the same conformational intermediates as GluN2A-containing receptors but differ in their ability to enter into the intermediate pathways. We will therefore address subunit-specificity of the failures and pathways, as well as physiological factors, such as pH and Zn^{2+}. These experiments will allow us to understand the functional diversity of NMDAR subtypes, which is also critical to unraveling the basis for neurological diseases.

Disclosures: M. He: None. **L.P. Wollmuth:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P088.07

Topic: B.02. Ligand-Gated Ion Channels

Support: F31 MH124283
R21 MH127822
R37 MH080046

Title: Direct visualization of triheteromeric NMDA receptors

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Abstract: Glutamatergic signaling via NMDA receptors (NMDARs) is critical in synaptic plasticity, brain development, excitotoxicity, and numerous degenerative and cognitive disorders. Each functional NMDAR comprises four subunits: two obligatory GluN1 subunits and two GluN2A-D or GluN3A-B subunits. Importantly, NMDARs with different GluN2 subunit compositions display strikingly different biophysical characteristics, and the GluN2 subunits also control unique protein interactions and signaling. Accordingly, the physiological characteristics of excitatory synaptic transmission and plasticity, as well as synaptic pathology, depend on the NMDAR subtypes expressed and trafficked to synapses. Thus, identifying how neurons control abundance of specific NMDAR subtypes has been a longstanding goal in neuroscience. Unfortunately, our understanding of these mechanisms has been crucially restricted by inability to visualize one of the key classes of NMDARs in neurons, triheteromeric receptors that contain GluN1 and two different GluN2 subunits. Indeed, in many parts of the brain including the hippocampus, triheteromeric NMDARs containing both GluN2A and GluN2B subunits are the most common NMDAR subtype. However, the subcellular distribution of triheteromeric NMDARs remains mysterious and the mechanisms controlling their trafficking to and from synapses remain almost totally unknown. Here, we introduce a new method for direct visualization of triheteromeric NMDARs in neurons using biomolecular complementation. We tagged the N-termini of GluN2A and GluN2B subunits with two components of split fluorescent proteins or of a split HaloTag enzyme that is catalytically active only when the two parts are brought within close proximity. Thus, after transfection of these tagged subunits, standard fluorescent imaging can be used to detect specifically NMDARs containing both GluN2A and GluN2B subunits in a single receptor complex. Whole-cell recordings demonstrate that activation of split-tagged NMDARs by glutamate is unaltered by the presence of the tags. Further, the split-tagged subunits do not undergo detectable interreceptor complementation, and neurons expressing the complementing receptor subunits displayed no morphological abnormalities. Using this tool, we find that triheteromeric receptors traffic avidly to synapses and display unique subcellular trafficking characteristics. These probes will fill longstanding gaps in our knowledge of NMDARs and lay necessary groundwork for investigation of other aspects of triheteromeric NMDAR trafficking in healthy neurons and disease models.

Disclosures: M. Anderson: None. **A. Nigam:** None. **J.W. Johnson:** None. **T.A. Blanpied:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Program #/Poster #: P088.08

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant T32NS007433
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NIH Grant R01AG065594

Title: Regulation of NMDA receptor channel block by intracellular calcium

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Abstract: N-methyl-D-aspartate receptors (NMDARs) are key mediators of neuronal Ca^{2+} influx. NMDAR-mediated Ca^{2+} influx plays a central role in synaptogenesis, synaptic plasticity, dendritic integration, and neuronal survival. However, excessive NMDAR activity can lead to buildup of pathological levels of Ca^{2+} inside neurons, which initiates cellular signaling pathways that result in neuronal death. Thus, NMDAR antagonists, particularly NMDAR channel blockers, remain a subject of great clinical interest. The NMDAR channel blocker memantine is a well-tolerated Alzheimer's disease medication that also shows promise in treatment of other neurological disorders. Interestingly, memantine enhances desensitization of NMDARs by stabilizing a Ca^{2+}-dependent desensitized receptor state. Consequently, memantine inhibits NMDARs more effectively in conditions that allow for increased influx and intracellular accumulation of Ca^{2+}. These features could allow memantine to preferentially target overactive NMDAR subpopulations, i.e., NMDARs in cells subjected to pathological Ca^{2+} influx. Here we systematically examine the effect of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) on NMDAR inhibition by memantine. Utilizing specially designed Ca^{2+}-buffering solutions and whole-cell patch-clamp recordings, we demonstrated that NMDAR channel block by memantine is directly related to $[Ca^{2+}]_i$, with memantine IC_{50} decreasing as $[Ca^{2+}]_i$ increases. IC_{50}s for the prototypical NMDAR channel blocker Mg^{2+} and another clinically important organic channel blocker, ketamine, were found to be unaffected by changes in $[Ca^{2+}]_i$. Interestingly, although we show that $[Ca^{2+}]_i$ increases desensitization of both GluN1/2A and GluN1/2B receptors, $[Ca^{2+}]_i$ only affects memantine inhibition of NMDARs containing the GluN2A subunit. Memantine IC_{50} measurements in cultured primary cortical neurons revealed that memantine inhibition of native NMDARs also depends on $[Ca^{2+}]_i$. Our experiments show that memantine inhibition of GluN1/2A receptors is dynamically regulated by fluctuations of $[Ca^{2+}]_i$ across both physiological and pathological ranges, and that memantine inhibition of a mixed population of native NMDARs containing both GluN2A- and GluN2B-containing receptors is $[Ca^{2+}]_i$ dependent. Thus, the $[Ca^{2+}]_i$ dependence of NMDAR inhibition by memantine has the potential to profoundly impact the effects of memantine on neuronal function.

Disclosures: M.B. Phillips: None. **N.V. Povysheva:** None. **J.W. Johnson:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P088.09

Topic: B.02. Ligand-Gated Ion Channels

Title: Characterization of light-sensitive NMDA receptor positive allosteric modulators

Authors: *Y. GE[1], Z. ZHANG[2,3], Y. WANG[1], A. WOOLLEY[2], M. DONG[2,4];
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Abstract: Light-switchable compounds are critical research tools for regulating receptor activity with a high degree of temporal and spatial specificity. Currently, there is no light-switchable modulator for N-methyl-d-aspartate glutamate receptors (NMDAR) ion channels, which are important drug targets for many central nervous system disorders. Our previous virtual screening approach identified several NMDAR positive allosteric modulators (PAMs), some of which contained an arylhydrazone backbone that can undergo E/Z isomerization under appropriate conditions. In this study, we investigated and optimized the photo-isomerization properties of several NMDAR PAMs as reversible photo switches. Combining analytical chemistry approaches and electrophysiology recordings of the HEK293 cells transiently expressing rat NMDARs containing GluN1/GluN2A or GluN1/GluN2B subunits, we found that two of the arylhydrazones compounds readily undergo *E*-to-*Z* isomerization under blue light, resulting in over 50-fold less potency in modulating the currents gated through two prominent NMDAR subtypes. To further optimize their photoswitchability, we characterized another compound HILKOD that undergoes both *E*-to-*Z* and the reversible *Z*-to-*E* isomerization using blue light and UV light, respectively. The two isomers also have substantially different bioactivities on NMDARs. We concluded that arylhydrazone compounds can be effective photo switches for NMDARs, and further optimizing these compounds may result in highly effective research tools for manipulating the physiological activities of NMDARs.

Disclosures: Y. Ge: None. **Z. Zhang:** None. **Y. Wang:** None. **A. Woolley:** None. **M. Dong:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Program #/Poster #: P088.10

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH R01GM128195

Title: NMDA receptor subtype dependence and kinetics of membrane to channel inhibition by (+)-MK-801

Authors: *A. NIGAM[1], M. WILCOX[2], J. W. JOHNSON[1];
[1]Dept. of Neurosci. and Ctr. for Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Jakob and Partners Consulting, Miami, FL

Abstract: MK-801 is a high-affinity NMDAR channel blocking antagonist. It is now widely used as a crucial research tool to investigate NMDAR properties and their contributions to synaptic transmission. Investigation of NMDAR channel blocking drugs such as MK-801 and memantine (approved by the FDA for treatment of Alzheimer's disease) also has broad therapeutic implications. NMDARs are highly calcium permeable tetrameric ionotropic glutamate receptors that are formed by pairing two GluN1 subunits with two GluN2 (A-D) and/or GluN3 (A-B) subunits. NMDAR channel blockers act by blocking ion flow at a site in the ion channel (the "deep site"). Glasgow et.al. (2018, Neuropharm 137, 344) showed that memantine can access the deep site via two paths: the traditional channel blocking path from the extracellular solution, or by associating with a "second site" from which memantine can transit to the deep site following NMDAR activation. We recently found that the second site is actually a reservoir of drug molecules located in the cell membrane; we thus renamed the phenomenon "membrane to channel inhibition" (MCI). Here we investigate MCI by MK-801 using tsA201 cells transfected to express NMDARs. We measured MCI concentration-inhibition curves for the GluN1/2A - GluN1/2D NMDAR subtypes. To ensure that MK-801 could not block NMDARs from the extracellular solution, we applied MK-801 in the absence of glutamate; removed MK-801 from the extracellular solution; applied 1 mM glutamate (all solutions contained 100 µM glycine); measured the minimum NMDAR-mediated current relative to control current (I_{MCI}/I_{Con}). We found that at -65 mV, the MK-801 MCI IC_{50} of GluN1/2A receptors (0.85 ± 0.04 µM) was not significantly different from the MCI IC_{50} of GluN1/2B receptors (0.67± 0.16 µM). Interestingly, we did not observe MCI following application of MK-801 at concentrations up to 10 µM to GluN1/2C or GluN1/2D receptors. We also examined the time course of MCI onset (τ_M) following application of 1 µM MK-801 and found that τ_M for GluN1/2A receptors (0.93 ± 0.03 s) was significantly different from τ_M for GluN1/2B receptors (1.20 ± 0.05 s). To determine the time course of MK-801 exit from the membrane we varied the time between termination of MK-801 application and glutamate application. Using GluN1/2A receptors and 10 µM MK-801, we found that MK-801 exits the membrane with a time constant of 7.06 ± 1.1 s, reflecting much slower kinetics than memantine. Overall, MK-801 MCI exhibits NMDAR subtype dependence and kinetic properties that shed light on the wide range of MCI characteristics that can be exhibited by NMDAR channel blockers.

Disclosures: A. Nigam: None. **M. Wilcox:** None. **J.W. Johnson:** None.

Poster

P088. Ionotropic Glutamate Receptors: NMDA Receptors

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P088.11

Topic: B.02. Ligand-Gated Ion Channels

Title: Controlling excitotoxicity and stabilizing serial activation of ionotropic glutamate receptors for a robust automated patch clamp assay

Authors: *A. YEHIA;
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Abstract: A robust ligand gated assay depends on the serial activation of the receptor forming a repeating, consistent and stable response. This is a major requirement for all manual and automated patch clamp studies of said receptors. Considering the effects of lingering agonists and activators on ligand-gated receptors, a complete and continuous extracellular solution replacement is key in the success of these assays. Ionotropic glutamate receptors such as NMDA receptors, when expressed in HEK293 cells, can lead to excitotoxicity of the host cells due to circulating natural agonists from neighboring cells. Hence, when expressed and activated, channel blockers are added to prevent excessive cell death. Although possible with manual patch clamp, effective in-assay removal of these blockers and natural agonists can pose a challenge to most automated system with high dependencies on external liquid handlers. Here we demonstrate how a unique in-assay solution exchange can alleviate most of these assay challenges with a continuous flow of wash solutions, providing a foundation for a consistent high throughput drug screening of ionotropic glutamate receptors. Data from glutamate receptors such as NMDA Receptors (NR2A/B/D) under various conditions of protective block will be presented.

Disclosures: A. Yehia: None.

Poster

P128. Excitability Control: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P128.01

Topic: B.08. Intrinsic Membrane Properties

Support: NARSAD Young Investigator Award
Charles Kaufman Foundation Grant
reative Arts, Research, And Scholarship (CARAS) Award

Title: Molecular Mechanisms of intrinsic excitability and axon initial segment plasticity

Authors: G. D. VITELLI[1], A. ISHAQ[1], W. BREW[2], **A. R. MOORE**[1];
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Abstract: Proper neuronal function is dependent on the brain's ability to produce stable high-quality output yet remain flexible in an ever-changing environment, a phenomenon commonly referred to as neural plasticity. At the cellular level, changes in external cues, such as experience or perturbation, lead to homeostatic adjustments of either the synaptic connectivity between neurons, the intrinsic electrical properties of individual neurons, or both in order to maintain balanced network activity. When these processes are disrupted stability cannot be maintained and long-term undesirable neurological consequences. An emerging feature in mental health disorders is a change in axon initial segment morphology and neuron excitability. Once thought to be a static structure, the axon initial segment has now been observed to be highly dynamic during development, in response to activity-dependent changes, and in disease. More specifically, an increase in neuronal activity can lead to a decrease in AIS length, whereas a decrease in activity can lead to an increase in AIS length. These structural changes allow the

neuron to maintain its activity within a given range, or setpoint, and can occur on a time scale of hours to days. However, despite the importance of AIS plasticity on neuronal excitability, the underlying molecular mechanisms regulating AIS length in response to neuronal activity remain largely unexplored. Recently, we identified the small Ras-like GTPase, Rem2, as an activity-dependent negative regulator of intrinsic excitability. More specifically, acute deletion of Rem2 leads to a significant increase in neuronal firing rate, independent of synaptic changes. In an effort to understand the contribution of intrinsic excitability changes in the context of Rem2, we examined the axon initial segment length following Rem2 knockdown in primary neuron cultures. We found that knockdown of Rem2 leads to a significant reduction in axon initial segment length and a proximal shift of the axon initial segment from the soma compared to control neurons. This data suggests, that Rem2 may play a role in regulating axon initial segment morphology and plasticity.

Disclosures: G.D. Vitelli: None. **A. Ishaq:** None. **W. Brew:** None. **A.R. Moore:** None.

Poster

P128. Excitability Control: Molecular Mechanisms

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Program #/Poster #: P128.02

Topic: B.08. Intrinsic Membrane Properties

Support: R21NS101482

Title: Thalamocortical neuron firing & circuit maturity is dependent on the expression of the transcription factor, Shox2

Authors: *I. FEBBO[1], V. WARKINS[1], A. J. SULLIVAN[1], N. VARGAS[1], L. A. SCHRADER[2];
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Abstract: Thalamocortical circuitry is central to the generation of sensory perception, disruptions of which have been linked to sensory perception disorders, such as autism, schizophrenia, and specific epilepsies. Thalamocortical neurons (TCNs) integrally support proper function of this circuit through tightly regulated firing activity and connectivity. While it is understood that TCNs send primary relay processes from the thalamus to sensory cortex and possess pacemaker capabilities, which are generated primarily by T-type and HCN current interplay, the transcriptional and epigenetic factors that are important for generation of these properties are unknown. Our lab has discovered that the transcription factor, Shox2, is highly expressed in the thalamus and important for expression of multiple ion channels in TCNs. Global Shox2 KO mice present with somatosensory deficits, their TCNs have reduced T-type and HCN currents, and the mRNA and proteins that mediate the expression of the channels that generate these currents are significantly reduced within the thalamus. To further characterize Shox2-expressing neurons and determine whether expression of Shox2 plays an integral role in their capacity to function properly within the thalamocortical circuit, we performed stereotaxic injections of GFP-cre virus into the somatosensory nucleus of the thalamus—ventrobasal (VB)—of Shox2fl/fl mice, creating a VB-targeted KO in GFP labeled Shox2 TCNs. Patch clamp electrophysiology analysis of Shox2 KO TCNs revealed an immature firing phenotype, increased input resistance and reduced T-type current compared to control

neurons. Further, whisker somatomotor function was impaired, and VB-specific Shox2 KO at PND6 disrupted cortical barrel formation. Altogether, these data show that Shox2 mediates TCN capacity to generate burst firing activity and integrate into the thalamocortical circuit, and presents as a target to further investigate for TCN maturation and function within TC circuitry.

Disclosures: I. Febbo: None. **V. Warkins:** None. **A.J. Sullivan:** None. **N. Vargas:** None. **L.A. Schrader:** None.

Poster

P128. Excitability Control: Molecular Mechanisms

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Program #/Poster #: P128.03

Topic: B.08. Intrinsic Membrane Properties

Support: FNRS Grant J.0148.19

Title: Characterization of the inhibitory effect of 1-(2,4xylyl)guanidinium on the pacemaking of midbrain dopaminergic (DA) neurons

Authors: K. JEHASSE[1], S. RINGLET[2], S. HARTMANN[3], H. C. CHUA[4], R. VITELLO[2], L. MASSOTTE[2], M. VITELLO[2], J. MELICHEROVA[6], P. MUSILOVA[6], K. SINIGAGLIO[7], L. KEEGAN[6], M. O'CONNELL[6], S. A. PLESS[5], D. ENGEL[8], J.-F. LIÉGEOIS[2], B. LAKAYE[2], J. ROEPER[9], ***V. SEUTIN**[1];
[1]Univ. of Liège, Liege, Belgium; [2]Univ. of Liège, Liège, Belgium; [3]Goethe Univ., Frankfurt, Germany; [4]Univ. of Copenhagen, Copenhagen, Denmark; [5]Dept. of Drug Design and Pharmacol., Univ. of Copenhagen, Kobenhavn O, Denmark; [6]Central European Inst. of Technol., Brno, Czech Republic; [7]Central European Inst. of Technol., Brno, Belgium; [8]GIGA-Neurosciences, Univ. of Liege, Liege, Belgium; [9]Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: We have recently shown that 1-(2,4-xylyl)guanidinium (XG), previously reported to be a blocker of gating pore currents, also inhibits the slow pacemaking of midbrain dopaminergic (DA) neurons (Jehasse *et al*., SFN abstract, 2019 ; Jehasse *et al*., Neuropharmacology, in the press). Further work was carried out to characterize this effect and try to determine the molecular target of XG. The inhibitory effect of XG was very reproducible throughout the midbrain: all slowly pacemaking DA neurons were inhibited by the drug at similar concentrations (IC_{50} around 400 µM). Since the carbonate salt of XG is not very water-soluble, we developed another salt (a mesylate) of XG, which is much easier to use, and which produced the same effect. Interestingly, XG was equieffective when applied inside DA neurons. A closely related molecule, 2-guanidinobenzimidazole, which had been shown to block the Hv1 proton channel, was much less effective, suggesting that the steric constraints for binding to the target of XG are rather strict. In voltage clamp, using the so-called pacemaker clamp technique, we could isolate a small inward XG-sensitive current operating near the threshold of the action potential. This current did not have the properties of a typical gating pore current. Using ion-substitution experiments, we found that the XG-sensitive conductance is carried both by Na^+ and Cl^-, with some competition between these two ion species. The dopamine transporter could be excluded as a target for XG. In addition, XG had no effect

on the biophysical properties of I_A and I_h. We finally asked whether the current could be due to editing of a transmembrane domain of an ion channel species. We found no molecular evidence for such editing in rat substantia nigra. Moreover, the pacemaking of these neurons was identical in WT mice and in Adar2(-/-) Gria2(R/R) mice, ADAR-2 being the main source of RNA editing in mammalian cells. In summary, our data shows that XG inhibits slow pacemaking of DA neurons by blocking a yet to discover membrane protein target which does not need RNA editing to be functional.

Disclosures: K. Jehasse: None. **S. Ringlet:** None. **S. Hartmann:** None. **H.C. Chua:** None. **R. Vitello:** None. **L. Massotte:** None. **M. Vitello:** None. **J. Melicherova:** None. **P. Musilova:** None. **K. Sinigaglio:** None. **L. Keegan:** None. **M. O'Connell:** None. **S.A. Pless:** None. **D. Engel:** None. **J. Liégeois:** None. **B. Lakaye:** None. **J. Roeper:** None. **V. Seutin:** None.

Poster

P128. Excitability Control: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P128.04

Topic: B.08. Intrinsic Membrane Properties

Title: Activation of vasopressin 1A receptors excites Type III/CRF neurons of the bed nucleus of the stria terminalis (BNST)

Authors: *W. FRANCESCONI, F. BERTON, S. H. OLSON, J. DABROWSKA;
Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL

Abstract: The bed nucleus of the stria terminalis (BNST) has emerged as a key brain region translating an exposure to unpredictable threats into sustained fear. In rats, dorsolateral BNST ($BNST_{DL}$) contains three types of neurons functionally classified as Type I, II, and III. The $BNST_{DL}$ is innervated by oxytocin (OT) and vasopressin (AVP) fibers and has high expression of OT (OTR) and AVP receptors (V1aR), but the roles of OTR and V1aR in the modulation of $BNST_{DL}$ activity remains elusive. Hence, we used *in vitro* patch clamp electrophysiology to determine if OTR or V1aR activation affects $BNST_{DL}$ activity in a cell-type specific manner. We recently demonstrated that OT directly increases the excitability and spontaneous firing of Type I neurons, indirectly inhibits the spontaneous firing of Type II neurons, whereas it reduces GABA-ergic inhibition in Type III $BNST_{DL}$ neurons, all in the OTR-dependent manner (Francesconi et al., 2021). Here, we demonstrate that application of AVP (0.2 μM) directly excites two types of $BNST_{DL}$ neurons, Type I neurons via OTR-dependent mechanism and Type III $BNST_{DL}$ neurons via V1aR-dependent fashion. In Type I neurons, AVP induced a leftward shift of input/output relationship, demonstrating a significant increment of steady state frequency of firing (SSF, $F(5, 42) = 9.471$, $P<0.0001$, n=9), which was blocked by OTR antagonist (d(CH2)5(1), D-Tyr(2), Thr(4), Orn(8), des-Gly-NH2(9)]-Vasotocin). In Type III neurons, AVP also induced a leftward shift of input/output relationship ($F(1, 23) = 95.14$, $P<0.0001$, n=6), which was blocked by selective and potent V1aR antagonist ($d(CH_2)_5^1$,$Tyr(Me)^2$,Arg^8)-Vasopressin). Notably, in the presence of the V1aR antagonist, Type III neurons remained silent and did not fire unless injected with current of 110 pA or more. Lastly, since Type III $BNST_{DL}$ neurons are putative corticotropin-releasing factor (CRF) neurons of the $BNST_{DL}$, we recorded the effects of AVP from CRF-$BNST_{DL}$ neurons of Cre-CRF transgenic rats (Cre-recombinase

under CRF promoter) injected with Cre-dependent AAV-mCherry into the $BNST_{DL}$. We identified the CRF-mCherry neurons as Type III and we show that AVP has a trend in exciting these Type III/CRF neurons. Our results demonstrate that whereas OTR activation reduces GABA-ergic inhibition in Type III neurons, V1aR activation directly excites Type III/CRF neurons of the $BNST_{DL}$. As CRF-$BNST_{DL}$ neurons were shown to mediate sustained fear, our results imply that V1aR activation in the $BNST_{DL}$ plays an important role in mediating this behavior.

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Poster

P128. Excitability Control: Molecular Mechanisms

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Program #/Poster #: P128.05

Topic: B.08. Intrinsic Membrane Properties

Support: Italian Ministry for University Education and Research (Prin: 2017K2NEF4)

Title: Histamine H_2 receptor activation enhances excitability of medium spiny neurons in the nucleus accumbens

Authors: G. ACETO[1], L. NARDELLA[2], C. COLUSSI[3], V. PECCI[2], S. NANNI[2,1], C. GRASSI[2,1], ***M. D'ASCENZO**[2,1];
[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [2]Univ. Cattolica del Sacro Cuore, Rome, Italy; [3]Natl. Res. Council, Rome, Italy

Abstract: Histaminergic neurons are exclusively located in the hypothalamic tuberomammillary nucleus, from where they project to many brain areas including the nucleus accumbens (NAc). The NAc integrates diverse monoaminergic inputs to coordinate motivated behavior. While the NAc express various histamine (HA) receptor subtypes, mechanisms by which HA modulates intrinsic excitability of medium spiny neurons (MSNs) in the NAc are still poorly understood. Using whole-cell patch-clamp recordings we found that pharmacological activation of postsynaptic H_2 receptors elevates the excitability of MSNs. The evoked firing of MSNs increased after seconds of local H2 agonist administration and remained elevated for minutes. Consistent with the negative modulation of A-type K^+ currents, H_2 receptor activation accelerated subthreshold depolarization in response to current injection, reduced the latency to fire, and diminished action potential afterhyperpolarization. The increased excitability was protein kinase A-dependent and associated with decreased A-type K^+ currents measured in voltage-clamp configuration. Furthermore, selective pharmacological inhibition of the Kv4.2 channel, the main molecular determinant of A-type K^+ currents in MSNs, mimicked the increased excitability induced by H2R activation. Together, our findings indicate that histaminergic transmission in the NAc increases MSN intrinsic excitability through H_2 receptor-dependent modulation of Kv4.2 channels.

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Poster

P128. Excitability Control: Molecular Mechanisms

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Program #/Poster #: P128.06

Topic: B.08. Intrinsic Membrane Properties

Support: CIHR Grant F16-00637

Title: Mitochondrial Ca^{2+} uptake by the MCU controls activity-evoked changes in Ca^{2+}-dependent excitability and energy metabolism in pyramidal neurons.

Authors: *C. GROTEN[1], B. A. MACVICAR[2];
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Abstract: Mitochondrial Ca^{2+} uptake via mitochondrial Ca^{2+} uniporter (MCU) is implicated in the regulation of mitochondrial functions and brain activity by its control of energy metabolism, Ca^{2+} signaling, ROS generation, and apoptotic signaling. Despite this, the involvement of this process in pyramidal neurons during action potential firing has not been clearly defined. To address this, we determined the relationship between spiking frequency and mitochondrial Ca^{2+} uptake in cortical and hippocampal pyramidal neurons ex vivo using simultaneous electrophysiology and two-photon microscopy. We then examined how mitochondrial Ca^{2+} uptake was linked to activity-evoked changes in metabolism, cytoplasmic Ca^{2+} signaling, and excitability. Current-clamp recordings from single cortical pyramidal neurons expressing the genetically-encoded mitochondrial Ca^{2+} reporter, mitoRGECO1.0, revealed a firing frequency threshold (5 Hz) above which a long-lasting change in the Ca^{2+} content of somato-dendritic mitochondria was observed. Such responses were also noted during stimuli which mimic endogenous firing patterns and were blocked by inhibiting the MCU using Ru360. The coupling between spike firing and mitochondrial Ca^{2+} uptake also varied between brain regions, with hippocampal neurons being more responsive than cortical neurons. Examination of neuronal metabolism with NAD(P)H autofluorescence demonstrated that changes in NADH consumption and generation associated with high frequency firing were strongly governed by the MCU. Additionally, blocking the MCU with Ru360 substantially enhanced the magnitude and duration of cytosolic Ca^{2+} signals, but only at firing frequencies above 5 Hz. This increase in cytosolic Ca^{2+} in the absence of MCU function resulted in an enlargement of the spike-evoked afterhyperpolarization and its associated membrane current, indicating that mitochondrial Ca^{2+} uptake reduces the Ca^{2+}-dependent activation of K^+ channels. Collectively, our results reveal that MCU-dependent mitochondrial Ca^{2+} uptake occurs in response to high frequency action potential firing to facilitate energy metabolism and reduce the negative feedback control of excitability in pyramidal neurons. We propose that MCU-dependent mitochondrial Ca^{2+} uptake can act through these mechanisms to facilitate pyramidal neuron function during the critical brain processes associated with high frequency signaling.

Disclosures: C. Groten: None. **B.A. MacVicar:** None.

Poster

P128. Excitability Control: Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P128.07

Topic: B.08. Intrinsic Membrane Properties

Support: NSF Grant 1943514
NIH Grant NS117686
NSF Grant 1750295
Heart and Stroke Foundation of Canada (G-18-0021605)

Title: A cell-permeable mitochondrial calcium uniporter inhibitor elicits asynchronous transmission at synapses

Authors: P. XU[1], R. J. NOVOROLSKY[2], J. J. WOODS[3], T. HUANG[3], J. J. WILSON[3], G. S. ROBERTSON[2], *R. B. RENDEN[1];
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Abstract: Mitochondrial Ca2+ uptake through the mitochondrial calcium uniporter (MCU) facilitate synaptic energy homeostasis and shape synaptic transmission. As MCU plays a vital role in bioenergetics, signal transduction, its dysfunction is related to many neurodegenerative diseases. Inhibition of MCU is a novel therapeutic strategy for neurodegenerative disorders. Ru265 is a new, selective, cell-permeable ruthenium complex and highly potent with respect to MCU inhibition. Treatment with RU265 reduces Hypoxic/Ischemic-induced sensorimotor deficits and brain injury. However, higher doses of Ru265 can increase the frequency and duration of seizure-like behaviors, which result in undesirable side effects. In this study, we report an asynchronous neurotransmitter release at synapses caused by Ru265. Whole-cell patch-clamp voltage recordings from postsynaptic MNTB principal neurons, which receive excitatory inputs from the calyx of Held, show that treatment with Ru265 elicits high-frequency of big events on synaptic spontaneous activity, and increased asynchronous release following a high-frequency (300 Hz) stimulus train. While increased asynchronous transmission following high frequency activity is suggestive of increased Ca2+ load in the terminal and impaired mitochondrial Ca2+ uptake, spontaneous synchronized synaptic transmission may be due to a second, independent mechanism. Acute viral perturbation was used to eliminate MCU expression at calyx terminal to determine the extent to which the MCU contributes to asynchronous release, and to test for off-target effects of Ru265. Similar experiments to test for spontaneous activity due to Ru265 are being conducted in primary neuronal cultures, where MCU has been deleted. Our study provides mechanistic insight into the off-target effect of Ru265 by determining other potential cellular targets in addition to MCU in electrically excitable cells. Result from this study will also support the therapeutic potential of MCU inhibition in the treatment of ischemic/reperfusion brain injury, and assist in design and validation of future compounds to engage MCU in neurons.

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Poster

P128. Excitability Control: Molecular Mechanisms

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Program #/Poster #: P128.08

Topic: B.08. Intrinsic Membrane Properties

Support: U.S. Department of Veterans Affairs Grant: BX002547
NIGMS Grant: GM134110

Title: A Mechanism for Delirium: the impact of neuro-virulent cytokines on neuronal signaling

Authors: *S. R. RAJAYER[1], S. M. SMITH[1,2];
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Abstract: Delirium is a common disturbance in attention and awareness that develops over hours-days, is a direct consequence of other medical conditions such as trauma, sepsis and other critical illness, and worsens long-term cognitive impairment. Neuro-inflammation represents a common pathway through which delirium-triggering diseases act. An absence of effective therapies emphasize the need for greater understanding of the pathophysiology of delirium. Glial cells sense systemic inflammation across the blood-brain barrier and become activated, releasing cytokines within the brain. In one disease model, systemic infection with neuro-virulent coronaviruses caused delirium and specifically increased levels of TNF-α, IL-1β, IL-6, IL-12 and IL-15 in the mouse brain. We tested how the panel of neuro-virulent cytokines (NVC) elicited by coronaviruses changed neuronal function. We incubated mouse neocortical cultures for 22-28 h with NVC as a model of delirium. Using whole cell patch clamp methods, we found that NVC treatment depolarized the resting membrane potential compared to control (-68 ± 1 mV versus -75 ± 1 mV; $P < 0.0001$, n = 28 and 21 respectively) without affecting the action potential characteristics. Delirium is often diagnosed due to altered responses to stimuli. We tested how NVC exposure altered the responses of neocortical neurons to changes in the microenvironment. The sensitivity to changes in external Ca^{2+} and Mg^{2+} concentrations from physiological (1.1 mM, $T_{1.1}$) to low (0.2 mM, $T_{0.2}$) levels increased the spontaneous activity in controls but not NVC-treated cells. ($P = 0.026$, ANOVA). In the control neurons, spontaneous firing rates of neurons were substantially increased from 0.02 ± 0.01 Hz to 2.1 ± 1.2 Hz ($P = 0.046$), while in NVC-treated neurons the change in frequency of spontaneous firing was absent with the divalent change (0.5 ± 0.4 Hz to 0.9 ± 0.3 Hz, n = 15, $P = 0.16$). Similarly, increases in evoked spiking (20-40 pA current injections) were present in control neurons but not in the NVC-treated cells following the decrease in external divalent concentrations ($P = 0.003$, 2WRM ANOVA, Control: 3.4 ± 1.6 Hz in $T_{1.1}$ vs. 11.4 ± 1.6 Hz in $T_{0.2,}$ n=28, $P < 0.0001$; N VC: 6.1 ± 2.0 Hz in $T_{1.1}$ vs. 6.2 ± 1.6 Hz in $T_{0.2,}$ n=21 p=0.99). The depolarization caused by $T_{0.2}$ application was unchanged by NVC treatment. Taken together, these findings point to a substantial and surprising reduction in the sensitivity of neurons to changes in the microenvironment following exposure to NVCs. Uncovering the mechanism by which this loss of adaptability occurs will enhance our understanding of the pathogenesis of delirium.

Disclosures: S.R. Rajayer: A. Employment/Salary (full or part-time):; Oregon Health and Science University. **S.M. Smith:** A. Employment/Salary (full or part-time):; VA Portland Healthcare System, Oregon Health and Science University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; U.S. Department of Veterans Affairs BX002547, NIGMS GM134110.

Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P186.01

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 NS117068

Title: Investigating the role of a neuronal tRNA methyltransferase in oxidative stress and brain development

Authors: *J. L. DUMOUCHEL[1], K. R. MADHWANI[2], C. HOGAN[4], K. M. O'CONNOR-GILES[3,5]; [1]Mol. Pharmacol. & Physiol. Grad. Training Program, [2]Neurosci. Grad. Training Program, [3]Dept. of Neurosci., Brown Univ., Providence, RI; [4]Lab. of Genet., Univ. of Wisconsin- Madison, Madison, WI; [5]Carney Inst. for Brain Sci., Providence, RI

Abstract: Proper development and function of the nervous system relies on dynamic regulation of neuronal genes during transcription and translation. Studies of transfer RNA (tRNA) modifying enzymes, mostly in yeast, have highlighted the importance of chemical modifications for tRNA stability and protein synthesis. In humans, mutations in tRNA modifying enzymes have been found to disproportionately affect the nervous system resulting in neurodevelopmental disorders as well as aberrant oxidative stress response. Yeast tRNA methyltransferase 9 (TRM9) methylates wobble uridine of the anticodon loop to reinforce cognate codon-anticodon pairings. Notably, TRM9 modulates the translation of specific mRNAs in response to DNA damage and oxidative stress. In animals, two TRM9 paralogs, ALKBH8 and TRMT9B have been identified. ALKBH8 has been shown to carry out the canonical wobble uridine methylation observed in yeast. While TRMT9B acts as a tumor suppressor, the mechanism is unknown. Using CRISPR-gene editing in *Drosophila*, we generated the first *in vivo* loss-of-function TRMT9B model. Consistent with its role in oxidative stress response in yeast, *TRMT9B* null mutants exhibit increased sensitivity to paraquat, a herbicide that induces reactive oxygen species. Following a single paraquat dose, 80% of *TRMT9B* null flies died within one day compared to 50% of wild-type flies and genetic rescue. Intriguingly, we initially identified TRMT9B from a RNAi screen for regulators of synaptic growth and function and found that loss of TRMT9B induces synaptic overgrowth and significantly diminishes neurotransmitter release. Previous studies have shown that oxidative stress can result in synaptic overgrowth. To understand whether TRMT9B's role in synaptic growth is linked to its role in regulating oxidative stress response and define the mechanism of TRMT9B function, we are assessing reactive oxygen species (ROS) levels at synapses using fluorogenic dyes specific for ROS, investigating a potential role for antioxidants in rescuing neurodevelopmental phenotypes, and conducting transcriptomic and proteomic studies. We will present our latest findings on TRMT9B's role in regulating oxidative stress during neurodevelopment.

Disclosures: J.L. Dumouchel: None. **K.R. Madhwani:** None. **C. Hogan:** None. **K.M. O'Connor-Giles:** None.

Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.02

Topic: C.01. Brain Wellness and Aging

Support: NIH R21 NS097945
NIH R01 AG054533
NIH 1R56 AG068394-01
NINDS P30 NS069375
NIH P30 CA124435

Title: Age-related neuroinflammation and pathology in the locus coeruleus and hippocampus: beta-adrenergic antagonists exacerbate impairment of learning and memory in aged mice

Authors: *A. K. EVANS[1], H. PARK[1], N. SAW[2], K. SINGHAL[3], G. OGAWA[2], R. D. LEIB[3], M. SHAMLOO[1];
[1]Stanford Univ. Sch. of Med., Palo Alto, CA; [2]Stanford Behavioral and Functional Neurosci. Lab., [3]Vincent Coates Fndn. Mass Spectrometry Lab., Stanford Univ., Palo Alto, CA

Abstract: The locus coeruleus (LC) is the main source of noradrenergic input to the forebrain and hippocampus, and may be vulnerable to degeneration and contribute to age-related cognitive decline and neuroinflammation. Additionally, inhibition of noradrenergic transmission by brain-permeable beta-blockers, commonly prescribed for hypertension, could exacerbate age-related cognitive impairment. This study was designed to test the effects of age and the acute effects of a brain-permeable beta-adrenergic agonist and antagonist on 1) learning and memory, 2) inflammation in plasma and the brain and 3) pathology in the LC and hippocampus. Young (3 months) and aged (18 months) male mice were administered propranolol (beta-blocker) or mabuterol (beta-adrenergic agonist) acutely around behavioral assessment in multiple learning and memory platforms. Inflammatory markers were evaluated in plasma and in the brain and evidence for microgliosis, pathology, and changes in the proteome were evaluated in the LC and hippocampus. An increase in hippocampal and LC microgliosis and inflammatory proteins in the hippocampus was detected in aged mice. We report pathological hyperphosphorylation of the postsynaptic NMDA receptor subunit 2B (NR2B) in the hippocampus, suggesting neuronal hyperexcitability. Furthermore, the aged proteome revealed an induction in proteins related to energy metabolism, and mitochondria dysfunction in the LC and hippocampus. In a series of hippocampal dependent behavioral assessment tasks, acute beta-adrenergic agonist or beta blocker administration altered learning and memory behavior in both aged and young mice. In Y-maze, propranolol and mabuterol differentially altered time spent in novel versus familiar arms in young and aged mice. Propranolol impaired Novel Object Recognition in both young and aged mice. Mabuterol enhanced trace learning in fear conditioning. Aged mice froze more to context and less to cue. Propranolol impaired contextual recall in aged mice. In conclusion, our data provide evidence for neuroinflammation in the locus coeruleus and hippocampus in aged mice alongside evidence for metabolic challenge in the locus coeruleus and extrasynaptic deficiency of NMDA receptor signaling in the hippocampus. These age-related changes in neurobiology were accompanied with heightened effects of beta-adrenergic pharmacology on learning and memory. Future studies will examine consequences of *chronic* beta-blocker administration for cognitive deficits, pathological progression, and enhanced neuroinflammation in the LC as well as other key regions in the aged brain.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.03

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG065233 (IR&VBF)
NIH Grant R01NS110749 (KZ)

Title: Additive effect of age and chronic intermittent hypoxia on mouse behavior

Authors: L. FRASSON DOS REIS, R. KELLY, V. B. FENIK, K. ZULOAGA, *I. RUKHADZE; Neurosci. and Exptl. Therapeut., Albany Med. Col., Albany, NY

Abstract: Introduction: Obstructive sleep apnea (OSA) is a growing sleep-related breathing disorder that has morbid metabolic, cardiovascular, and neurocognitive sequeale. Due to recurrent apneic events during sleep, OSA patients chronically experience intermittent hypoxia and sleep fragmentation leading to cognitive impairment and neurodegenerative changes in several brain regions. The prevalence of obstructive sleep apnea is dramatically increased with age. While intermittent hypoxia may further exacerbate neurocognitive deficits in elderly OSA patients, we sought to investigate the effect of chronic intermittent hypoxia (CIH), an animal model of OSA, on cognitive function in aged mice using the open field and object place behavioral tests. **Methods:** Twenty young (3-4 months-old) and old (16-20 months-old) wild type C57BL/6 male mice were subjected to CIH (5 young and 5 old mice) and sham-treatment (5 young and 5 old mice). The CIH groups were exposed periodically to the room oxygen levels (21% O2 for 3 min) and a nadir (10% O2 for 4 min) applied from 7:00 AM to 5:00 PM daily for 35 days. The sham-treated groups were exposed to identically timed room air exchanges. After CIH exposure, all mice were subjected to behavioral testing. Anxiety-like behavior and general locomotor activity were tested with the open field and the spatial memory, with the object-location memory test. **Results:**In the open field test, old sham mice spent more time at the center of the field compared to young sham mice (10.5% $\pm$ 7.6 (SD) vs. 7.70% $\pm$ 3.9; $p<0.05$) whereas the CIH treatment increased the time spent in center in both young (16.7% $\pm$ 4.7) and old mice (23.7% $\pm$ 2.4; $p<0.001$), by two-way ANOVA. However, there was no difference in the level of activity or traveled distance between the groups. In the object-location memory test, the relative times for exploring the new location of an object were approximately 60% in all groups, except for the CIH-treated old mice, which tended to spend less than 50% of the time.**Conclusions:** The results obtained in the open field test suggest that aging and CIH have negative additive effect on the level of anxiety, rather than on the general locomotor activity in mice. **Support:** NIH Grants R01AG065233 (IR&VBF) and R01NS110749 (KZ)

Disclosures: L. Frasson dos Reis: None. **R. Kelly:** None. **V.B. Fenik:** None. **K. Zuloaga:** None. **I. Rukhadze:** None.

Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01NS116058
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NIH Grant R01AG053999
NIH Grant R01HL118474

Title: Diabetes-related Cerebral Amylin Vasculopathy Induces Brain Hypometabolism

Authors: *E. WINFORD[1], N. VERMA[2], A. KUMAR[2], S. DESPA[2], F. DESPA[2];
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Abstract: Background: Type-2 diabetes is a metabolic disorder that increases the risk for cerebrovascular diseases and dementia. We and others reported previously that this risk is associated with elevated blood levels of amylin (an amyloidogenic hormone synthesized and co-secreted with insulin), which promotes amylin amyloid deposition in the brain microvasculature (cerebral amylin vasculopathy). We also showed that inducing amylin dyshomeostasis in rats by pancreatic-specific expression of human amylin (amylin from rodents is non-amyloidogenic) leads to cerebral amylin vasculopathy and neurological deficits. Here we tested the hypothesis that cerebral amylin vasculopathy is a contributing factor to diabetes-associated brain hypometabolism. **Methods:** We conducted brain RNAseq analysis and proteomics in 16-month old rats expressing human amylin in the pancreas (HIP rats), amylin knockout (AKO) rats, and normal rats expressing wild-type (WT) rat amylin (n =10 males/group). Library and construction, and sequencing was performed using commercial service (Omega Bioservices). Briefly, sequence reads were aligned to the Rattus norvegicus genome (rn5) using STAR. Individual sample reads were quantified using HTseq and normalized via Relative Log Expression (RLE) using DESeq2 R Library. Isolated brain homogenates from WT and HIP (n =7/group) rats were used for western blot analysis for enzymes significantly changed in RNA seq analysis that is important in the glycolytic pathway. **Results:** In the brains of rats with amylin vasculopathy (HIP rats), RNA seq analysis shows a significantly altered pathway important for metabolism compared to WT littermates. The genes in these pathways were associated with glycolysis and revealed that amylin significantly decreases the expression of these proteins. Many of these pathways were inversely regulated in AKO vs. WT rats. **Conclusion:** Increased amylin levels in the circulation provokes cerebral amylin vasculopathy causing significant alteration of the brain gene expression. Cerebral amylin vasculopathy is a contributing factor to diabetes-related brain hypometabolism through the dysregulation of enzymes important in the glycolytic pathway.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.05

Topic: C.01. Brain Wellness and Aging

Support: CIHR grant PJT-159493
Ontario Graduate Scholarship

Title: Oxidative Stress Reduces proNGF Transport and Causes Neurodegeneration in Basal Forebrain Cholinergic Neurons

Authors: *M. FAHNESTOCK[1], A. SHEKARI[1], C. WU[2];
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Abstract: Profound and early basal forebrain cholinergic neuron (BFCN) degeneration is a hallmark of Alzheimer's disease (AD). We sought to determine whether mechanisms related to oxidative stress, a longstanding hypothesized contributor to aging and AD, account for this neurodegeneration. BFCNs depend for survival and function on neurotrophins like nerve growth factor (NGF) which are retrogradely transported from BFCN target tissue. We have recently shown that the retrograde transport of proNGF, the only detectable form of NGF in the brain, is reduced with age in cultured BFCNs and coincides with the loss of proNGF receptor tropomyosin-related kinase A (TrkA). We found that elevation of intracellular oxidative stress via antioxidant deprivation significantly reduced both TrkA immunoreactivity and proNGF retrograde transport in rat BFCNs cultured in microfluidic chambers. TrkA levels are partially regulated by protein tyrosine phosphatase 1B (PTP1B), an enzyme whose activity is reduced by the oxidation of a cysteine residue within its active site. siRNA knockdown of PTP1B and pharmacological PTP1B antagonism via selective inhibitor TCS401 significantly reduced TrkA levels in BFCNs. Furthermore, TCS401 treatment reduced proNGF retrograde transport in BFCNs and reduced axonal uptake of proNGF-KKE, a mutant form of proNGF that only binds TrkA. Treatment of BFCNs with thioredoxin-1 and thioredoxin reductase, antioxidants responsible for the reactivation of oxidized PTP1B, significantly increased TrkA levels and rescued proNGF uptake and transport in BFCNs following antioxidant deprivation. Lastly, oxidative stress resulted in axonal degeneration in the presence of either proNGF or proNGF-9/13, a mutant proNGF that binds only to $p75^{NTR}$. Degeneration did not occur in the presence of either proNGF and thioredoxin-1 or proNGF-KKE. Our results suggest that, during aging and in AD, increased oxidative stress reduces TrkA levels and proNGF transport through a PTP1B-dependent mechanism. TrkA loss and impaired proNGF retrograde transport result in BFCN degeneration and may contribute to memory loss in aging and AD.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.06

Topic: C.01. Brain Wellness and Aging

Support: NIH grant 1R21AG068769-01
NIH grant 5R35GM127045-03

Title: Apolipoprotein E regulates ferroptosis vulnerability in astrocytes

Authors: *S. E. V. RICHARDS[1], E. L. RICQ[1], M. L. YANG[1], S. L. SCHREIBER[2];
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Abstract: Recent studies suggest that cell loss by ferroptosis is of interest in neurodegenerative disease, including late onset Alzheimer's disease (LOAD). While evidence suggests that both neurons and microglia are susceptible to ferroptosis, there is little direct evidence of ferroptosis susceptibility in other glial subtypes. Furthermore, the mechanisms which confer ferroptosis vulnerability in central nervous system (CNS) cell types are largely unexplored. Here, we present evidence that astrocytes are vulnerable to ferroptosis and that this vulnerability is regulated by apolipoprotein E (apoE), the primary lipid and cholesterol transport protein of the CNS. ApoE exists as three isoforms in humans: apoE2, apoE3, and apoE4, with apoE4 conferring significant risk for LOAD. Experiments in immortalized targeted replacement mouse astrocytes reveal that all apoE isoforms confer protection from ferroptosis, but that apoE4 is notably deficient in this capacity. Whole-cell lipidomics and downstream analyses reveal that broad dysregulation of lipid storage may underlie enhanced ferroptosis vulnerability in apoE4-expressing astrocytes. This work establishes apoE as a regulator of ferroptosis vulnerability in astrocytes and provides evidence of a novel mechanism by which apoE4 may confer risk for neurodegenerative disease.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.07

Topic: C.01. Brain Wellness and Aging

Support: CONACYT 110-19

Title: Expression and activity of kynurenine monooxygenase on human astrocytoma.

Authors: *G. VÁZQUEZ CERVANTES[1], B. PINEDA OLVERA[2], D. RAMÍREZ ORTEGA[3], A. SALAZAR[4], D. F. GONZALEZ ESQUIVEL[5], S. ZAVALA[4], D. REMBAO BOJORQUEZ[4], V. PEREZ DE LA CRUZ[6];
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Abstract: Glioblastoma multiforme (GBM) is the most frequent and lethal of the primary brain tumors, with median overall survival ranging from 10 to 18 months and a five-year survival of less than 5 %.

GBM remains an incurable disease. GBMs are highly heterogeneous tumors whose landscape is modeled by immunomodulatory and metabolic mechanisms elicited by malignant cells. Among these mechanisms, overexpression of the indoleamine-2, 3-dioxygenase (IDO), the rate-limiting enzyme of tryptophan catabolism through the kynurenine pathway (KP), has been associated with a poor prognosis in patients with GBM. However, the expression and activity of downstream enzymes of the KP, such as kynurenine monooxygenase (KMO), remains poorly understood in GBM pathophysiology. Thus, the aim of this work was to analyze KMO mRNA and protein expression as well as KMO activity inhuman GBM cells lines and in patient-derived GBM samples. KMO mRNA levels were quantified by RT-qPCR, KMO protein expression was determined by flow cytometry and immunofluorescence, KMO activity was evaluated by HPLC in A172, LN18, U87, and U373 cells, and in patient-derived GBM samples. Genomic analysis of KP enzymes expression was performed using TGCA gene expression data. KMO was expressed and active in GBM cells as well patient samples with a heterogeneous pattern. Furthermore, our results are in accordance with the bioinformatic analysis that showed that KMO is expressed in both low-grade gliomas and GBM, favoring the long arm of the KP. These results demonstrate the novel expression and activity of KMO in GBM which could have metabolic and immunomodulatory implications in the tumor microenvironment.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.08

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant MH-093723
CIHR #153175
NARSAD Award #25637

Title: Elevated neuropeptide (SST, BDNF) expression induces ER stress and altered proteostasis

Authors: *T. TOMODA[1], M. L. MACDONALD[2], M. CHIKINA[2], W.-H. YU[1], E. SIBILLE[3];
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Abstract: Neuropeptides are secretable polypeptides that are produced in response to intrinsic and extrinsic neural activities and play a range of neuromodulatory roles across brain circuitry. Combined transcriptomic and proteomic analyses demonstrated significantly altered expression of a group of neuropeptides in aging brains and brain disorders, as exemplified by downregulated BDNF, SST, CRH, CORT and NPY among others. In contrast, non-secreted intracellular peptides are seldom affected by the same conditions. Neuropeptides are initially produced as long precursor molecules and then processed through the endoplasmic reticulum (ER) and trafficking vesicles to become smaller bioactive mature

peptides. To understand the mechanisms for age- or disease-associated universal downregulation of neuropeptides, we hypothesized that excess demand for neuropeptide precursor processing may cause ER overload or maladaptive ER stress, leading to altered protein homeostasis or proteinopathies. To test this hypothesis, we chose preproBDNF and preproSST as prototypical neuropeptide precursors and show that forced expression of these neuropeptides, but not the processed mature form (for SST), in neurons induces ER stress and protein aggregation, two hallmarks of cellular aging or altered proteostasis. We next used quantitative mass-spectrometry to show changes in both soluble and insoluble proteome that highlight biological functions related to ER stress, chaperones, unfolded protein binding, protein quality controls and post-translational modifications (73 proteins enriched in the insoluble fraction upon preproBDNF expression, q-values from 10^{-3} to 10^{-9}). Together these preliminary results support the hypothesis that elevated production of neuropeptides can induce ER stress-related biological changes and that this cellular risk is mediated by processing of the precursor peptide.

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Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

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Program #/Poster #: P186.09

Topic: C.01. Brain Wellness and Aging

Support: NIA R01 AG055449
NIA R01 AG068055
NIA P30 AG028383
NIGMS S10 OD023573

Title: Cortical Iron Disrupts the Anatomical Connectivity of Working Memory Networks by Damaging Proximal White Matter Microstructure in Older Adults

Authors: *V. ZACHARIOU, C. E. BAUER, B. T. GOLD;
Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: Aging is associated with accumulation of non-heme brain iron, which has been linked with oxidative stress, demyelination and cognitive decline. For instance, several previous studies have reported negative associations between iron concentration in the brain and working memory performance. However, the mechanisms by which excess brain iron interferes with working memory are not well understood. One possibility could be that increased non-heme iron concentrations in brain regions that support working memory, increase oxidative-stress-related injury to proximal white matter (WM) which can disrupt the anatomical connections between them. Here, we explored this possibility using quantitative susceptibility mapping (QSM), an in-vivo MRI technique for measuring iron concentration in brain tissue, in conjunction with fMRI, diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). A cohort of 113 cognitively normal older adults (69 women; age range: 60-86) performed an N-Back visual working memory task inside a 3T Siemens Prisma MRI scanner (64-

channel head coil). Using whole-brain fMRI activity from this task, we identified a network of bilateral brain regions in which the magnitude of activity in response to the N-Back task was significantly stronger than a control task. These regions included the anterior and posterior cingulate cortex, the dorsolateral prefrontal cortex, the middle frontal gyrus and the inferior parietal lobules. Then, using each of these regions as a seed, probabilistic tractography was conducted to map the WM connectivity between the seeds. In addition, QSM values were extracted from each of the seed ROIs as a measure of iron concentration. Voxelwise, linear regressions were then conducted between QSM values and (1) neurite density (ND), (2) radial diffusivity (DR), both of which are measures of WM microstructure integrity. All voxelwise regressions were constrained within a mask of the WM network we identified using probabilistic tractography and controlled for participant age. We found that iron concentration extracted from frontal-lobe seed ROIs predicted lower ND and higher DR in frontal but not parietal lobe regions of the WM network. Conversely, iron concentration extracted from parietal-lobe seed ROIs predicted lower ND and higher DR in parietal but not frontal lobe regions of the WM network. Based on these findings, we conclude that in older adults, non-heme iron in brain regions supporting working memory can disrupt their anatomical connectivity by damaging proximal WM microstructure.
Figure1: https://tinyurl.com/VZSFN2021

Disclosures: V. Zachariou: None. **C.E. Bauer:** None. **B.T. Gold:** None.

Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P186.10

Topic: C.01. Brain Wellness and Aging

Support: Spanish Ministry of Science and Innovation Grant PGC2018-098557-B-I00
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Title: Chaperone-mediated autophagy is a cytoprotective response of photoreceptors during aging and retinal diseases

Authors: *R. GOMEZ-SINTES[1,2], I. TASSET-CUEVAS[2], E. GAVATHIOTIS[3], A. CUERVO[2], P. BOYA[1];
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Abstract: Defective proteostasis is one of the hallmarks of aging cells and tissues. Out of the different components of the proteostasis network, we are interested in autophagy and its changes with age in retina. In this study we focus on a selective form of autophagy known as chaperone-mediated autophagy (CMA).

We have previously shown that regulation of CMA in the retina is unique, since contrary to other organs that respond to a blockage in CMA with upregulation of macroautophagy, loss of CMA in retina is not compensated for. In this work, we set to understand the physiological role of CMA in the retina and the potential beneficial effects of upregulating this selective form of autophagy as an effective intervention to delay consequences of aging in the retina and to ameliorate degeneration in age-related retinal pathologies. To that effect, we have used genetic approaches to modulate CMA in vivo. Using a mouse model deficient for LAMP-2A, the lysosomal membrane protein essential for CMA, we have found that CMA blockade leads to impaired visual function. Conversely, mice that overexpress LAMP-2A show higher resistance to chemically-induced photoreceptor damage and are more protected against the visual function decline associated with normal aging. Overall, our results support a cytoprotective role for CMA in retina, which becomes essential under conditions, such as aging, and also highlight the feasibility of upregulating CMA against retinal degeneration.

Disclosures: R. Gomez-Sintes: None. **I. Tasset-Cuevas:** None. **E. Gavathiotis:** F. Consulting Fees (e.g., advisory boards); Selphagy. **A. Cuervo:** F. Consulting Fees (e.g., advisory boards); Selphagy. **P. Boya:** None.

Poster

P186. Metabolism, Oxidative Stress, and Cellular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P186.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Assessing behavioral impairment after Doxorubicin Chemotherapy in Rats

Authors: *B. POUDEL[1], T. KEENE[1], J. L. CHEATWOOD[2];
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Abstract: Chemotherapy can notably lengthen the survival of cancer patients. Nevertheless, it has been associated with deficits in cognition and memory, delayed processing speed, and executive function which is widely recognized as chemotherapy-induced cognitive impairment or Chemo brain. In addition, it also causes the disruption of hippocampal cell proliferation and neurogenesis, increased oxidative stress, and disruption in white matter. Doxorubicin is a reactive oxygen species producing antineoplastic Anthracycline agent that adversely affects hippocampal neurogenesis and induces apoptosis. Twelve young adult female Long Evans hooded rats were assigned to either the Control(0.9% saline) or Dox groups (6mg/kg IP injection; once weekly for 4weeks). Rats were assessed on several behavioral tests including the string-pulling task, bar walk test, and open field test. Afterward, two individuals blind to the treatment group calculated the average time duration, number of attempts to pull the string, number of misses, total number of mouth contacts before and after treatment for the string-pulling task, number of deep slips, slight slips, and the total number of slips for bar walk test. Similarly, the number of entries to the center, number of entries to the corners, time spent at the center vs corner, and latency to first enter and exit the center was calculated for the Open field test and compared between two groups. Students t-test was performed across the groups. No significant differences were detected between Dox-treated and

Control rats which suggests that the Dox-treatment produced little or no significant peripheral neuropathy that disrupted performance on the motor task we used.

Disclosures: B. Poudel: None. **T. Keene:** None. **J.L. Cheatwood:** None.

Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P440.01

Topic: D.06. Auditory & Vestibular Systems

Support: NIDCD DC018561

Title: Hdac3 regulates gene expression within the auditory cortex during the formation of discriminative auditory memories.

Authors: *G.-E. GRAHAM[1], M. S. CHIMENTI[2], K. L. KNUDTSON[2], D. N. GRENARD[1], L. CO[1], M. VELEZ[3], T. TCHOU[1], K. M. BIESZCZAD[1];
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Abstract: The ability to form lasting memory for sensory experiences over a lifetime requires the induction of experience-dependent sensory system plasticity. Memories for sound meaning require experience-dependent changes within the auditory system for comprehension of sound and sound-guided action. Epigenetic mechanisms are powerful controllers underlying experience-dependent changes that can have lasting effects on neuronal function that lead to robust changes in behavior. Inhibition of the epigenetic histone deacetylase 3, HDAC3, enables *de novo* DNA transcription, which is necessary for neural plasticity and long-term memory that guides behavior. HDAC3 has been shown to regulate the precision of auditory memories by facilitating auditory cortical (ACx) plasticity when its function is blocked (Bieszczad et al., 2015; Shang et al., 2020; Rotondo & Bieszczad, 2020). However, it is largely unknown which genes HDAC3 controls for its effects on auditory memory and learning-induced ACx plasticity. RNA-sequencing on ACx samples was performed to determine genome-wide effects of blocking HDAC3 during auditory discrimination training. Our results suggest that the inhibition of HDAC3 amplifies the magnitude of learning-induced gene expression compared to vehicle and naïve groups. In addition and interestingly, there are only a handful of unique genes that are *differentially* expressed between HDAC3 inhibited animals compared to animals with uninhibited HDAC3. Identified DEGs were: *Adamts13, U6, Cabin1, Rexo4, Snhg11, Zfhx2, Celf5,* and *Ms4a6e*. We have further utilized single molecule fluorescent *in situ* hybridization (smFISH) technologies to target specific genes of interest *c-fos, egr1,* and *nr4a2,* which are under the control of HDAC3 in other systems. Combining bulk RNA-seq with more sensitive and cell-type specific smFISH techniques has allowed determination of both broad and more subtle quantitative changes in HDAC3-mediated learning-induced gene expression in the auditory system. Together, these results define the role of HDAC3 by its action on genetic targets

within the auditory cortex that may be key for neuroplasticity events that support the consolidation of highly precise and lasting auditory memories.

Disclosures: G. Graham: None. **M.S. Chimenti:** None. **K.L. Knudtson:** None. **D.N. Grenard:** None. **L. Co:** None. **M. Velez:** None. **T. Tchou:** None. **K.M. Bieszczad:** None.

Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P440.02

Topic: D.06. Auditory & Vestibular Systems

Support: NIDCD DC018561

Title: Subtle changes to task demands engage categorically different forms of learning-induced cortical neural plasticity that underlie memory enhancements mediated by HDAC3-inhibition

Authors: *A. SHANG[1], K. M. BIESZCZAD[2];
[1]Rutgers Univ., Piscataway, NJ; [2]Psychology, Behavioral and Systems Neurosci., Rutgers The State Univ. of New Jersey, Piscataway, NJ

Abstract: Epigenetic mechanisms that regulate transcription are powerful modulators of learning-induced neuroplasticity and long-term memory (LTM) formation. Inhibition of histone deacetylase 3 (HDAC3i) has been shown to facilitate LTM formation in the adult brain (McQuown & Wood, 2011). Previous work has demonstrated a role for HDAC3-i to promote the formation of highly precise memory for learned sound-cues with substrates in the auditory cortex (AudCtx). In rats trained on either single-tone detection, two-tone discrimination, or tone-cued extinction tasks, pharmacological HDAC3i during post-training consolidation promoted the formation of highly sound-specific memory, assessed behaviorally on a cued memory test (Bieszczad et al., 2015; Shang et al., 2019; Rotondo & Bieszczad, 2020, 2021). The increases in LTM specificity occurred with concomitant decreases in AudCtx tuning bandwidth (thereby increasing neural selectivity for the specific sound feature) only in sites tuned to the learned tone-frequency. This led to the hypothesis that HDAC3 has a role to modify AudCtx tuning bandwidth (BW) in the service of making memories more specific to behaviorally relevant sound features. We tested this hypothesis by training adult male Sprague-Dawley rats (n = 12) on a more perceptually challenging version of a frequency discrimination task. There were no group differences in the ability to perform the more difficult task. Consistent with prior work, memory testing revealed highly frequency-specific cued behavior in HDAC3i-treated animals (vs. vehicle). Surprisingly, multiunit recordings did not find narrower tuning BW for AudCtx sites tuned to either of the tones in HDAC3i-treated animals. Instead, we identified effects of HDAC3i on the magnitude and variability of sound-evoked responses across a range of frequencies. These results imply that HDAC3 does not simply control cortical tuning BW to promote the formation of precise sensory LTM, but instead likely acts on natural activity-dependent processes that are dictated by task demands. The more perceptually difficult task likely engaged activity-dependent processes that promoted encoding strategies better suited to the increased task difficulty. More broadly, these findings indicate that different forms of learning-induced plasticity in AudCtx may be redundantly

and non-linearly linked to select forms of behavioral change. These results highlight the importance of design in behavioral tasks to engage desired activity-dependent processes that can be harnessed and reinforced using pharmacological intervention like HDAC3i to promote cortical and behavioral function for individualized remediation.

Disclosures: A. Shang: None. **K.M. Bieszczad:** None.

Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P440.03

Topic: D.06. Auditory & Vestibular Systems

Support: NIH R01DC018621

Title: Cellular mechanisms underlying intrinsic plasticity in the zebra finch auditory cortex

Authors: *Y. LU, C. D. MELIZA;
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Abstract: In zebra finches and other songbirds, the auditory system undergoes a sensitive period where the acoustic environment shapes auditory processing that supports auditory perception of vocalizations. In the caudal mesopallium (CM), a cortical-level auditory area implicated in discriminating and learning species-specific vocalizations, there is subset of neurons that only fire transiently at the onset of current injections (i.e., phasic firing). Phasic firing can enhance the reliability and selectivity of neural responses to complex acoustic stimuli. Previous work shows phasic excitability increases during the sensitive period for song memorization. Phasic excitability increases in parallel with the proportion of CM neurons that express Kv1.1, a low-threshold potassium channel that facilitates phasic firing. These correlated changes in intrinsic plasticity (IP) and Kv1.1 expression only occur in a noisy acoustic environment, suggesting that an experience-dependent mechanism regulates expression of Kv1.1 and its localization to the plasma membrane. Here, we first investigated the cellular mechanisms underlying this IP. We stimulated CM neurons in brain slices under current clamp to determine the intrinsic dynamics, followed by post-hoc Kv1.1 expression analysis. We found that Kv1.1-positive neurons were significantly more phasic than Kv1.1-negative neurons (n=39). However there were Kv1.1-positive neurons with tonic excitability. This suggests Kv1.1 expression is necessary but not sufficient for phasic excitability. During the recording, we observed a subset of tonic neurons become phasic over the course of several minutes of currents injection (n=26). Thus, we hypothesized IP could be induced through a mechanism of activity-dependent membrane expression of Kv1.1. To test this, we first compared the change of intrinsic excitability of tonic neurons under 25 minutes of current injection to that where the neurons were held around the resting potential. Then to test the dependence of intrinsic plasticity on Kv1.1, we applied 4AP, a blocker of voltage-gated potassium ion channels, to the neurons that showed IP after the currents injection. We found that CM neurons showed activity-independent IP (n=38), and that the IP was reversed by 4AP (n=7). This suggests Kv1.1 may drive IP in an activity-independent manner. Currently, we are performing perforated patch to control for cell dialysis, the artifacts of *in vitro* whole-cell recording, that might

emerge in the IP of the recorded neurons. Next, we will test the dependence of IP on calcium influx by loading the internal solution with BAPTA.

Disclosures: Y. Lu: None. **C.D. Meliza:** None.

Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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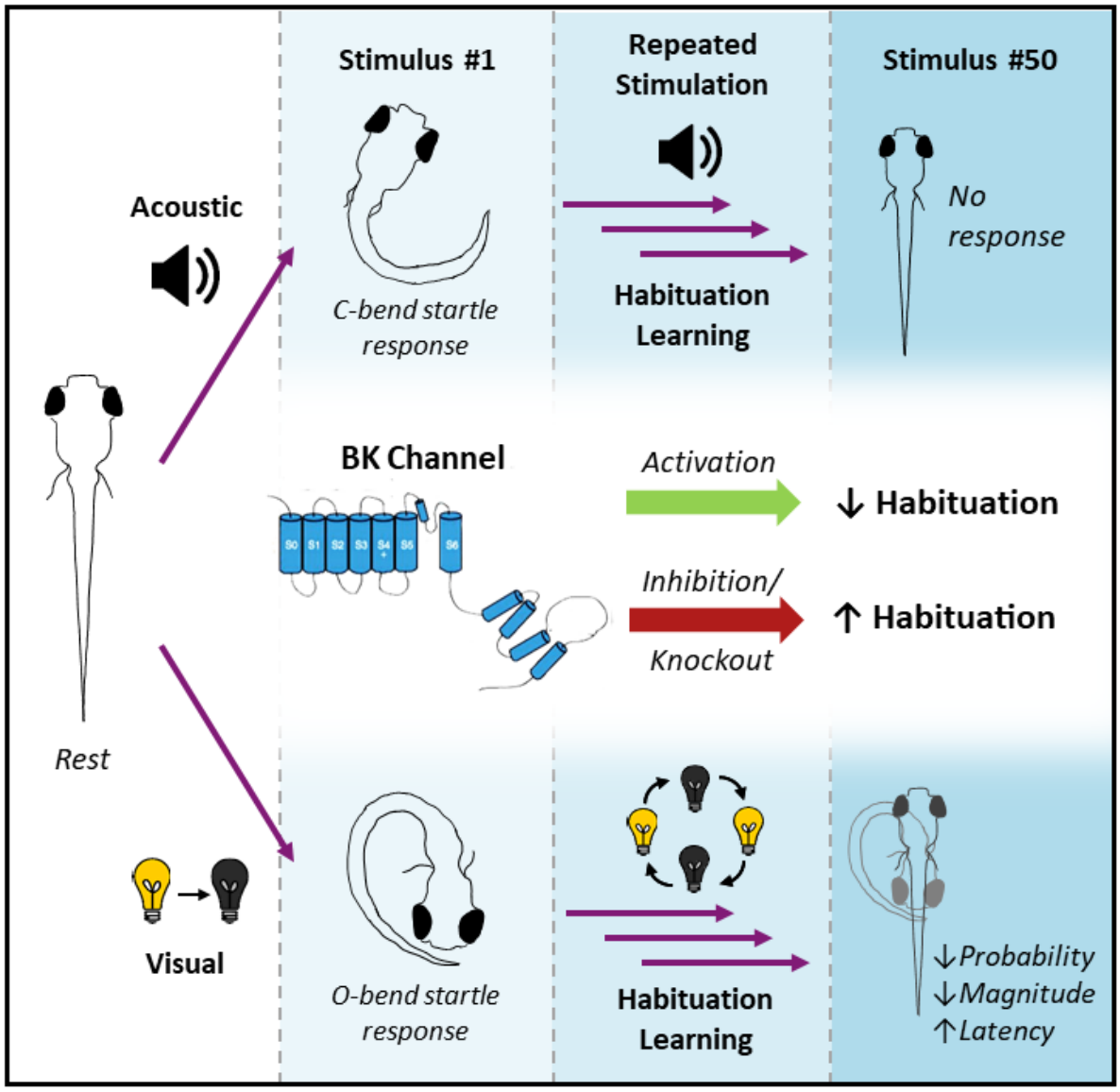
Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant K99NS111736
NIH Grant 9R01NS118921

Title: Voltage- and calcium-activated potassium (BK) channel disrupts short-term startle habituation

Authors: *Y. WIESENFELD[1,2], J. C. NELSON[1,3], M. GRANATO[1];
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Abstract: Habituation is an evolutionarily conserved learning process involving repression of a response to repeated stimuli. Enabling animals to selectively focus on pertinent stimuli, it is thought to be a basis for more complex types of learning. Studies in vertebrates and invertebrates identified genetic and circuit processes regulating habituation, though its molecular basis remains unclear. Recent evidence suggests that dynamic changes in the calcium- and voltage-gated K^+ (BK) channel regulate short-term habituation of startle responses. Also, mutations of the channel are linked to human disorders involving habituation deficits, including ADHD and schizophrenia. Yet studies show conflicting effects of BK channel activation on habituation learning. We first employed pharmacological manipulations of channel activity to evaluate its role in acoustic and visual startle habituation in zebrafish. We found that BK channel opening using meclofenamic acid weakened habituation learning in both systems, while channel closing using paxilline enhanced habituation. Next, we generated loss-of-function BK channel mutants using CRISPR-Cas9 genome editing to validate the antagonistic role of BK channel activity on habituation learning. Animals with a 305 kb deletion in the *kcnma1a* gene, one of two paralogs encoding for the pore-forming α-subunit of BK channels in zebrafish, demonstrated enhanced acoustic habituation and a longer startle latency to dark flashes compared to siblings, supporting the results of our pharmacological experiments. Our findings paradoxically suggest that promoting neurotransmitter release by decreasing potassium conductance *suppresses* startle responses. We propose that the predominant role of the BK channel in startle habituation is at the level of inhibitory neurons. In the future, *in vivo* calcium imaging of individual neurons may help pinpoint where in the startle circuitry BK channels influence habituation learning. Understanding how the channel disrupts habituation will provide insight into the mechanisms most critical for this adaptive process.



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Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P440.05

Topic: D.06. Auditory & Vestibular Systems

Title: Processing of valence in the mouse auditory cortex

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Abstract: The auditory cortex is the primary site of sound processing within the brain, however processing of non-auditory information within this region is being increasingly discovered. Learning to associate stimuli emotional or motivational valence is a critical skill in survival, and disturbances in these associations are found in a range of diseases such as PTSD or schizophrenia. While alterations to tone frequency processing have been seen to be affected by associations with rewarding or aversive stimuli, it is unclear how these factors intersect at the neuronal level, and whether neurons within the auditory cortex have innate, conditional or long-term valence responsiveness independent of sound. Longitudinal two-photon calcium imaging was used to assay neurons in the auditory cortex during the conditioning, recall and pair switching of pure tones with both rewarding and aversive stimuli. Following conditioning, a subset of neurons in the auditory cortex were shown to respond to valence coded stimuli when either rewarding or aversive stimuli were presented alone, these neurons were composed of cells with and without tone responses. These valence responsive cells were predominantly active when either rewarding or aversive stimuli were presented but could also show responses to both valences. Once the initial conditioning pairs were reversed, subsets of neurons could undergo a switching of their stimuli response to the opposing valence, as well as gaining a new or losing the initial conditioned response. The valence responsive cells appear to form ensembles with tone responsive cells and potentially indicate a local mechanism to influence emotionally linked auditory information within the auditory cortex.

Disclosures: J.D. Johnson: None. **Z. Li:** None.

Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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Title: Activity in mouse motor cortex reflects action and its expected sensory consequences

Authors: *B. E. HOLEY, D. M. SCHNEIDER;
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Abstract: Throughout sensory cortices, neural activity is influenced by behavior. While behavior-related modulation can be generic (e.g. gain control), it can also be precise, such as suppression in the auditory cortex of neural responses to sounds that are predictable consequences of an animal's movements. Suppression of neural responses to self-generated sounds has been observed in humans, monkeys, and mice, and likely involves motor cortical projections to auditory cortex. In the mouse, projections from the secondary motor cortex (M2) are active during behavior and target inhibitory networks in the auditory cortex (AC), consistent with a role for M2 in mediating predictive suppression. However, it remains unknown what information M2 sends to AC during sound-generating movements. We ask whether M2

activity reflects purely movement-related information, or also reflects expectations about the sensory consequences of a movement. To answer these questions, we trained mice to push a lever with their right forelimb to achieve a water reward. At a fixed position, the lever produces a predictable and experimentally controlled sound, which the mice perceive as being self-generated. After training with a single predictable sound, we record the activity of M2 cell populations during the lever behavior. During electrophysiology, the lever first produces the tone that mice had learned to expect during training. We find that a majority of the recorded M2 population is active during the lever behavior, including preparatory activity before movement initiation and a large fraction of cells with peak firing rates just before and after the self-generated tone. We used optogenetic stimulation of ChR2+ M2 terminals in A1 to antidromically identify the subset of recorded cells that project to A1. A1-projecting M2 cells have activity patterns similar to the broader M2 population, but they are more likely to be active around the time of the tone. After producing 50-100 trained tones, the sound produced by the lever movement was unexpectedly and permanently switched to a novel tone. Interestingly, while mice lever behavior remains stable, we find a sub-population of M2 cells, including A1 projectors, that significantly change their firing rates after the tone change. Some of these neurons change their activity prior to the tone, indicating that these changes cannot only be accounted for by the occurrence of the novel tone. The timescale of changes varies from rapid (i.e. upon the first novel sound) to gradual (accumulating over trials). Together, these findings suggest that M2 not only represents motor-related aspects of a forelimb movement, but also the acoustic consequences of the movement.

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Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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Topic:

Support: NIH Grant 5R01DC012557-09
NIH Grant 5P01NS074972-07

Title: Neural and behavioral variability in auditory perceptual learning

Authors: *K. A. MARTIN[1], C. J. BREDENBERG[1], E. P. SIMONCELLI[1,2], C. SAVIN[1], R. C. FROEMKE[3,4,5,6];
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Abstract: Perceptual learning is associated with altered cortical representations of task-relevant stimuli in trained animals relative to naive ones. Despite their association with perceptual improvement, such changes in neural tuning are typically not measured throughout learning. Additionally, there is a large degree of variability in perceptual learning rates across animals, which is largely ignored when recording and interpreting neural activity. To address these limitations, we developed an experimental and

computational framework for describing how sensory representations change during auditory perceptual learning.
We recorded from a population of neurons throughout auditory conditioning using two-photon imaging of layer 2/3 excitatory neurons in the auditory cortex of mice. To obtain water reward, mice learned to to distinguish a single, center frequency (11-16 kHz) from non-center frequencies by licking left and right, respectively. Discrimination performance improved over 10-45 days through multiple phases of learning (N=52 animals).
Across trained animals, despite similar trained behavioral performance, we observed two distinct tuning profiles of excitatory neurons. Specifically, individuals exhibited either a relative enhancement or suppression of the frequencies reported as center. Despite the variability in neural responses, there was a consistent increase in number of neurons with a maximum response a quarter octave away from the behavior discrimination threshold (N=10 animals). Additionally, we found these neurons had the steepest slope at the behavior discrimination threshold (N=10 animals). Thus, we found a relative increase of neurons that are most sensitive to detecting minor differences in frequency around the behavior discrimination threshold, potentially facilitating improvement in the discrimination between frequencies that are similar but are classified differently behaviorally.
To make sense of the across animal variability in tuning, we trained a network model by reward-modulated Hebbian synaptic learning (Williams, 1992) to learn the same task. We found that the simulated network learns at similar rates as real animals. The model captures the across-animal variability in tuning, specifically capturing the suppression or enhancement of center frequency representations. Overall, both data and model reveal nontrivial learning dynamics associated with perceptual learning in auditory cortex, with initial tuning driving across-animal variability in the emerging representations.

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Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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Topic: D.06. Auditory & Vestibular Systems

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Title: Plasticity in layer 1 of auditory cortex during auditory perceptual learning

Authors: *A. M. LEMESSURIER[1], K. A. MARTIN[1], C. E. OLIVER[1], R. C. FROEMKE[2];
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Abstract: Auditory perceptual learning, in which subjects learn to recognize and discriminate acoustic stimuli, is associated with changes in the tonotopic organization of responses to sound in auditory cortex [1]. Frequency tuning in auditory cortex neurons can change depending on behavioral relevance and context, and this contextual modulation as well as behavioral performance depends on activity in

inhibitory circuits [2]. Stimulation of neuromodulatory centers projecting to cortex can speed perceptual learning and induce tonotopic map plasticity [3,4]. The circuit mechanisms mediating the influence of neuromodulators on inhibitory networks are under investigation. Interneurons in layer 1 (L1) receive input from long-range neuromodulatory and intracortical inputs, and target the dendrites of pyramidal cells as well as layer 2/3 (L2/3) interneurons, positioning them to gate integration of neuromodulatory and sensory input [5]. We hypothesize that plasticity in L1 is a crucial component of auditory perceptual learning. We trained 5 mice on an appetitive, 2-alternative forced-choice tone recognition task [6] while measuring activity in NDNF interneurons on each day of training using chronic 2-photon calcium imaging. Each mouse initially achieved <80% correct discriminating a center tone and a foil spaced 1.5 octaves apart before the introduction of additional foils spaced 0.25, 0.5, 1, and 1.5 octaves surrounding the target. After 28 +/- 7 days of training each mouse correctly identified tones on 76 +/- 4% of trials. Within each mouse, NDNF neurons displayed a variety of tuning profiles for tones used in the task at the end of training, including a relative suppression of responses to the target tone in some neurons, as well as enhanced responses in others. Additionally, tuning in NDNF neurons was task modulated - tuning curves differed within most cells between the task context and passive tone presentation outside of the task context. These results suggest that tuning in NDNF interneurons may be plastic over the course of training, and that activity in these neurons may shape the context-dependent activity in downstream neurons.

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Poster

P440. Auditory Processing: Neuronal Adaptation and Plasticity

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Cochlear Contract (PI: J. Thomas Roland, Jr., MD)

Title: Behavioral and physiological approaches for studying auditory learning in rats with cochlear implants

Authors: *A. E. HIGHT[1], E. G. GLENNON[3], D. N. WAITMAN[4], Y. CHENG[5], J. K. SCARPA[6], M. INSANALLY[7], M. A. SVIRSKY[2], R. C. FROEMKE[8];
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Abstract: Cochlear implants (CIs) are auditory neuroprostheses that restore hearing to over 500,000 humans world-wide, including over 3,000 at our clinic at NYU since 1984. The CI restores hearing by bypassing damaged parts of the sensory transduction epithelium of the inner ear and directly stimulates primary afferent neurons via pulses of electrical current. Despite significant distortion in the encoding of sound, human cochlear implant users can fully identify spoken words without the aid of other sensory cues. Significant variability, however, exists in peak speech comprehension outcomes; our hypothesis is that central plasticity underlies variability in CI outcomes. To test this hypothesis, we have developed a behaviorally and physiologically-validated system for studying cochlear implants in rats (King et al. 2016, Glennon et al. 2021). Moreover, we have previously developed micro-electrocorticography (µ-ECoG) arrays for chronic tracking of sound evoked responses over rat auditory cortex in freely moving rodents (Insanally et al. 2016).
Here, we trained rats on a self-initiated two-alternative forced-choice (2AFC) task to examine perceptual learning in a more complex version of our previous go/no-go task. Normal hearing rats were first trained to nosepoke-left for 4 kHz center tones and nosepoke-right for all other presented frequencies. Next, trained rats were bilaterally deafened and unilaterally fitted with an 8-channel cochlear implant. CI implanted rats were retrained with the center 4 kHz tone replaced by a single intracochlear stimulating electrode. All rats trained on the acoustic version of the task eventually reached high discrimination performance (n=12, overall hit rate > 80%) and CI implanted rats reached high discrimination performance within 2-3 weeks (n=4, overall hit rate >75%). We also implanted µ-ECoG arrays over the primary auditory cortex to compare and track the reliability of sound and CI-evoked responses, both acutely (n=4) and chronically (n=2). Single-trial acoustic-evoked measurements indicated reliable evoked activity and the spatial distribution of activity enabled the detection of network topography. Single-trial measurements during CI-stimulation revealed reliable evoked responses to intracochlear electrode stimulation (d-prime >1, evoked vs baseline activity). Network topography was not obvious for activity evoked by stimuli across the electrode array. These results demonstrate the efficacy of the CIs in restoring behaviorally relevant auditory cues in bilaterally deafened rats. Our next step is to relate this adaptation period to network-level evoked activity across the primary auditory cortex.

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Poster

P459. Subcortical Visual Pathways II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P459.01

Topic: D.07. Vision

Support: DFG Emmy-Noether KR 4062/4-1

Title: Monosynaptic activation of inhibitory neurons in mouse superior colliculus by retinal ganglion cells in vivo

Authors: *C. GEHR[1], J. SIBILLE[2], J. KREMKOW[3];
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Abstract: The superior colliculus (SC) is a midbrain structure that receives direct inputs from retinal ganglion cells (RGCs) but whether excitatory (ExN) and inhibitory (IN) SC neurons differentially integrate retinal activity *in vivo* is unknown. We have recently developed an innovative approach to measure large populations of RGCs simultaneously with their postsynaptic SC targets *in vivo* using Neuropixels probes (Sibille et al., SfN 2021). This study revealed that RGCs strongly drive synaptically connected SC neurons among some weaker connections. However, this study lacks the distinction between cell-types of the postsynaptic SC neuron and it remains an open question whether these strong connections are cell-type specific. Here we examine whether there are differences in the connection strength of monosynaptic retinal activation onto SC ExNs and INs by studying retinal inputs onto SC INs and ExNs. It could be that the strong retinal afferent inputs are preferentially found onto SC INs whereas the weak inputs project onto SC ExNs. This would be similar to thalamo-cortical circuits (TC) where cortical INs receive strong thalamic input (Swadlow 2002, 2003) while the afferent drive onto ExNs is usually weak (Kremkow et al. 2016; Bereshpolova et al. 2020). Alternatively, the wiring in retino-collicular circuits could follow a different principle where the afferent input onto SC INs and SC ExNs is similar in strength. To address these two possibilities, we combined our novel approach of recording RGC inputs onto SC neurons (Sibille et al. 2021 SFN) with optotagging of SC INs in the VGAT-ChR2 mouse line. Connected RGC-SC pairs were identified using cross-correlation analysis and connection strength was estimated from the efficacy of RGC spikes driving postsynaptic spiking in SC neurons (Reid 1995; Bershpolova et al. 2020). Our preliminary results indicate that both SC INs and ExNs can be strongly driven by retinal inputs; furthermore, both populations also receive weak RGC inputs (number of connected pairs: RGC-SC IN = 59, RGC-SC ExN = 142), not showing a significant difference in synaptic efficacy between SC ExN and INs ($p > 0.05$, Wilcoxon rank-sum). Interestingly, monosynaptic activation of SC INs by RGCs appears to be similar in strength as compared to the afferent thalamic drive onto cortical INs. However, in contrast to the weak activation of cortical ExNs, putative SC ExNs also receive strong afferent inputs. In summary, our preliminary results suggest that ExNs and INs in the SC are strongly driven by their afferent retinal inputs which implicates that the wiring in the retino-collicular circuit follows different principles compared to thalamo-cortical circuits.

Disclosures: C. Gehr: None. **J. Sibille:** None. **J. Kremkow:** None.

Poster

P459. Subcortical Visual Pathways II

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Program #/Poster #: P459.02

Topic: D.07. Vision

Support: DFG Emmy-Noether KR 4062/4-1

Title: Large-scale in vivo paired recordings with Neuropixels probes reveal strong and specific connections between retina and midbrain in mammals and birds

Authors: *J. SIBILLE[1], C. GEHR[1], J. BENICHOV[3], H. BALASUBRAMANIAN[1], K. TEH[1], T. LUPASHINA[1], D. VALLENTIN[4], J. KREMKOW[2];
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Abstract: The output of the retina is carried by retinal ganglion cells (RGCs) along parallel functional pathways to multiple areas distributed across the vertebrate brain. The functional organization of the synaptic connections between RGCs and their postsynaptic target neurons is largely unknown. Here, we discovered that high-density Neuropixels probes allow the measurement of large populations of RGC axons where they form synaptic contacts, in vivo. The electrophysiological signature of RGC afferent inputs is made of a triphasic waveform composed of the axonal action potential, the axonal terminal response and, finally, the corresponding responses from the synaptically connected dendrites. The signal is spread across multiple recording sites, capturing the axonal synaptic contact field of individual RGCs in vivo. Consequently, midbrain neurons can be recorded simultaneously with their presynaptic RGC inputs, at large scales reaching up to 200 functionally connected pairs in individual recordings. Furthermore, we confirmed that these large-scale paired recording are possible in both the mammalian superior colliculus (mouse, Mus musculus) and the avian optic tectum (zebra finch, Taeniopygia guttata). Using our novel approach to study the spatial organization of retinal axons within the midbrain, we discovered that retinal mosaics are mapped onto the midbrain isomorphically with single cell precision. Functionally, we show that single RGC axons connect to their target neurons with strong and specific connections, i.e. a limited functional convergence and log-normally distributed connection strength. Overall, our results show that high-density electrodes can capture multiple neuronal compartments simultaneously in vivo, including afferent axons and their synaptically evoked dendritic responses as well as somatic activity of local neurons; permitting large-scale paired recordings between brain regions. In addition, we conclude that the retinotectal connectivity follows a common organizing principle in mammals and birds that provides a precise and reliable representation of the visual world to neurons in the midbrain.

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Poster

P459. Subcortical Visual Pathways II

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Program #/Poster #: P459.03

Topic: D.07. Vision

Support: Medical Research Council (MRC)
The Sir Henry Dale Fellowship from the Wellcome Trust and Royal Society (200501)

Biotechnology and Biological Sciences Research Council grant (R004765)

Title: Separate populations with different response dynamics project to visual thalamus and periaqueductal gray in the superior colliculus of mouse

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Abstract: The superior colliculus (SC) projects to other brain centres through multiple pathways, which are thought to be important in rapid, visually guided behaviours. Projections from the SC to the visual thalamus and the periaqueductal gray (PAG) may be important for behaviour, however the extent to which these projections are anatomically distinct remains poorly understood. Moreover, whether these projections are functionally distinct, in terms of visual tuning and dynamics, is not known. We assessed the anatomical and functional segregation of these pathways in adult male C57BL6/J mice.
To assess anatomical segregation we injected CTB conjugated to different fluorophores into the visual thalamus and periaqueductal gray. We found that thalamus-projectors were concentrated in the optic layer, whereas PAG-projectors were mainly in the intermediate and deep layers. At the interface between the optic and intermediate layers, thalamus and PAG-projectors formed intermingled but separate populations of neurons.
To assess functional segregation we injected retrogradely-transported Cre virus into an area, to gate expression of GCamp7s in the SC. We implanted a lens above the SC and measured the global, calcium-dependent fluorescent signal while presenting visual stimuli to head-fixed mice free to run on a treadmill. In both projection populations this global signal was responsive to approaching and translating objects, preferred slower visual speeds, and preferred novel visual stimuli. Thalamus-projectors showed more sustained responses, while PAG-projectors primarily responded to the onset of visual stimuli. Both populations showed increase in calcium signal around the onset of locomotion.
In summary, we found parallel projections from SC to visual thalamus and PAG. The tuning of visual responses in the two pathways was similar but the dynamics of response were not. The different dynamics may be adaptive, allowing possibility of rapid responses to visual objects via projections to PAG, and sustained analysis of the same objects via projections to visual thalamus.

Disclosures: T. Wheatcroft: None. **A. Saleem:** None. **S. Solomon:** None.

Poster

P459. Subcortical Visual Pathways II

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Topic: D.07. Vision

Support: NEI Grant 1R01EY030138
RPB-CDA

Title: Trans-seq decodes a specific mammalian retinotectal synapse assembled by nephronectin

Authors: *F. WANG[1], N. Y. TSAI[1], K. TOMA[1], C. YIN[1], J. TAKATO[4], E. L. PAI[2], J. L. RUBENSTEIN[3], E. M. ULLIAN[1], X. DUAN[1];
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Abstract: Precise neural circuit assembly is necessary for the brain to process complex sensory information and produce proper behaviors. While significant progress has been made on classifying mammalian neuronal types and understanding molecular mechanisms for local neural circuit assembly, there is a lack of systematic methods to map long-range synaptic connections and decode the underlying molecular determinants of such connectivity. Here, we developed Trans-Seq to fulfill this task, bypassing tedious anatomical and functional measurements. Trans-Seq efficiently maps connectivity across neuron types and reveals information of their corresponding transcriptional profiles, thereby uncovering candidate molecules that may confer wiring specificity. Trans-Seq uses a versatile and optimized fluorescent anterograde transsynaptic tracer, enabling isolation and transcriptional profiling of individual post-synaptic partners of genetically or regionally defined presynaptic cells. Using mouse retinotectal connections as a model system, we applied Trans-Seq to study how long-range synaptic specificity is achieved from the eye to the brain. By applying the anterograde tracer to all retinal ganglion cells (RGCs), the subsequent Trans-Seq allowed us to classify all retinorecipient neuron types in the superior colliculus (SC). Furthermore, we identified distinct input patterns onto these SC recipient neurons by conducting differential Trans-Seq from two distinct RGC subclasses. Through such characterizations and comparisons, we identified a unique and specific synaptic connection from αRGCs to Nephronectin-positive wide-field neurons (NPWFs) in the SC. This synaptic pair was subsequently validated using genetic labeling, electrophysiology, and retrograde tracing. Furthermore, we revealed, using Trans-seq transcriptomics data, that the synaptic pair is wired together via interactions between presynaptic Integrin-α8β1 and post-synaptic Nephronectin. To our knowledge, Nephronectin is the first cue discovered in mammalian SC to confer retinotectal synaptic specificity at neuronal type resolution. These results demonstrate how Trans-Seq efficiently maps long-range synaptic connections at neuron-type resolution and simultaneously captures molecular determinants for synaptic specificity. This new platform offers a new avenue to decode circuit assembly across brain regions. Using molecular and genetic tools gained from circuit mapping, we are pursuing new directions to link these genetically defined parallel retinotectal circuits to different visual evoked behaviors, such as looming responses or prey-capture behaviors.

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Poster

P459. Subcortical Visual Pathways II

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Topic: D.07. Vision

Support: NIH R01EY026286
NIH K99EY031783

Title: Characterization of visual response properties and connectivity of Wide-field vertical neurons in the mouse superior colliculus

Authors: *E. SAVIER, H. CHEN, K. MCHANEY, J. CANG;
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Abstract: Vision is a sense that serves many different ethological functions across species. Visual information can be used to either detect preys or predators, and therefore generate orienting or escaping responses. The superior colliculus has been implicated in the orchestration of these behaviors. Within this structure, at the interface between the primary and the secondary visual pathway, lay the wide-field vertical neurons (WFV). WFV are a conserved morphologically defined cell-type found across many taxa from reptiles to highly visual mammals, independently of their visual ecology. These neurons display wide arborization and typical bottlebrush distal tips which form connections with retinal ganglion cells axonal terminals. In mammals, these neurons receive direct inputs from the retina and the primary visual cortex, and have the pulvinar as a known target, however, their brain-wide connectivity remains to be identified. These cells display peculiar response properties, but despite their ubiquity and unique morphology, their contribution to vision remains elusive.
In this study, we have characterized WFV morphology, connection, and visual response properties *in vivo* in the laboratory mouse. Sparse retrograde tracing using an intersectional approach revealed their exquisite morphology and projection patterns. Two-photon calcium imaging in awake mice using a transgenic Cre-line targeting specifically WFV (NTSR1-Cre) confirmed their unique response properties. WFV showed a strong preference for small moving stimuli and a slight bias for certain directions. Interestingly, visual responses to distinct visual stimuli showed variable degrees of adaptation upon repeated presentation. In addition, Cre-dependent rabies tracing unraveled a variety of sources of input which had not been described previously.
These results place WFV as a major integrator of visual information in the superior colliculus. Their adaptation to looming stimulus suggest a role in ethologically relevant function in avoiding inappropriate responses, while sustained responses to small moving stimulus might be linked to attentional processes and orienting behaviors. Taken together, this initial characterization paves the way to elucidate the role of these neurons in visual behavior.

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Poster

P459. Subcortical Visual Pathways II

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Topic: D.07. Vision

Support: NIH Grant EY029703
NIH Grant EY02162
Unrestricted grant from Research to Prevent Blindness

Title: Efficiency of retrograde labeling by rAAV2-retro-hSyn viral vector in the rat retinocollicular pathway.

Authors: *R. NANJAPPA, M. D. DILBECK, J. R. ECONOMIDES, J. C. HORTON;
Ophthalmology, Univ. of California San Francisco, San Francisco, CA

Abstract: Viral vectors allow tracing of neural circuits and hold potential for pathway-specific manipulation. Efficiency of labeling depends upon the viral serotype, the promoter used to drive expression of the gene of interest, and the neural pathway being probed. In 7 rats we injected a 50:50 mixture of two tracers, rAAV2-retro-hSyn-EGFP and rAAV2-retro-hSyn-mCherry, using electrophysiological recordings to guide placement into the visually responsive layers of the superior colliculus. A single injection was made on either one side or both, concentration 1.9 - 2.2 x 10^{13} vg/ml, total volume 1-2 µl. In vivo fundus imaging was performed 3 - 20 days afterwards. No labeling was present at 3 days, but later, retrogradely labeled retinal ganglion cells (RGCs) became visible. Most cells were labeled by both EGFP and mCherry, but clear examples of single-labeled cells were present. In one animal, the fundus image was aligned with the post-mortem retinal flatmount to establish that the in-vivo labeling truly corresponded to RGCs. In all rats, it was evident that only a minority of RGCs was virus-labeled. At best, 20% of DAPI-stained cells in the ganglion cell layer exhibited EGFP or mCherry fluorescence. The concordance of labeling by the 2 fluorophores was surprisingly imperfect, confirming observations from fundus photography. For example, in one heavily labeled field 717 cells exhibited mCherry, 532 exhibited EGFP, but only 357 cells exhibited both. To determine the percent of cells comprising the retinocollicular pathway that were retrogradely labeled by the viruses, we mixed Fluorogold into the injection pipette. Unfortunately, this strategy severely reduced the amount of retinal EGFP and mCherry labeling. We therefore staggered the injections, first injecting a mixture of the two viruses, followed 4 weeks later by Fluorogold at the same site. In the injection case showing the most robust labeling, 32% of retinocollicular cells were labeled (517 mCherry/1588 Fluorogold). We conclude that: 1) In-vivo fundus photography can be used to image RGCs labeled by fluorophore-expressing viral vectors transported retrogradely from the superior colliculus, 2) Some RGCs exhibit only a single label, despite the same virus encoding either label being mixed together in the injection pipette, 3) Addition of Fluorogold to the injection pipette containing the viruses impairs fluorophore expression, and 4) rAAV2-retro-hSyn succeeds at labeling, at most, only a third of the RGCs that projects to the superior colliculus in the rat.

Disclosures: R. Nanjappa: None. **M.D. Dilbeck:** None. **J.R. Economides:** None. **J.C. Horton:** None.

Poster

P459. Subcortical Visual Pathways II

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Program #/Poster #: P459.07

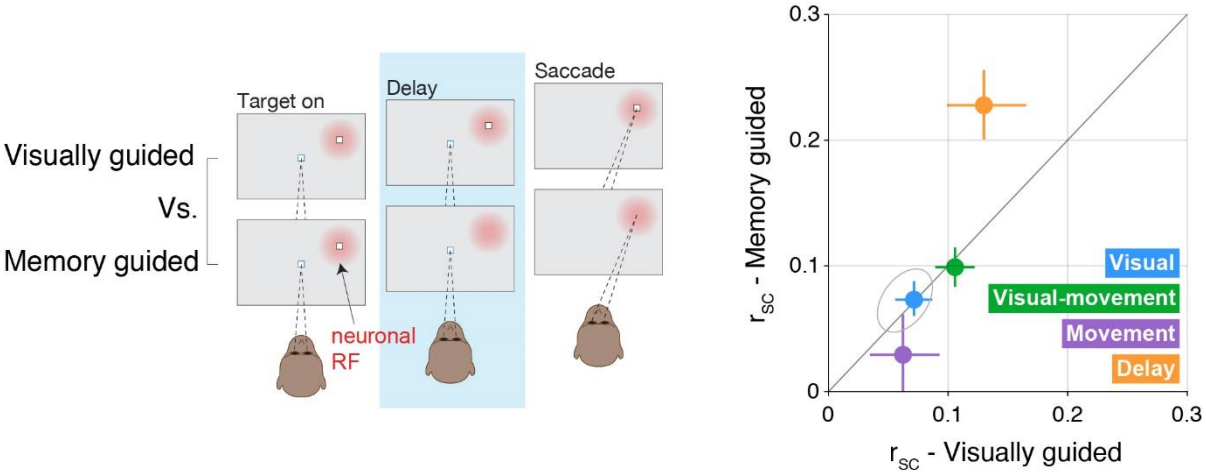
Topic: D.07. Vision

Support: ZIA EY000511

Title: Correlated variability across neurons in primate superior colliculus depends on functional class

Authors: *L. N. KATZ, G. YU, J. P. HERMAN, R. J. KRAUZLIS;
Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: Neuronal responses to repeated presentations of the same stimulus are variable, and often correlated between pairs of neurons in a population. Such correlated variability (spike count correlations, r_{SC}) can constrain how information is read out across the brain and is therefore a key property of the neural code that guides behavior. A large body of work has identified that the degree of r_{SC} is influenced by behavioral goals and by intrinsic properties of the neurons such as tuning. However, investigations of r_{SC} have tended to take place within a brain region, without taking local microcircuits into account. Such microcircuits can serve different functions, reflect different processing stages, and be associated with either feedforward or feedback signals, likely leading to distinct degrees of r_{SC} within the region.Here we report that r_{SC} depends on functional class, a neuronal property thought to reflect membership in a distinctive microcircuit. We recorded from populations of neurons (n = 672) in the macaque superior colliculus (SC), a structure that contains neurons with well-defined functional classes. During an oculomotor working memory task, different classes of SC neurons exhibited differing degrees of r_{SC}. Neurons functionally classified as “visual” or “movement” exhibited modest degrees of r_{SC}, while those classified as “delay” (which exhibit persistent activity in the absence of sensory input) displayed the highest degree of r_{SC}, especially during the delay epoch of the task. The higher degree of r_{SC} in delay neurons was more pronounced during memory guided saccades than visually guided, and was present only among pairs of neurons within SC on one side of the brain, not between SCs.The dependence of r_{SC} on functional class indicates that subpopulations of SC neurons occupy distinct circuit niches with different modulatory inputs. Overall, these findings highlight the importance of considering functional class when interpreting the significance of r_{SC} in the SC, and more broadly, in other regions of the primate brain.



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Poster

P459. Subcortical Visual Pathways II

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Program #/Poster #: P459.08

Topic: D.07. Vision

Support: NIH R01EY026286

Title: Visual response properties of VIP- and SST-positive neurons in the mouse superior colliculus

Authors: *V. J. DEPIERO[1], Y. LIU[1], J. N. CAMPBELL[1], J. CANG[1,2];
[1]Biol., Univ. of Virgina, Charlottesville, VA; [2]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The superior colliculus (SC) and its non-mammalian homologue the optic tectum is a midbrain structure important for visual processing, multimodal integration, and sensorimotor transformation. In mice, more than 85% of retinal ganglion cells project to the superficial SC, making it the most prominent visual center in this species. Here, we investigate the function of superficial SC neurons from two readily available mouse lines, the vasoactive intestinal peptide-expressing (VIP)-IRES-Cre mice and the somatostatin-expressing (SST)-IRES-Cre mice. By crossing these mice with the Ai9 reporter line and virally expressing GCaMP6f, we recorded visually evoked neuronal responses in the SC of awake animals using two-photon fluorescence calcium imaging. Our suite of visual stimuli allows us to extract various feature-specific aspects of visual processing, including direction and orientation selectivity, response to a looming disk, and receptive field mapping. We also use RNAscope to validate the spatial distribution and reveal excitatory/inhibitory identity of these cells by co-staining for vesicular glutamate transporter 2 (VGluT2), vesicular GABA transporter (VGAT) and VIP or SST in wildtype animals. We find that VIP expressing neurons are sparsely labeled in the most superficial layer of the SC. Visual responses of VIP neurons show less selectivity to direction, orientation, and looming stimuli than neighboring VIP negative neurons. The receptive fields of VIP positive neurons show highly overlapping ON and OFF subfields. On the other hand, SST neurons are predominantly labeled throughout the lower visual layers of the superficial SC. SST positive neurons also have overlapping ON and OFF receptive fields and have a similarly low preference of direction selectivity as their neighboring SST negative neurons. Finally, unlike what is observed in the cortex, VIP-positive neurons in the SC actually express VGluT2, a marker of excitatory neurons; and SST-positive neurons in the SC express VGAT, confirming that they are in fact inhibitory cells. Together these findings show that VIP- and SST-positive neurons in the visual layers of the SC are likely distinct cell types of visually responsive neurons that respond to both ON and OFF stimuli but lack strong tuning toward a particular visual feature. These data will aid future studies to understand how excitatory and inhibitory neurons process visual information in the SC.

Disclosures: V.J. DePiero: None. **Y. Liu:** None. **J.N. Campbell:** None. **J. Cang:** None.

Poster

P459. Subcortical Visual Pathways II

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P459.09

Topic: D.07. Vision

Support: NIH ZIA EY000511

Title: Attention-related activity emerges in mouse superior colliculus through learning

Authors: *K. K. COVER, L. WANG, K. ELLIOTT, R. J. KRAUZLIS;
Lab. of Sensorimotor Res., NEI, Bethesda, MD

Abstract: Visual selective attention is not wired into the brain fully formed and immutable but is learned and refined as animals interact with their environment. Among the brain structures that could play a central role in this process, the superior colliculus (SC) stands out because of its highly conserved role in coordinating behavioral responses to visual events and its functional link to mechanisms of reinforcement learning in the basal ganglia. Here we investigated this process by studying neuronal activity in the mouse SC at different stages of learning of a covert visual selective attention task. In our visual attention task, mice learned to detect an orientation change in one of two Gabor patches with the location of the potential change indicated by a preceding spatial cue. We recorded neuronal spiking activity during this task in superficial and deeper SC layers in three cohorts of mice that possessed different levels of expertise: task-naïve (N=6 mice, n=417 units), intermediate learners (N=5, n=429), and experts (N=4, n=378). We found several markers of attention-related SC activity that differed by expertise and SC laminar location. Response habituation of SC neurons for task-relevant visual events was greatest in the deeper layers of naïve mice and was significantly less prominent in intermediate and expert mice. In contrast, response habituation was weaker in superficial SC layers and varied little across expertise levels. Attention-related modulation - defined as enhanced activity evoked by the visual stimulus at the cued location during the delay period prior to the orientation change - was absent in task-naïve mice, emerged with intermediate learners, and was largest in the expert mice. This attention-related modulation was also more pronounced in the deeper SC layers. Together, these results demonstrate that specific components of SC neuronal activity related to visual selective attention emerge over time in particular SC layers as mice learn the value of spatial cues and visual events.

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Poster

P459. Subcortical Visual Pathways II

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Program #/Poster #: P459.10

Topic: D.07. Vision

Support: NIH Grant EY029703
NIH Grant EY02162
NIH Grant OD011107
Unrestricted grant from Research to Prevent Blindness

Title: Interdigitation of Ocular Inputs to the Macaque Superior Colliculus

Authors: *M. D. DILBECK, Z. R. SPAHR, J. R. ECONOMIDES, R. NANJAPPA, J. C. HORTON;
Univ. of California San Francisco, San Francisco, CA

Abstract: Approximately 10% of retinal ganglion cells project to the superior colliculus in the macaque. Hubel, LeVay, and Wiesel (1975) injected a radioactive tracer into one eye in 4 macaques to label the ocular inputs to the superior colliculus. Axon terminals were present in the stratum griseum superficiale, aggregated into irregular clumps of silver grains separated by unlabeled gaps. By analogy with the ocular dominance columns in layer 4C of striate cortex, they concluded that the unlabeled holes corresponded to inputs from the other eye. An alternative interpretation is that inputs from the two eyes are largely overlapping, with the unlabeled gaps corresponding to zones within the superficial gray that receive no direct ocular input. Such an anatomical arrangement might explain why virtually all tectal cells are binocular, unlike cells in layer 4C of striate cortex, which are mostly monocular. To address this issue, we performed experiments in 2 macaques. In the first animal, tritiated proline was injected into the right eye and the pattern of radiolabeling was examined in serial 30 μm sections through the entire superior colliculus. The results confirmed the prior report of Hubel et al, by showing marked aggregation of silver grains with interspersed unlabeled zones. There were also regional differences in the density and laminar distribution of the proline label that depended on location within the visual field representation. In the second animal cholera toxin B - Alexa 488 was injected into the right eye and cholera toxin B - Alexa 594 was injected into the left eye. The superior colliculus was sectioned serially at 40 μm and the two fluorescent labels were compared in each section. The main finding was that the two labels tended to interdigitate: conspicuous gaps in one label were usually filled by a cluster of the other label. Rarely, gaps in both labels coincided. Throughout much of the superior colliculus, the labels from the two eyes showed extensive overlap. We conclude that ocular inputs to the macaque superior colliculus form a dovetailed mosaic, but unlike a fine piece of joinery, there is much intermingling in projections. There also exist laminar and regional differences in the density of label from each eye that are related to visual topography.

Disclosures: M.D. Dilbeck: None. **Z.R. Spahr:** None. **J.R. Economides:** None. **R. Nanjappa:** None. **J.C. Horton:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P518.01

Topic: E.03. Basal Ganglia

Title: Functional diversity of identified dopamine substantia nigra neurons in freely moving mice

Authors: *D. SCHENKEL, M. KUHN, S. BETZ, G. SCHNEIDER, J. ROEPER;
Johann Wolfgang Goethe-University Frankfurt, Frankfurt, Germany

Abstract: Dopamine substantia nigra (DA SN) neurons are a major target of Parkinson's disease (PD) and their degeneration is thought to contribute to the core motor impairments such as bradykinesia in PD. However, the functional relevance of electrical activity patterns of DA SN neurons for the control of voluntary movement is unclear. Also, there is considerable diversity among DA SN neurons. Alves da Silva and colleagues (2018) showed that about 50% of recorded DA SN neurons transiently increase and about 25% of recorded DA SN neurons decrease their firing rate shortly before the initiation of self-paced

movement in the open field. To study these neurons in awake behaving mice in detail, we performed extracellular single-unit recordings of DA SN neurons in awake freely moving mice, while simultaneously recording their head and body movements using an accelerometer and a video-tracking software. In our data set of n = 61 (N = 18) pharmacologically identified DA SN neurons, we confirmed the functional diversity with regards of transient responses in close associations to spontaneous movement initiation.To differentiate between DA SN neurons with distinct axonal projections, we currently establish retrograde tagging methods.

Disclosures: D. Schenkel: None. **M. Kuhn:** None. **S. Betz:** None. **G. Schneider:** None. **J. Roeper:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P518.02

Topic: E.03. Basal Ganglia

Support: NIH grant R01DA041705

Title: Sodium channel inactivation and maximal firing rates in dopamine neuron subpopulations

Authors: *T. ZIOUZIOU[1], C. J. KNOWLTON[2], N. HAMMER[1], C. C. CANAVIER[2], J. ROEPER[1]; [1]Inst. for Neurophysiology, Neurosci. Ctr., Goethe Univ., Frankfurt, Germany; [2]Cell Biol. and Anat., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

Abstract: Based on electrophysiological properties, dopamine (DA) midbrain neurons can be segregated into two main subpopulations: conventional DA neurons projecting to dorsal striatum or the lateral shell of nucleus accumbens and atypical DA neurons projecting - among others - to medial shell and core regions of nucleus accumbens or the medial prefrontal cortex. While some of their distinct biophysical properties (Lammel et al. 2008) and different firing pattern in vivo (Farassat et al. 2019) have already been described, their differences regarding maximal firing rates and their distinct onset of depolarization block have not yet been studied in detail. By systematically exploring the parameter space of a computational single-compartment model of DA neurons, we identified slow inactivation of voltage-gated sodium channels as a candidate mechanism that might differentiate between conventional and atypical DA neurons. In particular, the model suggested that conventional DA neurons enter depolarization at lower firing rates because of enhanced slow inactivation of voltage-gated channels and that depolarization block could be overcome by injection of additional depolarizing current. This prediction was tested with projection-specific in vitro patch-clamp experiments in identified and retrogradely labeled DA neurons. We confirmed that lateral shell-projecting, conventional DA neurons entered depolarization block at lower frequencies (17.0 ± 3.3 Hz; n = 7, N = 3) compared to the medial shell-projecting, atypical DA neurons (31.9 ± 4.6 Hz; n = 13, N = 3). In addition, only lateral shell-projecting, conventional DA neurons triggered an action potential (amplitude 37.5 ± 10.2 mV, peak slope 15.1 ± 4.8 V/s, threshold for spike generation = 5 V/s; n = 7, N = 3) induced by additional depolarizing current injection during depolarization block, while atypical DA neurons showed a significantly slower and smaller depolarizing

responses (amplitude 17.7 ± 3.8 mV, peak slope 4.5 ± 1.7 V/s, threshold for spike generation = 5 V/s; n = 13, N = 3). To further test the predictions of the computational models, we currently study gating properties of voltage-gated sodium channels in defined conventional and atypical DA neurons.

Disclosures: T. Ziouziou: None. **C.J. Knowlton:** None. **N. Hammer:** None. **C.C. Canavier:** None. **J. Roeper:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P518.03

Topic: E.03. Basal Ganglia

Title: Projection-specific hierarchical organisation of somato-dendritic dopamine 2 receptor inhibition among midbrain dopamine neurons

Authors: *N. HAMMER, B. FISCHER, S. STOJANOVIC, J. ROEPER;
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Abstract: Most midbrain dopamine (DA) neurons are inhibited by activation of somato-dendritic D2-autoreceptors (D2R) (1). In their landmark paper, Beckstead et al. demonstrated the presence of synaptic D2R signalling between pre- and postsynaptic DA neurons in midbrain slices in vitro (2). In addition, spontaneous D2R mediated IPSCs were recorded in DA neurons showing functional dendro-dendritic vesicular DA release between midbrain DA neurons (3). Previous studies from our group reported different D2R and GIRK2 expression levels in midbrain DA neurons projecting to distinct target areas (4), but the functional contribution of synaptic and extrasynaptic D2R signaling within and across these DA subpopulations is currently unknown. Distinct somato-dendritic D2R-signaling might also contribute to the different functional in vivo properties we recently identified (5).Therefore, we recorded electrically evoked, D2R-mediated slow inhibitory postsynaptic currents (eIPSCs) in retrogradely identified DA neurons in vitro. These sulpiride-sensitive sIPSCs displayed kinetics and current peak amplitude ranges in agreement with previous studies (2). However, we observed significant differences in peak D2R-sIPSC amplitudes between DA neurons projecting to ventral (i.e. lateral shell of the nucleus accumbens (lNAcc), medial shell of the nucleus accumbens (mNAcc)) and dorsal striatum (e.g. dorsomedial striatum (DMS), dorsolateral striatum (DLS)). Mean eIPSC amplitudes of lNAcc-projecting DA neurons displayed at least two-fold larger currents compared to DA neurons projecting to other compartments of the striatum (lNAcc: 27.1 ± 2.5 pA (n = 21); mNAcc =12.2 ± 3.1 pA (n = 9); DMS = 16.3 ± 1.4 pA (n = 23); DLS =12.5 ± 1.3pA (n=18).To investigate the interaction between defined DA subpopulations, we developed a projection-specific viral approach to optogenetically excite a projection-selective pool of presynaptic DA neurons while recording a single postsynaptic DA neuron with retrogradely defined axonal projections. Optogenetically stimulating presynaptic DA neurons projecting to DLS while recording a DA neuron projecting to lNAcc, we recorded robust optically-evoked, sulpiride-sensitive D2-IPSC (oIPSC) ($lNAcc_{DLS}$: 14.9 ± 3.7 pA (n = 13). In contrast, when reversing pre- and postsynaptic DA neurons, little to no oIPSCs were recorded in DLS projecting DA neurons (DLS_{lNAcc}: 3.6 ± 1.4 pA (n = 9). These results suggest a lateral-to-medial hierarchical organisation of D2R-inhibition among distinct DA subpopulation

in the midbrain. (1) Lacey et al. 1987(2) Beckstaed et al. 2004(3) Gantz et al. 2013(4) Lammel et al. 2008(5) Farassat et al. 2019

Disclosures: N. Hammer: None. **B. Fischer:** None. **S. Stojanovic:** None. **J. Roeper:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

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Program #/Poster #: P518.04

Topic: E.03. Basal Ganglia

Title: An in vivo patch-clamp study of K-ATP Channels in midbrain dopamine neurons

Authors: *R. EGGER, J. ROEPER;
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Abstract: We have recently established deep in vivo patch-clamp recordings of dopamine (DA) midbrain neurons in mice (Otomo et al. 2020). We now apply this approach to study the functional role of ATP-sensitive potassium (K-ATP) channels. We have previously demonstrated that the expression of K-ATP channels in DA neurons in the medial substantia nigra (SN) are required for in vivo burst firing and in turn for novelty-induced exploratory behavior (Schiemann et al. 2012). However, the moment-to-moment contribution of K-ATP channels to ongoing in vivo activity of DA neurons has not yet been explored. To address this question, we added 100 µM of the K-ATP channel blocker tolbutamide to the internal pipette solution to inhibit these channels selectively in the target cell in vivo. Previous control experiments comparing electrical in vivo activity in on-cell and whole-cell mode demonstrated stable firing pattern and gave no evidence that in vivo whole-cell patching *per se* altered intrinsic K-ATP channel activity (Otomo et al. 2020). When dialyzing tolbutamide into DA SN neurons, we observed distinct effects. In n = 11/22 cells, the firing frequency rapidly increased, which was accompanied by a net membrane depolarization. Some of these cells (n = 7 of 11) went into depolarization block, from which they were rescued by injection of negative currents. In contrast, DA neurons in the ventral tegmental area (VTA, n = 11) did not alter their in vivo firing activity in response to tolbutamide dialysis. This preliminary data set suggests that in a least a subset of DA SN neuron K-ATP channels are continuously open and shape ongoing electrical activity. Similar to previously reported for pancreatic alpha-cells (Göpel et al. 2020) open K-ATP channels in some DA neurons might be necessary for action potential firing. References:
Göpel et al. (2000) J. Physiol 528:509-20.Otomo et al. (2020) Nature Communications 11:6286
Schiemann et al. (2012) Nature Neuroscience 15:1272-80

Disclosures: R. Egger: None. **J. Roeper:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

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Topic: E.03. Basal Ganglia

Support: NIH Grant NS097185

Title: Bidirectional spike frequency adaptation in neurons of the external globus pallidus

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Abstract: In the external segment of globus pallidus (GPe), the neurons fire continuously even in the absence of synaptic input. The balance of afferent excitation and inhibition changes the net synaptic current and thereby the firing rates of each cell. An increase in striatal inhibition in GPe is associated with models of Parkinson's disease and is expected to reduce the average firing rate, but in most studies the change in firing rate is modest or even undetectable. This is unexpected because GPe neurons have long been known to be very sensitive to transmembrane currents, although the current steps used in those studies have been brief (0.5-1 s), disregarding possible adaptation. The sensitivity of two kinds of GPe neurons, identified by expression of either parvalbumin (PV) or Npas1, were studied in mouse slices using 20 s current pulses. As reported by others, both neuron types were usually spontaneously active. On average, PV neurons fired faster and were more regular, but there was overlap between the distributions of these for the two groups. Both adapted their firing rates as expected at the onset of a depolarizing current step. Increases in firing rate caused by depolarizing currents decayed on a similar time scale in both cell types. There was some recovery of firing rate during hyperpolarizing pulses in both cell types, with larger currents required to maintain silence for 20 seconds than was required to initially silence firing. However, PV and Npas1 cells differed in this escape of firing during hyperpolarization. Whereas Npas1 neurons could readily be silenced for the entire 20 s period by modest injected currents (<50 pA), PV neurons routinely resumed firing after a few seconds, despite currents 2-3 times larger. PV and Npas1 cells were readily differentiated from each other by this one measurement. The ability of PV cells to overcome hyperpolarizing current was also evident in their membrane potential trajectories during the hyperpolarizing pulse, consisting of a slow depolarizing ramp leading to firing at increasing rates throughout the pulse. The results suggest that PV neurons, which target the subthalamic nucleus and basal ganglia output neurons are less likely to be silenced by prolonged striatal inhibition than Npas1 neurons, which do not project to basal ganglia output neurons. PV neurons' firing has a much higher sensitivity to transient changes in the balance of synaptic excitation and inhibition than to its DC average.

Disclosures: C.J. Wilson: None.

Poster

P518. Cellular Physiology of the Basal Ganglia

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Program #/Poster #: P518.06

Topic: E.03. Basal Ganglia

Support: NIH/NINDS Grant NS097185

Title: Local connectivity alter spike responses in network models of globus pallidus pars externa

Authors: *E. OLIVARES[1], M. H. HIGGS[2], C. J. WILSON[1];
[1]Univ. Texas San Antonio, San Antonio, TX; [2]Oklahoma Med. Res. Fndn., Oklahoma City, OK

Abstract: Globus pallidus pars externa (GPe) is traditionally considered a relay nucleus that inverts the signal arriving from striatum and passes it to the basal ganglia output neurons, but interconnections between the GPe neurons may alter those signals. GPe neurons are autonomous oscillators whose local axon collaterals create an active inhibitory network, but spike timing correlations among GPe neurons have been elusive. We constructed network models of GPe to investigate the effects of local connectivity on firing and responses to stimuli. Because GPe neurons are oscillators, we simulated them using phase models that predict the time of the next spike considering all the synaptic inputs arriving during the inter-spike interval (ISI). We experimentally measured the firing rates, and phase resetting curves of 19 GPe neurons in mouse brain slices. Using this dataset, we generated 1000 artificial neurons with diversity similar to that of the recorded neurons. As the connectivity pattern in GPe is not fully known, we tested the network in two different architectures: small-world and random. Each network was created using the same set of 1000 neurons and the same total number of connections (10/neuron). At steady state, the two networks produced similar distributions of firing rates and coefficient of variation of ISI. Pairwise correlations and cross-correlations were scarce and mostly limited to monosynaptically connected pairs. When stimulated by a shared inhibitory input, the post-stimulus time histogram (PSTH) of the networks showed a biphasic response that is rapidly damped by the network synaptic interaction. The network decreased the size and reduced cell-to-cell differences in the initial decrease in response probability by a differential balance in the effect of external inhibition and local disinhibition. The initial response perturbed the network stationary probability distribution of phases, increasing the density of neurons at late phases in their firing cycles. As the external inhibition decays, the neurons held by inhibition at late phases resumed their phase advance, generating a transient increase in firing probability, this secondary response was limited to the fastest neurons in the network. Our results were robust across the network architectures and show that in sparsely coupled networks of heterogeneous autonomous oscillator neurons like GPe, the local inhibitory activity does not generate a global synchrony. We also show that during the response to shared inputs, the local interactions reduces the temporal reverberation of the stimulus in the network, presumably allowing a more effective temporal discrimination of external stimuli.

Disclosures: E. Olivares: None. **M.H. Higgs:** None. **C.J. Wilson:** None.

Poster

P518. Cellular Physiology of the Basal Ganglia

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Program #/Poster #: P518.07

Topic: E.03. Basal Ganglia

Support: NIH/NINDS Grant NS097185

Title: Local inhibition in the GPe controls the firing patterns of GPe neurons and shapes their responses to external input

Authors: *J. A. JONES[1], M. H. HIGGS[2], C. J. WILSON[2];
[1]Univ. of Texas at San Antonio, San Antonio, TX; [2]Biol., The Univ. of Texas at San Antonio, San Antonio, TX

Abstract: The external globus pallidus (GPe) is a network of autonomous oscillators that influence all basal ganglia nuclei through their widespread axonal projection patterns. Two neuronal superclasses with distinct projection patterns dominate the GPe, parvalbumin-positive (PV) and neuronal PAS domain protein 1-positive (Npas1) neurons. PV and Npas1 GPe neurons exhibit different ranges of autonomous firing activity and provide ongoing GABAergic input streams to one another through local axon collaterals. To determine the effect of local inhibition on the firing patterns of PV and Npas1 GPe neurons, we obtained perforated-patch, current-clamp recordings in coronal slices of the GPe from male and female mice before and during GABA-A receptor blockade. GABA-A blockade had variable effects on GPe neurons' firing rates and regularity. PV neurons with high spontaneous IPSP rates exhibited large increases in firing rate and regularity following blockade, whereas Npas1 neurons showed variable firing rate changes that were weakly correlated with blockade. These results suggest that local collaterals in the GPe exert stronger control of PV firing than Npas1 firing, although they receive a similar synaptic barrage. In addition to the local inhibition, PV neurons receive a powerful inhibition from GABAergic striato-pallidal neurons of the indirect pathway. To determine whether local collaterals propagate indirect pathway inputs through the GPe network, we recorded spontaneous IPSCs of GPe neurons while applying brief light pulses to indirect pathway striato-pallidal axons expressing channelrhodopsin. Evoked striato-pallidal synaptic input reset periodic IPSCs from local collaterals, showing that striato-pallidal inhibition is propagated through the GPe network. To determine whether local collaterals from PV neurons shape spiking responses to external inhibition, we recorded from single PV neurons while applying brief inhibitory pulses to all PV neurons in the GPe network using archaerhodopsin both before and after blocking synaptic inhibition from local collaterals with GABA-A receptor blockade. Brief optogenetic inhibition of PV neurons transiently reduced both their firing rates and IPSP rates. After GABA-A blockade, optogenetic inhibition produced greater reductions in firing rate and greater spiking reset. These results suggest that local collaterals in the GPe reduce the magnitude of PV neurons' responses to external inhibition but may increase the bandwidth of GPe signaling by removing prolonged oscillatory responses.

Disclosures: J.A. Jones: None. **M.H. Higgs:** None. **C.J. Wilson:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.01

Topic: E.04. Voluntary Movements

Support: NIH R25

Title: Dynamic recruitment of cell-type specific inhibition in premotor cortex during motor learning

Authors: *S. E. ARROYO, S. BARATI, K. GANGULY;
UCSF, San Francisco, CA

Abstract: Motor learning depends on coordinated changes in neuronal population dynamics in both premotor (M2) and motor (M1) cortex. Prior work supports a model in which M2 relays contextual information to M1, thereby exerting a top-down modulatory influence on M1 activity. However, the synaptic mechanisms that mediate the evolution in M2 population dynamics over the course of motor learning are not well understood. To investigate how cell-type specific inhibition contributes to emergent neural dynamics in M2 during motor learning, we have recorded from vasointestinal peptide (VIP) and somatostatin (SST) expressing inhibitory interneurons across several days as mice learned a skilled reach-to-grasp task. Neuronal activity was recorded by selectively expressing a genetically encoded calcium indicator (GCaMP 7f) in SST or VIP neurons. Transfected neurons were then imaged using microendoscopic, single-photon techniques, allowing for simultaneous recording from large ensembles of genetically identified neurons in freely moving and behaving mice. Over the course of five behavioral sessions, mice learned to reach for a small food pellet reward (a skill that has been previously shown to depend on motor cortex), manifesting as a five-fold decrease in reaction time and 1.5-fold increase in reach success. In early behavioral sessions, both SST and VIP neurons were recruited around the time of reach onset. Over the course of learning, SST recruitment was shifted to the right (later in time with respect to reach onset), and as a population SST interneurons were increasingly co-activated in a narrow temporal window. In contrast, VIP recruitment was shifted to the left (earlier in time with respect to reach onset) and as a population VIP recruitment became less synchronous with learning. These data suggest that VIP neurons in particular may be important in shaping preparatory activity and processing contextual information in the pre-reach epoch. Consistent with this theory, presentation of a distractor auditory tone in the inter-trial period resulted in VIP but not SST activation. Together, these findings demonstrate that specific classes of inhibitory cells are recruited in a temporally divergent manner over the course of motor learning. This cell-type specific segmentation of inhibition may be an important synaptic mechanism for defining distinct temporal windows of preparatory motor processing in M2.

Disclosures: S.E. Arroyo: None. **S. Barati:** None. **K. Ganguly:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.02

Topic: E.04. Voluntary Movements

Support: ISF-1801/18
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Title: Impaired motor adaptation in the absence of cerebellar signals in behaving monkeys

Authors: *S. ISRAELY[1], R. HAREL[2], F. MAWASE[3], Y. PRUT[1];
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Abstract: The cerebellum plays a major role in motor learning and adaptation. In human and non-human primates, cerebellar control of motor output is primarily mediated through its impact on the motor cortex. However, little is known about the way that cerebellar signals shape motor cortical activity to allow efficient adaptation to external perturbations. We addressed this question by studying the changes in motor behavior and motor cortical activity during a motor adaptation task, while manipulating cerebellar outflow. Monkeys (n=2) were trained to wear an exoskeleton (KINARM system), and make center-out movements to 1 of 8 pre-cued targets and adapt to a velocity-dependent force field (FF). A reversible block of cerebellar outflow was introduced using a High Frequency Stimulation (HFS) electrode chronically implanted in the ipsilateral superior cerebellar peduncle. We found that blocking cerebellar outflow during FF trials significantly limited motor adaptation, as manifested by an increase in residual errors (measured as the deviation from a straight path) relative to control FF trials. This effect was especially pronounced when errors were measured in the early phase of movement (up to 250 msec), which is largely dominated by feedforward control. Next, we used a state space model to quantify the properties of the adaptation process. We found that cerebellar HFS significantly limited adaptation through a reduction in sensitivity to errors (15.1%, and 21.2%, $p << 0.001$ for both monkeys), not by an increase in the rate of forgetting ($p=0.26$ and $p=0.46$). Finally, we ruled out the possibility that cerebellar HFS impaired adaptation by simply adding noise to the external perturbation. Although we found that applying HFS led to a significant increase in motor variability compared to control trials, this variability did not trigger an adaptive response, suggesting that HFS increased internal noise. Importantly, we found no correlation between the change in error sensitivity and the level of internal noise either during the control or the HFS trials. These results suggest that blocking cerebellar outflow leads to increased internal noise and decreased error sensitivity. The net outcome of these (at least partially independent) events is impaired motor adaptation.

Disclosures: S. Israely: None. **R. Harel:** None. **F. Mawase:** None. **Y. Prut:** None.

Poster

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Title: Global and subtype-specific modulation of cortical inhibitory neurons orchestratedby acetylcholine during motor learning

Authors: *C. REN[1], K. PENG[3], R. YANG[4], W. LIU[1], C. LIU[2], T. KOMIYAMA[1];
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San Diego, La Jolla, CA; [3]Interdepartmental Neurosci. Program, Yale Univ., New Haven, CT; [4]Sch. of Biol. Sci., Georgia Inst. of Technol., Atlanta, GA

Abstract: Inhibitory neurons (INs) consist of distinct subtypes with unique functions, and their subtype-specific modulation shapes excitatory circuits during various sensory and cognitive processes. Previous studies on INs mainly focused on single brain regions, and thus it remains unclear whether the modulation of IN subtypes occurs globally across multiple regions. Here, we monitored the activity of different cortical IN subtypes at both macroscale and microscale in mice learning a lever-press task. We found that learning evoked a global modulation of IN subtypes, not only in the primary motor cortex but throughout the cortex. The initial learning phase involved strong movement-related activation of vasoactive intestinal peptide-expressing inhibitory neurons (VIP-INs) and weak activation of somatostatin-expressing inhibitory neurons (SOM-INs). Furthermore, inactivating VIP-INs increased SOM-IN activity during movements and impaired initial learning. Concurrently, cortical cholinergic inputs from the basal forebrain were more active during the initial learning phase but became less engaged over learning. Manipulation of the cholinergic system impaired motor learning and differentially altered movement-related activity in cortical IN subtypes. Pharmacological manipulation of different cholinergic receptor subtypes further revealed that the cholinergic modulation of IN activity was largely through nicotinic receptors. These results reveal that motor learning involves a global and subtype-specific modulation on cortical INs mediated through the cholinergic system, which likely regulates the excitatory circuits distributed across the cortex.

Disclosures: C. Ren: None. **K. Peng:** None. **R. Yang:** None. **W. Liu:** None. **C. Liu:** None. **T. Komiyama:** None.

Poster

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Program #/Poster #: P532.04

Topic: E.04. Voluntary Movements

Support: DARPA TNT N66001-17-2-4010

Title: Effects of stimulation timing on performance improvements evoked by vagus nerve stimulation

Authors: A. BRZECZKOWSKI[1], B. KNUDSEN[2], A. C. SKUBAL[2], M. LALUZERNE[2], M. LALUZERNE[2], J. C. WILLIAMS[2], K. LUDWIG[3], *A. J. SUMINSKI[1];
[1]Neurolog. Surgery, [2]Biomed. Engin., [3]Biomed. Engin. and Neurolog. Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: The pairing of a task and a sufficient level of stimulation, either natural or artificial, is known to elicit plastic changes in neural circuits. In particular, pairing vagus nerve stimulation (VNS) with behavior has been shown to drive cortical plasticity during auditory discrimination and motor tasks as well as promote functional rehabilitation after injury. It remains unclear, however, whether the plasticity inducing mechanism is related to activation of neuromodulatory centers or the optimization of arousal state, underscoring the need to better understand the mechanisms by which stimulation of peripheral

nerves acts to drive plasticity in neural circuits and enhance behavioral performance. Here, we evaluate how acquisition of a novel motor task is modulated by VNS presented prior to task performance (i.e. priming) similarly to stimulation presented during task performance (i.e. peristimulus) and if these gains are mediated by changes in the engagement of neuromodulatory centers, arousal mechanisms or some combination of the two. Male Long-Evans rats (n = 27) weighing 200-250g were operantly trained to perform a reach and pull task that required them to pull with a predetermined force to receive a pellet reward. Successful acquisition of thes task was determined when they were able to pull with greater than 120g of force on more than 75% of trials over a 10 session period. Rats were randomly assigned to one of 5 cohorts to measure the effects of VNS and arousal based stimulation on learning rate: 1) priming VNS, 2) peristimulus VNS, 3) priming vibrotactile, 4) peristimulus vibrotactile and 5) unstimulated control. Rats in the VNS cohorts were implanted with a bipolar cuff electrode on their left vagus nerve while those in the vibrotactile cohorts wore a sweater with a vibrotactile stimulator placed at the base of their neck. Priming VNS (800uA, 30Hz, cathode leading biphasic pulses 100us/phase) and vibrotactile stimulation were delivered for 120s prior to the start of training, whereas peristimulus VNS (same parameters as priming) and vibrotactile stimulation were delivered for 500ms immediately following each successful pull. We compared the number of sessions to reach task proficiency and variations in pulling force between rats in each cohort. Preliminary data suggests there is no difference in the number of sessions to reach task proficiency or success rates between cohorts suggesting that an arousal based mechanism may be responsible for reported performance improvements.

Disclosures: A. Brzeczkowski: None. **B. Knudsen:** None. **A.C. Skubal:** None. **M. LaLuzerne:** None. **M. LaLuzerne:** None. **J.C. Williams:** None. **K. Ludwig:** None. **A.J. Suminski:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: NIH Grant PLACEHOLDER

Title: Reachmaster3d, an experimental platform capable of the precise 3d measurement of whole-arm kinematics as rodents perform freely-behaving reaches.

Authors: *B. NELSON[1], S. IBRAHEEM[2], E. NGUYEN[3], K. E. BOUCHARD[4];
[1]Univ. Of California, Berkeley Neurosci. Grad. Program, Berkeley, CA; [2]Electrical Engin. and Computer Sci., [3]Univ. of California, Berkeley, Berkeley, CA; [4]UCSF, UCSF, San Francisco, CA

Abstract: Reaching is an essential behavior occurring in three dimensions (3-D). Rodents perform dexterous reaching behaviors, however rodent reaching has mainly been quantified during low-dimensional behavioral tasks and resulting kinematic measurements are not-in 3-D. There exists a need for behavioral assays, using high-dimensional tasks, to measure whole-arm reaching kinematic variables in 3-D during freely-behaving reaching. Here we present ReachMaster-3D, a novel assay capable of measuring reaching 3-D kinematics from freely-behaving male rats reaching to a handle varied in position

from 0 to 3 task dimensions. We examine measures of task performance and effect of task complexity on trajectories and velocities extracted using the ReachSplitter-3D system. We then use 3-D kinematic variables within current motor control models to quantify the effects of task dimension on kinematic variability.
ReachMaster and the accompanying ReachSplitter3D library produce robust (<4mm) 3-D kinematic (position, velocity, acceleration) predictions across 27 unique whole-arm and body segments during continuous reaching experiments in an unsupervised manner. To perform this task we developed a behavioral classification pipeline to classify and finely segment reaching behaviors using supervised learning. Using as inputs 3-D kinematics and accompanying sensor data from the ReachMaster assay into a set of pre-trained random forest classification algorithms that separate out unique reaching phenotypes at sub-millisecond temporal resolution, we show that ReachSplitter-3D reliably distinguishes between behavioral subtypes during reaching. We then present a model that performs event detection and segmentation within our high-dimensional time-series datasets. We analyze resulting segmented kinematics across similar reaching classes using trajectory minimization and second-order feedback control models across two unique task paradigms. Our central hypothesis is that modulation of task dimension structures variability in the 3-D kinematics of rodents. Our current research extends the current understanding of freely-behaving rats reaching in 3-D task environments, necessary for modern translational research in kinesiology and neurophysiology of reaching that seeks to fully rehabilitate or restore natural reaching behavior in humans. Our future research will seek to uncover cortical surface representations of kinematic variables during reaching in rodents utilizing the novel research methods shown.

Disclosures: B. Nelson: None. **S. Ibraheem:** None. **E. Nguyen:** None. **K.E. Bouchard:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

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NVidia (GPU grant)
Brain Research Foundation (BRF Seed Grant)

Title: Evolution of gross forelimb and fine digit kinematics during skilled reaching acquisition in rats

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Abstract: The ability to learn dexterous motor skills is a fundamental aspect of human behavior. However, the underlying neural circuit mechanisms for dexterous skill learning are unclear. Advancing our understanding of motor skill learning requires the integration of modern neuroscientific techniques

with a rigorously characterized dexterous task. The development of automated rodent skilled reaching with paw tracking allows detailed analysis of how reach-to-grasp kinematics evolve during learning. We assessed how both 'gross' forelimb and 'fine' digit kinematics changed as rats learned skilled reaching. We found that improvements in fine motor control evolved on a longer timescale than improvements in gross motor control. These results suggest that gross and fine motor components of dexterous skill are learned over different timescales to improve performance.

Disclosures: A. Bova: None. **K. Ferris:** None. **D.K. Leventhal:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P532.07

Topic: E.04. Voluntary Movements

Support: NIH Grant NS105478

Title: Quantifying dexterous finger movements in nonhuman primate models of spinal cord injury

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Abstract: Cervical spinal cord injury (SCI) leads to difficulty in controlling hand function, largely due to a reduced ability to perform individuated finger movements. Specifically, impairment in the ability to accurately coordinate skilled hand actions (e.g., precision grip between the thumb and index digits) is a well-established deficit of injury. Nonhuman primate models of SCI provide a tractable means to evaluate the effectiveness of novel treatment interventions. However, detailed temporal information (weeks to months) of hand movement kinematics during recovery is lacking; there is little information on the precise time course with which control improves, nor how recovered abilities quantitatively compare to hand performance before injury within the same subjects. Here we explored the use of DeepLabCut, an open-source deep learning toolset and markerless tracking system, in combination with a standard behavioral task to quantify nonhuman primate performance in a precision grip task. We examined two monkeys (1 SCI impaired and 1 unimpaired) on a Brinkman Board task, which involves retrieving rewards from shallow wells of varied sizes and orientations. Simultaneous recordings were made from two different angles (from the side and top of the hand motion) using two GoPro Hero7 Black cameras (1920 x 1080 pixels, 120 fps). Four neural networks were trained (corresponding to the four potential animal and camera angle combinations) and 400 manually annotated images were used to train each of

the networks. Parameters included in the tracking were the knuckles and the fingernails of each of the individual digits. This allowed target parameters to be tracked on the remaining frames. The outputs of each of the deep learning models were then subjected to further kinematic analysis. Specifically, three different behavioral outcomes were quantified for assessment of dexterous hand movement: the unimpaired subject had max finger separation of 0.78 cm, max middle digit extension of 4.93 cm, and preshaping distance change of 1.16 cm; the impaired subject had max finger separation of 0.89 cm, max middle digit extension of 4.06 cm, and preshaping distance of 1.18 cm). Our preliminary results suggest that this approach is a possible method to examine performance over the SCI recovery period. In future work, we plan to apply this analysis in the same subjects in order to quantify and compare long-term changes in motor control before SCI and during recovery.

Disclosures: R.D. North: None. **R. Wurr:** None. **R. Macon:** None. **C. Mannion:** None. **J. Hyde:** None. **A. Torres Espín:** None. **E.S. Rosenzweig:** None. **R. Huie:** None. **A.R. Ferguson:** None. **M.H. Tuszynski:** None. **M.S. Beattie:** None. **J.C. Bresnahan:** None. **W.M. Joiner:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P532.08

Topic: E.04. Voluntary Movements

Support: FRM - fondation Yolande Calvet- PhD grant #ECO201806006853

Title: Dopaminergic control of the primary motor microcircuits during motor skill learning.

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Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder affecting predominantly dopaminergic neurons from the midbrain. In addition to motor deficits, impairment of motor skill acquisition is also a recurrent feature in PD. Evidence tends to show that the primary motor cortex (M1) could be a putative target for deep-brain stimulation in PD patients. M1 is instrumental for both the acquisition and the maintenance of motor skills. It receives direct dopaminergic inputs from the midbrain which are crucial to learn a new motor skill confirming the potential role of M1 in cognitive deficits of PD. In M1, cortical GABAergic parvalbumin-positive (PV) neurons are known to exert a strong regulation over cortical activity and are recruited for motor execution. They also feature a specific extracellular matrix, called perineuronal nets. This matrix, wrapping the somata and proximal dendrites, mainly of PV neurons, is known to limit plasticity phenomena. We hypothesized that dopamine in M1 plays a crucial role in acquiring new motor skills through the modulation of PV neurons activity. Using ex vivo electrophysiology, imaging, and optogenetics in mice performing a skill reaching task, we investigated the structural, neuronal, and synaptic plasticity of M1 microcircuits, particularly on PV neurons and perineuronal nets, exerted by dopamine inputs. We first demonstrated that training mice to learn a new skill reaching movement induced a decrease in the excitability of M1 PV neurons and in the synaptic transmission of PV to pyramidal cells. In addition, we found that motor skill learning induced a

decrease in the intensity of perineuronal nets, which may allow the opening of a plasticity window in M1. Moreover, in M1 dopamine-depleted trained mice, PV excitability, synaptic transmission and perineuronal nets expression are altered. Our data provide a better understanding of the role of dopamine in motor skill learning.

Disclosures: J. Cousineau: None. **J. Baufreton:** None. **M. Le Bon-Jego:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.09

Topic: E.04. Voluntary Movements

Support: Brain Research Foundation Seed Grant

Title: Striatal dopamine dynamics during skilled motor learning in mice

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Abstract: Coordinated multi-joint limb and digit movements - “manual dexterity” - underlie both specialized skills (e.g., playing the piano) and more mundane tasks (e.g., tying shoelaces). Impairments in dexterous skill cause significant disability, as occurs with motor cortical injury, Parkinson's Disease, and a range of other pathologies. Clinical observations, as well as basic investigations, suggest that cortico-striatal circuits play a critical role in learning and performing dexterous skills. Furthermore, dopaminergic signaling in these regions is implicated in synaptic plasticity and motor learning. Nonetheless, the role of ventral and dorsal striatal dopamine (DA) signaling in manual dexterity remain poorly understood. Here, we use fiber photometry paired with the genetically encoded dopamine sensor dLight to investigate striatal DA release as mice learn and perform single pellet skilled reaching. DA release in ventral striatum is tightly linked with reach initiation early in learning but decreases as the DA response shifts to the trial onset cue. In dorsal striatum, DA release dips slightly prior to reach onset before increasing during reaching. Reach onset-linked DA release in both areas shifts towards lower latency as skill improves. These findings suggest that DA dynamics during skilled motor behaviors change with learning and are differentially regulated along the dorsal-ventral striatal axis.

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Poster

P532. Reaching Control: Motor Learning: Animal

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P532.10

Topic: E.04. Voluntary Movements

Support: NIH NINDS K99/R00-NS101127
Frank & Evangeline Thompson Opportunity Fund
Steve Palermo Foundation

Title: Differences of initial and corrective directional tuning in M1 during precision reaching

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Abstract: Precision reaching tasks often require corrective submovements for successful completion. Most studies of reaching have focused on single initial movements, and the cortical encoding model was implied to be the same for all submovements. However, corrective submovements may show different encoding patterns from the initial submovement across the population. We compared individual neuron's preferred direction, depth of modulation, spatial location, and speed between initial and corrective submovements as well as how corrective submovements overall might exhibit an independent encoding pattern. Two rhesus macaques were trained to perform a precision center-out task designed with small targets to encourage correction. Neural activity from single units in primary motor cortex and associated behavioral data were recorded to evaluate movement characteristics. Neural population data and individual neuronal firing rates were examined for encoding differences between initial and corrective submovements identified with a peak finding algorithm to identify peaks in hand speed. Individual neurons were fit with a linear regression model that included the two-dimensional reach direction, hand position, and hand speed to predict firing rate. For both initial and corrective submovements, the largest effect remained movement direction. However, the influence of reach direction decreased with corrective submovements owing to increased information regarding speed and position of the hand in the workspace. While a majority of neurons did retain the same directional tuning, we observed a significant subset changed their preferred direction up to 180° between initial and corrective submovements. The depth of modulation in a neuron's firing rate between the preferred and anti-preferred reach directions also showed considerable variation between initial and corrective, especially when adjusted for movement speed. There were both individual neurons that were mainly active only during initial submovements and others with significantly increased gain in firing rate for the small corrective submovements. These findings all suggest that different neural encoding patterns exist for initial and corrective submovements within the cortex. The overall variance in firing rate was nearly as large for the corrective submovements even though they were considerably smaller amplitude. We hypothesize that this variation in how neurons change to encode small, corrective submovements might allow for a larger portion of the neural space being used to encode a greater range of movements with varying amplitudes and levels of precision.

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Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.11

Topic: E.04. Voluntary Movements

Support: Natural Sciences and Engineering Research Council of Canada Grant
Canadian Institutes of Health Research Grant

Title: Npas4 expression in somatostatin-expressing interneurons regulates excitatory-inhibitory remodeling in the primary motor cortex during motor learning

Authors: *P. SERRANO[1], J. YANG[1], X. YIN[1], S. CHEN[2];
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Abstract: Motor learning requires repetitive training to acquire highly skilled and reproducible movements. This learning process has been shown to trigger cell-type specific remodeling of excitation and inhibition among different neuronal cell types in the primary motor cortex (M1). Specifically, dendritic spines of M1 pyramidal neurons (PNs) undergo reorganization that coincides with subtype-specific remodeling of two major inhibitory interneurons: the somatostatin-expressing inhibitory neurons (SOM-INs) and parvalbumin-expressing inhibitory neurons (PV-INs). More importantly, during motor learning, SOM-mediated inhibition plays a key role in regulating the learning-induced spine reorganization and motor skill acquisition. However, the molecular mechanisms underlying the motor learning-induced excitation-inhibition remodeling remain poorly understood. Here, we identified that the activity-dependent transcription factor *Npas4*, is specifically expressed in SOM-INs, but not in PV-INs or PNs, during motor learning. Combining *in vivo* two-photon imaging with a head-fixed pellet reaching motor learning task, we found that both regional knockout (KO) and SOM-IN specific KO of *Npas4* impaired motor learning by altering spine elimination during the learning-induced spine reorganization process. Moreover, to investigate the functional role of NPAS4 in SOM-INs, we employed a newly developed NPAS4-driven Robust Activity Marking (NRAM) System to identify NPAS4-expressing neurons in awake and behaving mice. Combined with *in vivo* calcium imaging of SOM-INs, we identified NPAS4-expressing SOM-INs ($NRAM^+$ SOM-INs), labelled during the early phase learning, and monitored their activity throughout the entire motor learning process. We found a reduction in the activity of $NRAM^+$ SOM-INs during reaching-related events compared to NRAM-negative SOM-INs. In addition, we observed that a large percentage of the $NRAM^+$ SOM-INs continuously showed lower activity during reaching-related events as training progress. Together, our results suggest that NPAS4 triggers a learning-specific transcription program in a distinct population of SOM-INs, which leads to reduction of inhibition to downstream PNs and promote stabilization of task-related spines throughout the course of motor learning.

Disclosures: P. Serrano: None. **J. Yang:** None. **X. Yin:** None. **S. Chen:** None.

Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.12

Topic: E.04. Voluntary Movements

Title: A role for hypothalamic orexin neurons in forelimb motor adaptation

Authors: *D. DONEGAN[1], C. KANZLER[2], J. BUSCHER[1], P. VISKAITIS[1], E. BRACEY[1], O. LAMBERCY[2], D. BURDAKOV[1];
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Abstract: Performing goal-directed movements in daily life requires our brains to adapt motor commands to reduce movement errors. Motor adaptation involves several behavioral and neural mechanisms, as identified in both human and animal models. However, the role of the hypothalamus in such skilled motor behaviors is unclear, despite accumulating evidence linking hypothalamic orexin/hypocretin neurons (HONs) to the motor system. Here, we demonstrate the involvement of HONs in forelimb movements and motor adaptation through a new force-field-based mouse model of motor adaptation that shares behavioral features observed in humans. Distinct HON activity patterns accompanied forelimb movements and motor adaptation. Optosilencing of these signals reduced the rate of motor adaptation by influencing sensory error-based adaptation. Unexpectedly, the optosilencing affected neither task execution rates nor motor outputs in tasks without adaptation, suggesting that the HON signals identified here are not required for general motivation. Thus, we identified a hypothalamic substrate that regulates motor adaptation.

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Poster

P532. Reaching Control: Motor Learning: Animal

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Program #/Poster #: P532.13

Topic: E.05. Brain-Machine Interface

Support: German Research Foundation (DFG) project 371923335
German Research Foundation (DFG) project 421703927
Branco Weiss Fellowship
Swiss National Foundation Grant Nr. 192678

Title: Unsupervised behaviour analysis and magnification (uBAM) using deep learning

Authors: B. BRATTOLI[1], U. BÜCHLER[1], M. DORKENWALD[1], P. REISER[1], L. P. FILLI[2], F. HELMCHEN[3], ***A.-S. WAHL**[4,5], B. OMMER[1];
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Abstract: Motor behaviour analysis is essential to biomedical research and clinical diagnostics as it provides a non-invasive strategy for identifying motor impairment and its change caused by interventions. State-of-the-art instrumented movement analysis is time- and cost-intensive, because it requires the

placement of physical or virtual markers. As well as the effort required for marking the keypoints or annotations necessary for training or fine-tuning a detector, users need to know the interesting behaviour beforehand to provide meaningful keypoints. Here, we introduce unsupervised behaviour analysis and magnification (uBAM), an automatic deep learning algorithm for analysing behaviour by discovering and magnifying deviations. A central aspect is unsupervised learning of posture and behaviour representations to enable an objective comparison of movement. Besides discovering and quantifying deviations in behaviour, we also propose a generative model for visually magnifying subtle behaviour differences directly in a video without requiring a detour via keypoints or annotations. Essential for this magnification of deviations, even across different individuals, is a disentangling of appearance and behaviour. Evaluations on rodents and human patients with neurological diseases demonstrate the wide applicability of our approach. Moreover, combining optogenetic stimulation with our unsupervised behaviour analysis shows its suitability as a non-invasive diagnostic tool correlating function to brain plasticity.

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.01

Topic: E.06. Posture and Gait

Support: NIDILRR 90REGE0005-01

Title: Impedance Control Networks for Modeling Spinal Segments

Authors: *F. MARCONI[1], S. MELL[2], P. RYALI[1], A. ESPINOZA ORÍAS[3], J. L. PATTON[4]; [1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Rush Univ., Chicago, IL; [3]Rush Univ., CHICAGO, IL; [4]Sensory Motor Performance Prog, Rehab Inst. Chicago, Chicago, IL

Abstract: Impedance Control Networks for Modeling Spinal Segments FrancescoMarconi, StevenMell, ParthaRyali, AlejandroEspinozaOrías, James Patton Exonet is anetwork of impedance elements (springs)that are able toproduce acomplex forceand torque patternamongst rigid bodies by varying the origins, attachments, and equilibriumpoints of impedance elements. One possible aspect of anExoNET model is tounderstand therelationbetweenstructure and muscular control of the spine. Forces developed by the momentarm and multiple stretched impedances cause torque. While wearable limbexodevices havebeendeveloped using this concept, this project focuses onunderstanding the torques possiblewhile controlling motionof spinal segments. We have reproduced the basic impedance networkbetweenthe lower and upper vertebral segments. This process required modifying the existingalgorithm towork with varying origins and attachments of the impedance elements inthenetwork. The second stepwas tomodify the algorithm towork ina3D environment. Finally, theimpedance elements were made togenerate both tensile and compressive forces toapproximate the constitutive equations of the intervertebral discs and articular surfaces; thenwill be used toreproduce more accurately the behavior of

anintervertebral disc. The resultingmodeling framework canbe used tounderstand the equilibrium control of physiologicalmovements and more importantly, evaluate pathological conditions and their surgicalinterventions. The resulting model allows new understanding with low computational burden,and should provide anew way tounderstand how equilibrium point control canbe achieved bythe nervous system.Supported by NIDILRR 90REGE0005-01

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

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Program #/Poster #: P560.02

Topic: E.06. Posture and Gait

Support: NSF Grant DGE-1315138
NSF Grant DGE-1842473
NIH Grant U01AG061389
NIH Grant T32-NS082128

Title: Age differences in adaptation of medial-lateral gait parameters during split-belt treadmill walking

Authors: *T. FETTROW[1], K. E. HUPFELD[1], H. REIMANN[2], J. T. CHOI[1], C. J. HASS[1], R. D. SEIDLER[1];
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Abstract: Title: Age differences in adaptation of medial-lateral gait parameters during split-belt treadmill walkingAuthors: Tyler Fettrow[1], Kathleen Hupfeld[1], Hendrik Reimann[2], Julia Choi[1], Chris Hass[1], Rachael Seidler[1]1. Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL 32605, United States2. Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE 19713, United States
Character Count: 2094/2300 Walking is inherently unstable, and more so in the medial-lateral (ML) direction than in the anterior-posterior direction. Therefore, ML control of balance must be actively controlled and adapted in different walking environments. A common method to assess gait adaptation is the split belt treadmill (SBT) paradigm. In this paradigm individuals must adapt their gait pattern to two treadmill belts moving at different speeds; then, when the belts return to the same speed, aftereffects of the adaptation are observed. Historically, SBT studies have focused on anterior-posterior (AP) spatiotemporal gait parameters because SBT is primarily an AP perturbation, but it is important to understand whether and how ML control adapts in this scenario. Furthermore, we know older adults struggle with the control of balance, so here we seek to determine whether ML balance adaptation differs in older age. We performed an analysis of SBT-induced changes in gait parameters including variables which inform us about ML balance control in younger (N=31; Age=22.3±3.9) and older adults (N=21; Age=71.7±4.6). We calculated the change relative to the average of the baseline slow condition for each

foot and each condition. Then, we calculated symmetry between the feet for seven gait parameters, three of which inform us about ML control of balance. Our primary finding is that younger adults showed sustained asymmetric changes in these ML balance parameters during the split condition of the SBT. Specifically, younger adults sustained a greater difference between their fast stance foot and their upper body, relative to the slow stance foot, in the ML direction. This finding when considered within the context of extant modeling work suggests that younger adults may be exploiting passive dynamics in the ML direction during the SBT which may be more metabolically efficient, whereas older adults seem to be more concerned about symmetry of the balance parameters. This also suggests that not all asymmetry has negative consequences, especially considering imposition of external constraints (SBT).

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.03

Topic: E.06. Posture and Gait

Support: NSF CAREER Award # 2002261

Title: Ultrasound echogenicity-based sensing and control of functional electrical stimulation to correct ankle joint dorsiflexion

Authors: Q. ZHANG, K. LAMBETH, A. IYER, Z. SUN, *N. SHARMA;
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Abstract: Drop foot is a typical symptom of weakened or paralyzed dorsiflexor's function after cerebral accidents and neurological disorders, which usually causes abnormal gait and ground tripping. Functional electrical stimulation (FES) is a potential technique for reanimating paralyzed muscles and correcting drop foot. FES induces orthotic effects at the ankle, and its closed-loop control is necessary to modulate stimulation intensity in response to time-varying physiological changes of the targeted muscles. Conventional closed-loop control relies mainly on ankle kinematics feedback, which may not wholly capture time-varying changes in muscle activation. Motivation exists to directly measure FES-evoked muscle activation and use it in closed-loop FES. Indeed invasive physiological measurements are feasible, but non-invasive measurements are preferable given comfort and reduced risks of infection with non-invasive sensing. In this study, we explored the use of ultrasound (US) echogenicity as an indicator of FES-evoked muscle activation. We hypothesized that including US echogenicity for estimating FES-evoked muscle activation would improve FES-elicited ankle control compared to an FES control approach without activation measurement feedback.A new sampled-data observer (SDO) was derived to estimate the muscle activation continuously from US echogenicity that was sampled at the rate of 50 Hz from the beamformed and processed images. The proposed US-based FES control was validated through treadmill walking experiments where five participants without disabilities walked at the speed of 0.6 m/s. The desired ankle joint trajectory during the walking swing phase was generated online based on the thigh

and shank orientations and angular velocities. The participants were asked to avoid voluntary dorsiflexor contraction during the swing phase. Three 2-minute walking trials that follow the 'FES off--FES on' sequence were collected. The experimental results show that the root mean square error (RMSE) between the desired and actual trajectories when applying the US-based FES control is 2.120.59, which is 20.5% ($p<0.01$) significantly less than the RMSE of the traditional FES control. The use of FES increased the mean dorsiflexion angle during the swing phase from -16.04 (without FES; the negative sign represents the plantarflexion) to -6.87 (with FES), which confirmed the effectiveness of using FES to correct drop foot. Our findings highlight the benefits of including muscle activation feedback measured by the US echogenicity and provide the potentials of the US-based FES control framework to achieve ground clearance for patients with drop foot.

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.04

Topic: E.06. Posture and Gait

Title: Changes in postural control and kinematic variables in response to ankle joint taping in professional basketball players

Authors: Z. ÖZTÜRK[1], *E. YıLMAZ[1], G. YıLMAZ[1], I. B. KUNT[1], T. D. AKSOY[2], B. YALÇıN[1], H. ARGUNşAH[1];
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Abstract: The major reason for recurrent ankle sprains, the most common cause of injury in team sports, is the chronic instability of the ankle joint, which could be related either to peroneal muscle weakness, proprioceptive deficits, or mechanical instability. Furthermore, it is a common injury for athletes who perform cutting maneuvers, landings, or frequent jumps or make contact with other players. In basketball, handball, soccer, and volleyball, ankle sprains represent from 60 to 90% of the injuries, and the 75% of the athletes affected have relapses that can force them to give up their competitive practice. For these reasons, several external ankle support systems have been designed. These systems attempt to support the ankle joint during rehabilitation and to prevent injury or its recurrence. Ankle taping has been one of the most common ankle support systems because it has been effective in restricting joint motion. The main purpose of ankle taping is to restrict ankle inversion and plantar-flexion motion. Non-elastic adhesive taping is used to prevent recurrence after an ankle sprain. Such taping restricts ankle inversion, as a prophylactic effect, reduce inversion movement speed and reduce the incidence of sprains. The reduction is generally greater for athletes with a history of ankle sprain, although positive effects have also been shown for those with no prior injury. However, it is not exactly clear if the ability for ankle taping to reduce the prevalence of ankle sprains is due to the mechanical restriction provided by the tape and/or due to the proprioceptive value of the adhesive tape. The purpose of this study is to investigate the effects of ankle taping on professional basketball players' postural control during the landing phase of the high jump and the potential for reducing the risk of injury. At the end of this study, the expectation is to

determine a significant difference between taped and non-taped subjects with the comparison of the kinematic data of ankle, knee, hip, and the mass center of gravity. Xsens MVN wearable motion capture system is used for data collection. It is a commercial, inertial sensor-based and portable motion capture system for full-body motion analysis. 12 elite male basketball players will participate in the study, and these players will perform five jumping trials with ankle taping and five jumping trials without ankle taping. According to the initial results, kinesio taping has the potential to increase strength and better performance and balance immediately after the application. In the frontal plane, taped participants were less ankle joint inversion (mean difference= 4.1 degrees SD= 0.658).

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

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Program #/Poster #: P560.05

Topic: E.06. Posture and Gait

Title: Emg-torque relationship differs during movement compared to isometric conditions

Authors: M. MILLER[1], ***D. LUDVIG**[1,2];
[1]Northwestern Univ., Chicago, IL; [2]Shirley Ryan AbilityLab, Chicago, IL

Abstract: Surface electromyography (EMG) can provide information regarding the force output of a muscle and is known to be a reliable predictor of joint torque during isometric conditions. In contrast, predicting joint torque during movement through EMG alone is more complex. Muscle properties, like the force-velocity and force-length relationships, may alter the EMG-torque relationship during movement conditions, though the exact effect of movement on EMG-torque relationship has been investigated only sparsely. During movement, muscle activation is not the only source of joint torque; external factors such as the mechanics of the environment and external power from the environment contribute to the measured torque at the joint. This makes it difficult to distinguish the torque due to muscle activation and determine the EMG-torque relationship. We have recently developed a method that can decouple the torque generated from the muscle from that generated by the external environment. Our objective was to determine whether the EMG-torque relationship differed during movement compared to isometric conditions, by leveraging our method to decouple muscle activation torque from external sources.
A pre-existing dataset which contained ankle muscle EMG and ankle torque recordings, as well as ankle impedance estimates from 10 subjects, while they produced cyclic contractions during both isometric conditions and imposed cyclic movements was used. The isometric EMG-torque relationship was computed by fitting an impulse response function (IRF) between the triceps surae EMG and the measured torque. For the movement trials, the torque due to muscle activation was first computed by subtracting off the torque due to the external environment, which was computed by convolving the impedance with the imposed movement. The movement EMG-torque relationship was computed by fitting a time-varying IRF between the triceps surae EMG and the torque due to muscle activation. We assessed the ability of

each model to predict torque during movement by computing the percentage of torque variance accounted for.
The EMG-torque models differed in the movement condition compared to the isometric condition. During isometric conditions, the isometric model was able to account for 86 ± 2% of the torque variance. During the movement task it was only able to account for 68 ± 6% of the variance. In contrast the time-varying movement model was able to account 87 ± 3% of the torque variance. These results demonstrate that the EMG-Torque relationship varies during movement, and this dynamic behavior must be accounted for to accurately estimate the user intent and volitional torque generated by subjects.

Disclosures: M. Miller: None. **D. Ludvig:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.06

Topic: E.06. Posture and Gait

Support: European Research Council (ERC) (FeelAgain grant agreement No. 759998)
Swiss National Science Foundation (SNSF) (MOVEIT No. 197271)
Innosuisse ICT program (n. 47462.1 IP-ICT)

Title: Restoring sensory feedback through a wearable non-invasive neurostimulation system improves functional outcomes in people with diabetic peripheral neuropathy

Authors: *L. CHEE[1], G. VALLE[2], S. RASPOPOVIC[3];
[2]Lab. for Neuroengineering, Dept. of Hlth. Sci. and Technol., [3]Dept. of Hlth. Sci. and Technol., [1]ETH Zürich, Zürich, Switzerland

Abstract: Diabetic peripheral neuropathy (DPN) is a common complication of diabetes and results in loss-of or abnormal sensation in extremities such as the feet and hands. Individuals with DPN have a decreased overall walking speed and are at a higher risk of falls because of decreased balance and postural control. Although these deficits are well documented, common interventions target the management of diabetes through narcotics or lifestyle changes and do not address the problem of sensory loss. A fully-portal system (called NeuroLegs) was designed to restore the lost or abnormal tactile and proprioceptive sensations in DPN patients with the goal of improving their functionality. NeuroLegs consists of a peripheral module on each leg as well a central control module. Each peripheral module consists of a force-sensorized insole and flexion-sensorized, electrode integrated sock connected to a portable electronics box secured around the ankle. This box communicates wirelessly with the controller in the central control module that processes the raw sensor data and controls the stimulator secured around the waist. The electrodes in the sock are placed around the ankle in a way that directly targets the branches of the tibial nerve that innervate the foot sole and the peroneal nerve that innervates the dorsal side of the foot. This allows for somatotopic tactile (foot sole force) feedback and position (ankle flexion) feedback. The NeuroLegs hardware is accompanied by custom designed software for sensation calibration and characterization so that details about the perception of the elicited sensation can be

recorded and analyzed. There is also a phone app for real-time monitoring of the sensors and fine adjustment of the stimulation. The complete NeuroLegs system is being implemented in DPN patients where performance in standard functional and balance tasks, walking kinematics, and metabolic consumption are being evaluated in order to develop a wholistic understanding of what is possible with sensory feedback. Developing a rough understanding of the currently unknown effects of sensory feedback will allow for better designed studies that focus on how sensory restoration can improve specific aspects of daily life in DPN patients.

Disclosures: L. Chee: None. **G. Valle:** None. **S. Raspopovic:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.07

Topic: E.06. Posture and Gait

Title: Investigation of Glenohumeral Internal Rotation Deficit Tendency of Adolescent Female Volleyball Players with Inertial Measurement Unit Based Motion Capture System during Passive and Dynamic Movements

Authors: E. YıLMAZ, *Z. ÖZTÜRK, E. KARAKAŞ, Y. EFE, B. YALÇıN, H. ARGUNşAH; Acıbadem Mehmet Ali Aydınlar Univ., Istanbul, Turkey

Abstract: Athletes who perform frequent overhead throwing and hitting motions are at high risk for shoulder injuries. Glenohumeral internal rotation deficit (GIRD) is common among volleyball players and is an adaptive process in which the dominant shoulder experiences a loss of its internal rotation (IR). GIRD can be defined by a loss of >20° of IR compared to the contralateral shoulder. The glenohumeral joint carries an important role in over-shoulder athletes. The increase in the external rotation within the glenohumeral joint, the more velocity the athlete can generate when throwing. This motion, when performed frequently, results in a difference in the range of motion (ROM) on the glenohumeral joint. This change of the ROM is defined as GIRD. From a sports medicine realm, the GIRD condition can create a basis for further injuries and early detection methods are required. This study hypothesizes that the sedentary participants and female volleyball players have different functional and anatomical shoulder joint range of motion values. This study aims to create a scientific basis for injury risk prediction of the dominant shoulder and determine the glenohumeral internal rotation deficit tendency of the elite volleyball players non-invasively. This study hypothesizes that volleyball players are prone to develop angular differences in dominant and non-dominant shoulders' range of motion during passive and active movements. Twelve age matched adolescent female players (age of 17.6±0.4, BMI of 21.11±1.08 and height of 170.6±1.7cm) performed jump serve, strike of the ball, horizontal internal- external rotation and internal- external rotation movements and group-based data were analyzed. This experimental study collected bilateral kinematic data from both dominant and non-dominant shoulders of 12 participants wirelessly with Xsens MVN. Each movement performed five times and the average value was calculated for each participant. T-test paired sample for means for dominant and non-dominant shoulders results indicated that ROM did not vary during flexion (dominant: 170.2°±4.5; non-dominant: 171.3°±6.1;

p=0.086). Contrarily, significant differences were obtained during Shoulder Horizontal Internal Rotation (dominant: 27.5°±8.3; non-dominant: 36.8°±7.9; p=0.0053). Shoulder Horizontal External Rotation was not significantly different (dominant: 92.7°±4.1 non-dominant: 89.3°±6.3 p=0.052), Shoulder Internal Rotation was significantly different (dominant: 54.3°±9.0; non-dominant: 65.2°±11.2; p=0.0000) motions and similarly Shoulder External Rotation was significantly different (dominant: 98.6±2.5 non-dominant: 90.3°±6.36.7, p=0.0032).

Disclosures: E. Yılmaz: None. **Z. Öztürk:** None. **E. Karakaş:** None. **Y. Efe:** None. **B. Yalçın:** None. **H. Argunşah:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

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Program #/Poster #: P560.08

Topic: E.06. Posture and Gait

Support: NIH Grant 90084097

Title: Perturbation-induced motor adaptation in monkeys during walking

Authors: *R. WEI, O. STANLEY, *K. CULLEN;
Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: Walking is one of the most practiced motor skills in daily life. It often takes place in unpredictable conditions (e.g. uneven surfaces). To maintain balance during walking, the brain integrates sensory signals from visual, somatosensory, and vestibular sources. Walking in different conditions puts different demands on the control of head movements to stabilize and maintain posture. This includes potential contributions of the angular and linear vestibulocollic reflexes (aVCR and lVCR) to head pitch on trunk, which exhibit different gain and phase characteristics dependent on the frequency of stimulation. Here we investigate the motor strategy nonhuman primates use to adapt to unpredictable conditions during walking.Method: Two rhesus macaques (1 male, 1 female) sat in a specially-built primate chair in which their heads could be free, fixed, or constrained to move only along the pitch rotation axis. The chair was mounted onto a linear sled, allowing the monkeys to walk along a 3.5-meter linear track, the ends of which could be rotated to enable bidirectional locomotion. 5 N perturbations were applied to the chair while the monkeys walked quadrupedally along the track. The Python package DeepLabCut was used to extract the animals' 3D posture for gait analysis. The motion was recorded by 4 high-speed cameras before, during, and after applying perturbations. Gyroscopes and accelerometers were used to record 3D linear and rotational head and body motion. Result: We observed that during resistive force perturbations: 1) monkeys' walking speeds decreased 2) stance duration increased 3) amplitude of hip joint movement decreased 4) head movement showed less fluctuation of pitch velocity. Furthermore, we observed an aftereffect of increased walking speed as well as increased linear and angular head motion after load release.Conclusion: Our results suggest monkeys adjust their motor commands to reduce detected discrepancy between predicted and actual leg movement during locomotion. The observed aftereffects suggest these changes are centrally controlled strategic adaptation rather than temporary

reflexive adaptations. These findings indicate this straightforward paradigm can help advance our knowledge of the coordination of gait and balance.

Disclosures: R. Wei: None. **O. Stanley:** None. **K. Cullen:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.09

Topic: E.06. Posture and Gait

Support: NIH grant R37-NS090610
American Heart Association predoctoral fellowship

Title: Somatosensory biases, sensitivity, and adaptability during post-stroke walking

Authors: *C. ROSSI[1,2], N. M. HILL[2], J. KELLER[2], I. M. SPEARS[1], K. A. LEECH[3], A. J. BASTIAN[2]; [1]Johns Hopkins Univ., BALTIMORE, MD; [2]Kennedy Krieger Inst., Baltimore, MD; [3]USC, Los Angeles, CA

Abstract: Somatosensory function is important for motor learning and, vice versa, learning of new movements can alter somatosensation. The bidirectional relationship between sensation and movement, including the neural substrates involved, is yet not fully understood. Here we explored this relationship by studying the sensory deficits that result from cerebral stroke, and how these deficits affect the motor and sensory learning driven by split-belt adaptation.

We first developed an adaptive forced choice task that measures sensation of leg motion speed during walking. Participants with cerebral stroke and healthy age-matched controls walked on a split-belt treadmill and reported which leg they felt was faster for a range of speed combinations. We found that controls had low biases and small just noticeable differences (JNDs) in leg speed sensation, whereas participants post-stroke could have large biases and JNDs. Note: a large bias indicates that a person senses that their leg speeds are equal when in reality they are not; a large JND indicates that a person cannot perceive small changes in leg speed. Participants-post stroke varied in their impairments: some showed both worse bias and JND than controls, others were impaired in only one domain, and still others showed no impairment.

We then studied how cerebral stroke and resulting sensory deficits impact split-belt adaptation. This type of learning is not limited to the motor domain: healthy adults also develop the false perception that the belts move at similar speeds during split-belt walking. Participants post-stroke and controls walked with the treadmill belts at different speeds for 10 minutes. We measured split-belt-induced changes to leg speed sensation bias (using our task), and walking pattern. Both groups adapted their gait during split-belt walking and exhibited aftereffects in their walking pattern. All participants also changed leg speed sensation bias. This demonstrates that the mechanisms underlying the sensory and motor learning driven by locomotor adaptation are intact in people with cerebral stroke, suggesting that they are mediated by noncerebral structures and unrelated to the level of leg speed sensory impairment. Furthermore, our results indicate that split-belt adaptation can be used to temporarily change motor asymmetries or sensory

biases in post-stroke walking, suggesting it may be a useful tool for sensorimotor rehabilitation.
Supported by R37-NS090610 to AJB and an American Heart Association predoctoral fellowship to CR.

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

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Program #/Poster #: P560.10

Topic: E.06. Posture and Gait

Support: NSF NeuroNex 201531
NSF IIS16081
GAANN Grant P200A150316

Title: Analyzing the Scale-dependent Force Contributions of Rat Hindlimb Muscles During the Swing Phase of Locomotion

Authors: *F. YOUNG[1], A. J. HUNT[2], M. C. TRESCH[3], C. HECKMAN[4], H. J. CHIEL[5], R. D. QUINN[1]; [1]Mechanical and Aerospace Engin., Case Western Reserve Univ., Cleveland, OH; [2]Portland State Univ., Portland, OR; [3]Biomed. Eng, Physical Med. and Rehab, Physiol., [4]Dept. of Physiol., Northwestern Univ., Chicago, IL; [5]Case Western Res. Univ., Cleveland, OH

Abstract: We have developed a process to analyze the relationship between the size-scale of an animal and the resulting activation profiles of individual hindlimb muscles. Large animals, which have heavy limbs, are able to use the inertial properties of their body to aid in motion. In contrast, smaller animals must rely on the elastic properties of their muscles to generate motion due to their lightweight limbs. Across size scales, the relationship between passive elastic and inertial properties changes dramatically. We are interested in the ramifications of scale-dependent relationships on the activation profiles of muscles because we hypothesize that they are the primary constraints for the types of control schemes that animals use for locomotion.
This work presents a neuromechanical model of the rat hindlimb with thirty-eight Hill-type muscles. Passive limb properties are calculated through an optimization process to replicate experimental hindlimb data. By working in a neuromechanical simulation environment, Animatlab, we are able to control muscle contractions via a simulated nervous system. The advantage of this environment is its ability to unify the neural and mechanical aspects of motion, providing insight into the spinal control systems that regulate locomotion.
Using a bottom up approach, we are able to determine the necessary motoneuron activation profiles to replicate a desired trajectory. We believe that the shape of these activation profiles will predictably change as the ratio of elastic and inertial forces shifts as a result of the size-scale of an animal. Our preliminary results demonstrate clear differences in the activation profiles of animals as a result of their scale-dependent properties: elastic properties dominate at small scales, whereas inertial properties dominate at large scales.

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.11

Topic: E.06. Posture and Gait

Title: Anticipatory gait adjustments during curb negotiation in response to the expectation for future stepping maneuvers

Authors: *C. CUI, A. KULKARNI, S. RIETDYK, S. AMBIKE;
Purdue Univ., West Lafayette, IN

Abstract: In daily activities, one often has to quickly adapt gait to sudden changes in the environment and simultaneously maintain gait stability. However, there is a potential trade-off between stability and maneuverability: high gait stability also resists voluntary maneuvers. Therefore, the purpose of our study is to investigate whether gait stability is actively modulated when there is high maneuverability demand in the future. We examined whether gait stability while stepping down from a curb changed when the next step could involve a foot targeting task. A target was projected at the preferred foot landing area of the step immediately after stepping down. Fourteen healthy adults (26.3$\pm$3.3 yrs.) participated in this study. In Baseline, subjects approached, stepped down from a 15 cm curb, and continued walking. Subjects then performed three target conditions in block-randomized order: Fixed target, Anterior-shift target, and Lateral-shift target. Heel contact while stepping down the curb could trigger an anterior or a lateral shift in this target, requiring quick maneuvers during the subsequent step. The probability of target shift was 50%. To isolate the effect of expected target shifts, we used the trials when the target did not shift and computed double support duration and the average gait speed. We also computed synergies in ground reaction forces during double support that stabilize whole-body linear and angular accelerations to quantify gait stability while stepping down. We found that compared with Baseline (1.6 m/s), gait speed was reduced for all target conditions ($p<0.01$), and it was slowest for the Lateral-shift condition (1.5 m/s). The double support duration increased from Baseline (102 ms) for all target conditions ($p<0.01$) and was longest for the Lateral-shift condition (110 ms). We also found that the synergy stabilizing angular motion about the anterior-posterior axis decreased for all target conditions compared to Baseline ($p<0.01$). Thus, anticipation of future gait maneuvers changed spatiotemporal gait characteristics and reduced the stability of angular motion in the frontal plane. While spatiotemporal changes are most pronounced for lateral maneuvers, the stability reduction is a general anticipatory synergy adjustment, independent of the direction of the upcoming maneuver. This novel finding demonstrates how gait stability is managed during complex maneuvers. We intend to determine the functional benefit of the reduced stability in performing the maneuvers, and whether stability reduction induces a cost for older or pathological populations in the form of increased fall risk.

Disclosures: C. Cui: None. **A. Kulkarni:** None. **S. Rietdyk:** None. **S. Ambike:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.12

Topic: E.06. Posture and Gait

Support: CIHR
FRQS
Edith and Richard Strauss Canada Foundation

Title: Advanced 3D vector space analysis to determine posture and gait dynamics

Authors: *J. FUNG[1,2], G. SORRENTO[3], V. GOUSSEV[2];
[1]McGill Univ., Montreal, QC, Canada; [2]Res. (site of CRIR and CISSS Laval), Jewish Rehabil. Hosp., Laval, QC, Canada; [3]Krembil Brain Inst. (CRANIA), Univ. Hlth. Network (UHN) Toronto Western Hosp., Toronto, ON, Canada

Abstract: INTRODUCTION: In functional locomotion, stability and mobility must be maintained despite small kinematic disturbances or control errors. Many complex, non-linear dynamical systems approaches have been used to quantify gait stability and disturbance. We propose a novel approach based on vector space analysis (VSA) to illustrate stability of the body's center of mass (CoM) and coordination of body segments and joint angles using 3D phase diagrams, which can distinguish the gait performance between healthy subjects and persons with chronic stroke. **METHODS:** Participants with chronic stroke and age-matched healthy controls walked at their preferred, comfortable speed on a servo-controlled and self-paced treadmill while viewing a 3D-animated virtual reality scene that was coupled to the instantaneous speed. They were instructed to maintain a comfortable, preferred speed (self-paced). Body motions were captured with a 6-camera VICON MX system and analyzed based on a 41-marker, Plug-in Gait model. The body's CoM and lower limb joint angles were computed and normalized in time to the stride cycles of the individual paretic limb (for stroke participants) or the equivalent right/left limb (for healthy controls). Velocity data were obtained by differentiating position/angles in time, and smoothed with a low-pass filter of 10 Hz. The VSA involves plotting 3D velocity vectors along with 3D mean trajectory points to construct a 3D phase diagram that embeds the 6D data set. This output is essentially a 3D plot of the velocity-position coordination of CoM or joint angles. The 3D velocity vector projections in each axis across the gait cycle were then squared and averaged. The mean sums of squares were then calculated for each direction and summed to represent the mean total kinetic energy related to the unit mass. The combined specific positional and kinetic energy can be evaluated using the mean Sobolev norm. **RESULTS:** The proposed VSA show distinct between-group differences in phase diagrams and Sobolev norms. The CoM velocity vectors are markedly increased in the mediolateral direction in the stroke participants compared to healthy control, indicating a compromise in mediolateral stability. Stroke participants show lower Sobolev norms, particularly in the paretic limbs of low functioning participants walking at slow speeds. **CONCLUSIONS:** VSA in 3D can reveal the dynamics of limb coordination and stability control during gait, as well as any disturbance such as coordination impairments or mediolateral instability in people with chronic stroke.

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Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P560.13

Topic: E.06. Posture and Gait

Title: Gait characteristics of adults walking with and without shoes.

Authors: *C. CHAU, A. PETE, M. ANDRADA, K. CIULLA, S. DONACHIE, P. SAWCHUCK; Nazareth Col., Rochester, NY

Abstract: The purpose of this study is to compare the kinematic and spatiotemporal parameters of locomotion in healthy adults with and without shoes. This study will help establish normative data. Six healthy adults age 22-23 were studied. Each subject completed three trials of walking on a level hard surface at self-selected speed whilst wearing socks and shoes and whilst wearing socks only. Kinematic data were recorded with 3D Motion Capture system (Vicon, Oxford, UK) using 11 cameras. Twenty-three retro-reflective markers were placed on pre-determined anatomical landmarks of the trunk, pelvis, and lower extremities using the modified Vicon lower extremities Plug-in gait model. Eight body segments were reconstructed. Anatomical joint angles were calculated. Spatiotemporal and kinematic gait parameters were processed utilizing the Vicon Nexus software. The variables analyzed include cadence, velocity, step length, stride length, swing and stance duration (expressed as a percent of cycle duration), pelvis, hip, knee, and ankle joint angular excursion. The Vicon Polygon software was used to generate averaged joint angular plots. Paired t-tests were used to compare gait parameters with and without shoes. Preliminary results showed that when walking without shoes, there was a statistically significant decrease in stride length (-10 cm), hip and knee joint angular excursion (-1.85 and -9.01 degrees, respectively). A decrease in step length (-6 cm), velocity (-0.16 m/s), swing duration (-2%), and an increase in stance duration (+ 2%) were clinically significant (Cohen's d). The preliminary findings showed gait changes when healthy adults walked without shoes as compared to with shoes. The findings are consistent with existing literature and suggest an increase in instability in gait without shoes[1]. Shoes have been suggested to offset the effects of external perturbations, allowing for the preservation of biomechanical stability[2]. In addition to biomechanical factors, possible differences in cutaneous input between the two conditions may also have partially contributed to the changes in locomotion.
1. Huang et al, Sensors 20, 6160, 2020.
2. Russo et al, Int. J. Environ. Res. Public Health 17, 4569, 2020.

Disclosures: C. Chau: None. **A. Pete:** None. **M. Andrada:** None. **K. Ciulla:** None. **S. Donachie:** None. **P. Sawchuck:** None.

Poster

P560. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: Virtual Only

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Program #/Poster #: P560.14

Topic: E.06. Posture and Gait

Support: NIH Grant P20GM109090
NIH Grant R15AG063106
NIH Grant R01NS114282

Title: Walking metabolic cost increases when synchronizing your steps to invariant or white noise visual cues but not pink noise

Authors: *A. CHARLES, P. ANTONELLIS, N. STERGIOU, A. D. LIKENS;
Biomechanics, Univ. of Nebraska, Omaha, Omaha, NE

Abstract: Introduction: Walking exhibits natural variations (i.e., stride length, stride duration) over several gait cycle repetitions that have a pink noise temporal structure. It has been hypothesized that these natural variations are associated with health, and their deterioration leads to disease. Thus, to restore healthy variations, previous studies have suggested synchronizing steps with variable external cues that have a pink noise structure. However, the influence of walking with such external cues on the metabolic cost of walking remains unclear. Therefore, this study aimed to investigate the effect of walking synchronization with cues that have various temporal structures on metabolic cost. **Methods**: Twenty-three participants performed four 12-minute walking trials on a 200-m indoor track, wearing footswitches on both of their heels. The Cosmed K5 recorded the metabolic rate. First, participants completed a self-selected pace trial (SPW), where the mean and standard deviation were computed from the baseline condition using a custom MATLAB code, in which inter-stride intervals were calculated. Those values were then used to create the three remaining trials where visual cueing was implemented. Then, the participants were instructed to synchronize their right heel strike with a bar moving vertically on augmented reality glasses. Participants walked under three visual conditions: pink noise, invariant (like the classic metronome), and white noise cueing. The order of conditions was randomized for each participant. **Results/Discussion:** Our data were analyzed with a Bayesian repeated-measures ANOVA. Relative to the SPW, both invariant and random conditions increased metabolic cost, unlike pink noise that was not different from SPW. These findings demonstrate that random and invariant visuals cueing are more costly metabolically as compared to self-selected pace walking. In addition, these results support the optimal human movement variability hypothesis, which suggests that optimal healthy variability is temporally structured, demonstrating pink noise. Therefore, implementing variable pink noise visual cueing in gait rehabilitation protocols would promote effective interventions without increasing metabolic cost.

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Poster

P589. Social Behavior: Hormones and the Microbiome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P589.01

Topic: F.02. Behavioral Neuroendocrinology

Title: Ot^+ pvn neurons regulate aggression and dominance hierarchy in wild-derived female mice.

Authors: *Y. SOFER, N. ZILKHA, S. CHUARTZMAN, T. KIMCHI;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Aggression and dominance hierarchy are basic social behaviors essential for the survival and reproductive success of most mammalian species. Typically, they are displayed whenever conspecifics have to compete for limited resources, such as food, water, territory, or access to mates. As a result, intra-sexual competition is higher in males compared to females as fertile females are a limited resource to males. Thus, males often express higher level of aggression and are most likely to form dominance hierarchy in a group. Therefore, most studies of the biological basis of intra-sexual aggression and dominance hierarchy have been focused on males. However, it has long been observed that females can also form dominance hierarchies. In this study, we aimed to investigate the role of OT^+ PVN neurons in the aggression of wild-derived female mice by comparing them to males. Wild-derived mice were chosen for their higher levels of aggression compared to the lab mouse strains, which might have lost these behavioral traits due to artificial selection and socially restricted environment while in captivity. We found that OT^+ PVN neurons of wild-derived females are activated during social interaction. Moreover, dominant (alpha) wild-derived females had more OT^+ PVN neurons than subordinate (sub) females in the group. In order to manipulate OT^+ PVN neurons, we established a wild-derived OT:Cre mouse line by backcrossing wild mice with transgenic lab mice, and validated its phenotype resembling that of the wild-derived mice.Using these novel wild-backcrossed OT:Cre mice, we virally ablated or activated OT^+ PVN neurons and performed a standard resident-intruder (RI) assay to examine territorial aggression towards adults and pups. In wild-derived females, we found that ablation of OT^+ PVN neurons reduces both adult and pup-directed aggression, whereas activation of this neuronal population promotes aggressive behavior. In contrast, similar manipulations of OT^+ PVN neurons in wild-derived males seem not to affect either of these aggressive behaviors. Finally, we found that genetic ablation of OT^+ PVN neurons abolishes the formation of dominant hierarchy in groups of wild-derived female mice. In contrast, male group dynamics are unaffected by the same manipulation. On the other hand, activation of OT^+ PVN neurons promotes dominance hierarchy in groups of wild-derived females without affecting groups of wild-derived males. These findings emphasize the importance of investigating both sexes in ethologically-relevant animal models and social contexts, in the study of socially relevant neuromodulators.

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Poster

P589. Social Behavior: Hormones and the Microbiome

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Program #/Poster #: P589.02

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH122622

Title: Oxytocin modulates an inverted U relationship between the rewarding properties of social interaction and the dose of those interactions

Authors: *J. H. TAYLOR, S. A. FEKADESELLASIE, E. BROWNE, N. POURSHIRAVI, M. WELCH, K. L. HUHMAN, H. E. ALBERS;
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Abstract: Although the rewarding properties of social interactions are well known, the relationship between the "dose" of social interaction (e.g., its duration and/or intensity) and the rewarding properties of those interactions has not been systematically evaluated. In the present study, we tested the hypothesis that there is an inverted U-shaped relationship between the dose of social interaction and its rewarding properties. More specifically, we propose that as the dose of social interaction increases, the rewarding properties of those interactions initially increase, then level off, and eventually decline. Using both an operant social preference test (OSP) and a conditioned place preference test (CPP), we exposed male and female Syrian hamsters to increasing doses of social interaction. In the OSP, social dose was operationalized as the intensity of the social stimulus. Specifically, we exposed hamsters (*Mesocricetus auratus*, n=80 males and 61 females) to either soiled bedding, a confined same-sex conspecific, or social interactions with one, five, or twenty same sex conspecifics. In the CPP, social dose was operationalized as frequency. We exposed hamsters (n=41 males and 40 females) to one, three, six, or nine days of social interaction with a same sex conspecific. In both the OSP and CPP, a robust inverted U-shaped dose response curve was observed as a function of social dose in males and females. Previously, we have shown that activation of oxytocin receptors in the ventral tegmental area (VTA) is necessary for the rewarding properties of social interactions. In the present study, we microinjected oxytocin (9 uM in saline) or saline into the VTA just prior to each of one, three, or six days of social interaction. We found that oxytocin injected into the VTA prior to three days of social interactions with same-sex conspecifics significantly increased the rewarding properties of those social interactions in females but not in males. These data support the hypothesis that there is an inverted U-shaped dose response curve between the dose of social interaction and its rewarding properties in males and females and that this dose response curve is modulated by oxytocin in the VTA in a sex-dependent manner.

Disclosures: J.H. Taylor: None. **S.A. Fekadesellasie:** None. **E. Browne:** None. **N. Pourshiravi:** None. **M. Welch:** None. **K.L. Huhman:** None. **H.E. Albers:** None.

Poster

P589. Social Behavior: Hormones and the Microbiome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P589.03

Topic: F.02. Behavioral Neuroendocrinology

Support: R01 AA019793
1 F31 AA028669-01A1

Title: Assessing the translational aspects of targeting the oxytocin system for Alcohol Use Disorder in socially-housed prairie voles (Microtus ochrogaster)

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Abstract: The broad and severe impact of Alcohol Use Disorder (AUD) necessitate development of efficacious treatments. Oxytocin (oxt)- a nonapeptide hormone with central roles in social behaviors- has drawn interest as a promising target of pharmacotherapy for AUD with its implicated role in mediating the processes associated with drug use and its social effects, which may serve to bolster abstinence. Oxt has been shown to decrease alcohol craving in humans and alcohol consumption in rodents. Results from our laboratory show repeated intraperitoneal (i.p.) oxt treatments to decrease drinking in socially-housed prairie voles and mice. However, whether intranasal (IN) administration- a translationally relevant route- is effective in decreasing alcohol consumption, whether IN oxt is able to act centrally and whether a small molecule can be designed to optimize pharmacokinetics remain to be determined. In this investigation, we tested whether IN oxt decreased alcohol consumption in prairie voles (*Microtus ochrogaster*)- a socially monogamous rodent species with demonstrated translational validity to humans through common mechanisms regulating social behaviors. Male and female cagemates underwent a continuous access two-bottle choice (CA-2BC; 5% alcohol, water) procedure to establish baseline measures of consumption, followed by treatment with oxt (5mg/kg or 10mg/kg, IN) or saline using a mixed cage design- with treated and untreated (control) animals housed in the same cage which more appropriately models human patients during medication-assisted maintenance of abstinence. Measures of consumption and behavior were recorded. The 10mg/kg dose significantly decreased alcohol consumption during the first hour after treatment. A recent study implicated the Receptor for Advanced Glycation End products (RAGE) in mediating the transfer of oxt into the brain. To test this, voles were given 1mg/kg of the high affinity, permanent RAGE antagonist FPS ZM1 (i.p.) or saline prior to treatment with 25µL oxt-(*leucine*-5,5,5-d_3, *glycine*-2,2-d_2) trifluoroacetate salt (oxt-d5, IN; 80IU/1mL). Concentrations of endogenous oxt and oxt-d5 simultaneously analyzed using liquid chromatography mass spectrometry. As a centrally acting nonapeptide oxt receptor agonist, LIT-001 offers the possibility of a more suitable pharmacokinetic profile, but still requires evaluation. Using a similar CA-2BC mixed-cage design, preliminary results indicate LIT-001-induced sustained decreases in alcohol consumption. Collectively, these results will serve to clarify whether oxt is a promising target for pharmacotherapy for AUD.

Disclosures: S. Potretzke: None. **A.E. Ryabinin:** None.

Poster

P589. Social Behavior: Hormones and the Microbiome

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant RO1 DA041529

Title: Impact of perigestational opioid exposure on juvenile play behavior, oxytocin receptor binding, and oxytocin neuronal number in male and female rats

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Abstract: Social behavior is an essential component of individual survival and reproductive success in rodents. Proper development of social behavior in adulthood can occur only when rodents experience rewarding social play during adolescence. Juvenile play behavior is mediated by several neurotransmitter systems, including endogenous opioids and oxytocin. Clinically, children exposed to opioids *in utero* have a harder time making friends and tend to spend more time alone, suggesting social behavior is less rewarding to these children. To elucidate the underlying neural mechanisms whereby opioids modulate social behavior, we developed a preclinical model in which female rats are exposed to clinically relevant levels of morphine prior to and throughout gestation, ending when pups are postnatal day 6. Juvenile play behavior of adolescent pups was observed at 25, 35, and 45 days of age. Our data show females exposed to opioids perigestationally had a significant reduction in social play, with a corresponding increase in time spent alone. Morphine-exposed females also initiated fewer pins and nape attacks. Together, this data suggests females perigestationally exposed to morphine are less motivated to participate in social play, potentially due to an alteration in the reward circuitry as a result of developmental morphine exposure. As oxytocin is a major neurohormone implicated in social reward and has been shown to interact with the endogenous opioid system, we are currently assessing changes in oxytocin expression and receptor binding in brain regions mediating social reward, including the nucleus accumbens and hypothalamic nuclei, across development following perigestational morphine exposure.

Disclosures: M.E. Vogt: None. **H.J. Harder:** None. **C.T. Searles:** None. **M.G. Gomez:** None. **A.J. Austin:** None. **A.Z. Murphy:** None.

Poster

P589. Social Behavior: Hormones and the Microbiome

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P589.05

Topic: F.02. Behavioral Neuroendocrinology

Title: Do gonadal hormones mediate sex differences in sociability?

Authors: K. HICKS[1], R. WITMER[1], X. CAMBI[1], M. BARNETT[2], E. BLUNT[1], D. RETTE[1], S. NIDORF[1], ***H. LOPEZ**[1];
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Abstract: Sociability - or the motivation to seek out social contact and interaction - is a core facet of social behavior. In non-human models, sociability is typically defined behaviorally as approach towards same-sex conspecifics and can be assessed using the 3-chamber sociability apparatus. We have previously observed a prominent sex difference in sociability between male and female rats when tested in this apparatus; males show significantly higher sociability compared to females. In this study, we explored whether this sex difference is mediated by the activational effects of testosterone or estradiol. Forty-eight male and forty-eight female Wistar rats were assigned to one of four treatment groups: 1) intact + vehicle,

2) gonadectomy (GDX) + vehicle, 3) GDX + testosterone propionate (TP; 500 μg/kg), 4) GDX + estradiol benzoate (EB; 20 μg/kg). GDX occurred on post-natal day (PND) 21, and hormone/vehicle treatment was administered daily between PND 35-48. On PND 46, subjects were run through an elevated plus maze (EPM) to assess general anxiety. On PND 47-48, sociability was assessed using the 3-chamber apparatus, with investigation time (of either a same-sex target or empty cage) being the principal dependent variable. Results revealed no significant effect of experimental treatment on anxiety in the EPM. With regards to sociability, we again found a significant sex difference, with males exhibiting more social investigation than females. However, there were no effects of treatment on sociability in males. In contrast, females did show significant treatment effects. GDX females given either vehicle or TP (but not EB) engaged in more social investigation than intact controls. This finding supports the hypothesis that estradiol may inhibit sociability. This work may help researchers better understand the relative utility and value of the 3-chamber sociability paradigm, and potentially clarify the role that gonadal hormones play in regulating social motivation during adolescence.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R01 AA025024
NIH Grant T32 AA007468

Title: Relationships between social rank and hypothalamic peptides in male and female mice

Authors: *H. FULENWIDER, A. RYABININ;
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Abstract: Social hierarchies are a feature of virtually all animal groups. The varying social ranks of subjects within these groups can significantly affect an individual's physical and mental health, with the lowest-ranked individuals, or subordinates, typically suffering the most adverse effects. More specifically, these subjects have been shown to exhibit various stress-related pathologies, such as increased hypothalamic-pituitary axis (HPA) activity, increased amygdalar corticotropin-releasing factor (CRF) levels, and even increased levels of drug intake, when compared to higher-ranked subjects. The goals of the current study were to characterize the formation and maintenance of social hierarchies in group-housed male and female C57BL/6J mice. We also aimed to investigate the relationship between social rank and hypothalamic oxytocin (OXT) and vasopressin (AVP) levels, two peptides with established roles in both social behaviors and the stress response. Mice were housed in same-sex groups of 4 in moderately enriched environments (48 x 37.5 x 21 cm, two fluid channels that allow for tracking of individual fluid intake, a curved plastic tube, a cotton nestlet square, and 1 bag of shredded paper nesting material). In these experimental conditions, neither male nor female mice exhibited severe agonistic interactions.

However, when social rank was measured by the tube test, we observed a consistently subordinate animal within each group. After approximately two weeks of tube tests, animals were euthanized and brains extracted, fixed, and sectioned for OXT and AVP immunohistochemistry (IHC). We found that the subordinate females had significantly more AVP+ cells in the paraventricular nucleus of the hypothalamus (PVN) compared to higher-ranking subjects. In contrast, subordinate males had significantly less AVP+ cells in the supraoptic nucleus (SON) compared to their higher-ranking counterparts. Lastly, we also found that both subordinate males and females had significantly more OXT+ cells in the SON than higher-ranking subjects. Overall, these findings demonstrate that there are relationships between social rank and hypothalamic AVP and OXT levels. Future studies will aim to assess these peptide levels in plasma as well, and to characterize whether these altered peptide levels are the product or cause of an individual's social rank, as well as to assess whether subordinates exhibit increased depressive- and/or anxiety-like behaviors compared to higher-ranking subjects.

Disclosures: H. Fulenwider: None. **A. Ryabinin:** None.

Poster

P589. Social Behavior: Hormones and the Microbiome

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R15MH113085

Title: Social environment alters behavior and dopamine D1 receptor density in female prairie voles (Microtus ochrogaster)

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Abstract: Prairie voles (*Microtus ochrogaster*) are socially monogamous rodents that also exhibit selective, long-lasting preferences for same-sex peers. Adult social relationships appear to be maintained by selective aggression in prairie voles, whereby once paired with new opposite- or same-sex partners, they display aggression toward conspecifics outside of their pair. In contrast, socially non-monogamous meadow voles (*Microtus pennsylvanicus*) rely on social tolerance rather than selective aggression to maintain their peer relationships. Despite the species-specificity of the role of selective aggression, investigation into the necessity and sufficiency of dopamine signaling in the formation of new relationships provides evidence of relationship type-specificity: Prairie vole mate bonds are dependent on dopamine, whereas peer relationships in both prairie and meadow voles are not. However, prairie vole peer relationships appear to be intermediate between prairie vole mates and meadow vole peers in terms of reward value. Rather than using exogenous pharmacological manipulations to assess dopamine signaling, the current study assessed endogenous structural changes in dopamine D1 receptor density across different social environments, including long-term maintenance of prairie vole peer relationships, prolonged social isolation, and mixed-litter groups. Unlike in prairie vole mate bonds, prairie vole peers

did not exhibit upregulated D1 binding after extended housing with new same-sex partners compared to controls paired with same-sex partners since weaning. However, social isolation upregulated D1 binding in prairie voles, consistent with correlations between binding and individual behavior in partner preference and social interaction tests that suggest that higher D1 binding correlates with more anti-social behaviors and fewer social behaviors. There were no housing or sex differences in behavior in the partner preference test, and all groups displayed robust preference for a partner over a stranger. Housing did impact stranger-directed social investigation in social interaction tests, with males exhibiting more sniffing than females, and group living females exhibiting more sniffing than control females. This study informs our understanding of the neural and behavioral consequences of different social environments in a highly social species. This study also contributes to growing evidence that the mechanisms underlying reproductive and non-reproductive relationships are distinct, and that elucidation of the latter is necessary to fully understand the mechanisms underlying social behavior.

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Poster

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Support: NIH R01 MH112356
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Sammons Enterprise

Title: Dissecting the contribution of host genetics and the microbiome in complex behaviors

Authors: *S. W. DOOLING[1,2,3], S. A. BUFFINGTON[1,4,3], M. SGRITTA[1,3], C. NOECKER[5], O. D. MURILLO[2], D. F. FELICE[1,3], P. J. TURNBAUGH[5,6], M. COSTA-MATTIOLI[1,2,3];
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Abstract: The core symptoms of many neurological disorders have traditionally been thought to be caused by genetic variants affecting brain development and function. However, the gut microbiome, another important source of variation, can also influence specific behaviors. Therefore, it is critical to unravel the contributions of host genetic variation, the microbiome, and their interactions to complex behaviors. Unexpectedly, we discovered that different maladaptive behaviors are interdependently regulated by the microbiome and host genes in the *Cntnap2*$^{-/-}$ model for neurodevelopmental disorders. Using several independent approaches, we found that the hyperactivity phenotype of *Cntnap2*$^{-/-}$ mice is caused by host genetics, whereas the social behavior phenotype is mediated by the gut microbiome.

Interestingly, specific microbial intervention with *L. reuteri* selectively rescues the social deficits and related changes in social-reward mediated synaptic transmission in *Cntnap2*$^{-/-}$ mice through upregulation of metabolites in the tetrahydrobiopterin (BH4) synthesis pathway. Independent of any microbial intervention, treatment with BH4 selectively rescues social deficits in mouse models for neurodevelopmental disorders. In addition, inhibition of BH4 synthesis prevents the *L. reuteri* mediated rescue of social deficits. Overall, our results suggest that both the brain and the gut microbiota may need to be targeted to fully and effectively reverse the core symptoms associated with some neurological disorders. Indeed, our findings that behavioral abnormalities could have distinct origins (host genetic vs microbial) may change the way we think about neurological disorders and how to treat them.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: SFI/12/RC/2273_P2

Title: Age-associated differences in social fear response are not dependent on the gut microbiota

Authors: *N. L. RITZ[1], C. S. M. COWAN[1], M. BROCKA[1], N. THUENE[1], J. NAGPAL[1], M. RODRIGUEZ ABURTO[1], D. A. SLATTERY[2], J. CRYAN[1];
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Abstract: Increasing evidence points towards a role of the gut microbiome in psychiatric disorders. Social anxiety disorder (SAD; or social phobia) is a common mental illness characterized by persistent fear of social situations which can severely limit the ability of sufferers to function in society. It has a high lifetime prevalence, but the currently available treatment options are limited and unspecific. The role of the microbiome in SAD is unknown. Moreover, although the microbiome has been implicated in fear responses and social behaviour, there is limited understanding of its role in social fear behaviours. To this end, we investigated whether microbiota depletion could alter social fear response in a mouse model of SAD. As fear responses vary across ages, we assessed the impact of microbiota depletion with antibiotics (ampicillin 1 g/L, vancomycin 500 mg/L, imipenem 250 mg/L, gentamicin 1 g/L) in male C57Bl/6J mice at two ages (30-day-old and 70-day-old; n=8-12). To induce appropriate social fear during conditioning, mice received foot shocks (2-4, 1 s, 0.6 mA) upon interaction with an unfamiliar conspecific. The following day, all mice underwent social fear extinction via six sequential social interaction tests with novel conspecifics introduced in each trial. Social interaction time between the experimental and conspecific mice was then measured. As expected, in control adult animals there was a significant extinction of social fear. In juvenile animals, this effect was exacerbated by decreased time spent in social interaction extinction trials with the conspecific mouse post-conditioning. However, antibiotic treatment

did not alter extinction behaviour in either age group. These data indicate that the response to social fear is affected by the age of the individual but is not modulated by microbiota depletion. Further research must be done to better understand the biological underpinnings that drive this age-associated social fear behaviour and investigate if there is a role of the microbiome in inter-individual differences.

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Poster

P613. Stress and Cognition

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Program #/Poster #: P613.01

Topic: F.04. Stress and the Brain

Support: RO1 Grant 361711

Title: The effects of early life adversity on risky decision-making and the orbitofrontal cortex transcriptome in male and female rats

Authors: *E. ORDOÑES SANCHEZ[1], C. C. BAVLEY[1], R. KARBALAEI[1], J. FLOWERS II[1], A. R. BONGIOVANNI[1], A. INGRAM[1], A. JEAN-LOUIS[1], A. CROSBIE[1], N. SEKHAWAT[1], C. S. ARDEKANI[1], M. E. WIMMER[2], S. B. FLORESCO[4], D. A. BANGASSER[3];
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Abstract: Early life stress stemming from poverty can have lasting effects that persist into adulthood. In order to study this form of stress in rats and how it affects cognitive processes related to substance use disorder (SUD), we used the limited bedding/nesting (LBN) model, in which dams and pups are exposed to a low resource environment from postnatal day 2-9. Previous work in the lab found that LBN reduces impulsive choices in males but not females, as measured with a delay discounting task. Here we tested whether LBN exposure would also alter risky choice behavior in a probability discounting (PD) task. In PD, a rodent must choose between two levers: a certain lever (always delivers 1 pellet) versus a risky lever (*sometimes* delivers four pellets). Odds of earning the large reward varied across five blocks (100%, 50%, 25%, 12.5%, 6.25%). We found that all LBN rats choose the risky lever less often than controls when the probability of earning a large reward was low [$F(4,376)=2.845$, $p=.024$]. A brain region important in mediating both impulsive and risk-based decision-making processes is the orbitofrontal cortex (OFC). To assess mechanisms by which LBN may affect these processes we completed RNA-sequencing on OFC tissue from adult rats (male control n=5; female control n=5; male LBN n=5; female LBN n=5). We used rank-rank hypergeometric overlap (RRHO) analysis to compare overall gene expression patterns in males and females induced by LBN. We found that LBN induced sex-specific changes in transcription. Specifically, we see a distinction between genes upregulated in males and downregulated in females due to LBN. We next narrowed our analysis to genes showing a significant difference between control and LBN and found 161 differentially expressed genes (DEGs) in males and

138 DEGs in females. These gene changes were largely sex-specific with only 18 common genes altered by LBN. KEGG pathway analysis revealed “retrograde endocannabinoid signaling” was significantly enriched in males but not females (adjusted p=.01), which may drive behavioral changes induced by LBN in males. Future studies aim to validate top gene targets, including one involved with the endocannabinoid system, with RNAScope. Collectively, these results suggest that LBN reduces impulsivity and risky decision making, protecting against cognitive changes that are related to risk for SUDs. Although initially unexpected, these findings add to a growing body of literature supporting the stress inoculation hypothesis: that some early adversity promotes later resilience. Understanding mechanisms that promote this stress resilience can lead to better treatments for SUD.

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Poster

P613. Stress and Cognition

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Program #/Poster #: P613.02

Topic: F.04. Stress and the Brain

Support: NSF 18-586

Title: Crf infusion into the medial septum modulates hippocampal cholinergic transmission in rats

Authors: *A. KNIFFIN, M. TARGUM, D. BANGASSER, V. PARIKH;
Psychology and Neurosci. Program, Temple Univ., Philadelphia, PA

Abstract: The cholinergic septohippocampal pathway (SHP) modulates hippocampal-dependent mnemonic processes, including spatial and contextual memory. Previously, studies have shown that rats exhibit impaired spatial memory on the novel object location task after 100 ng infusion of corticotropin releasing factor (CRF) into the medial septum (MS). However, a clear sex difference emerged at a low dose of CRF (3ng), with only males exhibiting impaired spatial memory. The mechanism by which MS CRF may be affecting spatial memory is unclear but could involve changes in hippocampal acetylcholine (ACh) levels, given that CRF_1 receptors are present on cholinergic neurons in the MS. Here we tested whether CRF in the MS can alter hippocampal cholinergic transmission via *in vivo* electrochemical recordings with choline sensitive microelectrodes. Adult male and female rats underwent intracranial infusions of artificial cerebral spinal fluid (aCSF) and CRF into the MS using a within-subject design. Basal changes in cholinergic transmission were recorded for 30 minutes following each infusion in the dorsal hippocampus. Depolarization pulses with potassium chloride were applied to stimulate ACh release locally in the terminal fields. MS CRF (100ng) infusion reduced the amplitudes of depolarization-evoked cholinergic transients by 25% (2.27±0.35 vs 3.01±0.37 with aCSF; t10=1.85; p=0.09) and this effect was similar between the two sexes. At this dose, changes in resting cholinergic levels tended to decline over the monitored 30-minute period following CRF infusion. Preliminary data in male rats

revealed no suppression of signal amplitudes with a low dose (3ng) CRF infusion, suggesting the effect of MS CRF on hippocampal cholinergic transmission are presumably dose-dependent. The clearance time of cholinergic signals remained unchanged between manipulations, indicating no disruption of transporter-mediated clearance mechanisms. Ongoing studies are examining the effects of low-dose CRF in female rats to investigate the above-mentioned sex differences in spatial memory performance. Taken together, our findings thus far indicate the MS CRF exerts an inhibitory effect on hippocampal cholinergic transmission in a dose-dependent manner. Future studies to delineate the mechanisms by which CRF regulates septohippocampal cholinergic circuitry may aid in the development of novel treatments for stress related psychiatric disorders as well as contribute to the basic understanding of stress-mediated changes in hippocampus-dependent cognitive functions.

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Poster

P613. Stress and Cognition

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Topic: F.04. Stress and the Brain

Title: Sex differences in the effects of acute stress on cognitive flexibility in rodents

Authors: *A. T. GARGIULO, I. C. RAVAGLIA, A. C. HAWKS, L. A. GRAFE;
Bryn Mawr Col., Bryn Mawr, PA

Abstract: Stress-related psychiatric disorders such as Post-Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD), of which cognitive impairment is a key phenotype, are twice as common in women compared with men. However, the literature describing the effects of stress on cognition and the potential sex differences associated with this relationship is equivocal, and the neurobiology underlying these sex differences is not fully understood. We are interested in probing how stress affects cognitive flexibility, which is the ability to adapt cognitive processing strategies to face new conditions in the environment; this skill is crucial in normal daily functioning. To explore sex differences in how stress affects cognitive flexibility, we trained adult male and female Sprague-Dawley rats (N = 48) to complete an automated attentional set-shifting paradigm, with acute stress applied prior to testing. Specifically, rats were first trained for 3 days in the automated attentional set-shifting task. On the fourth day, rats were exposed to acute (30-min) restraint stress prior to testing on the set-shifting paradigm. As gonadal hormones are known to influence the stress response, we tracked the estrous cycle using vaginal lavage in our female rats. Following testing, rat brains were extracted and immunolabelled for *c-fos* (a marker of neural activity) in the prefrontal cortex, which is a critical brain region in executing the cognitive flexibility task. Our results indicate that female rats consistently show higher stress behavior throughout restraint than males, and this varied by phase of the estrous cycle. In addition, females made more perseverative errors and displayed more omissions in the attentional set-shifting task than males, and these results again varied by estrous phase. Lastly, *c-fos* immunoreactivity in the prefrontal cortex after the attentional set shifting task differed by sex. The results suggest that there are sex differences in restraint stress behavior, subsequent cognitive flexibility, and neural activity. Moreover, it appears that

female gonadal hormone status influences these measures. Further research should examine the mechanisms by which stress acts on the brain in females and males to influence cognition.

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Poster

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Topic: F.04. Stress and the Brain

Support: 5P50MH119569

Title: Stress Influences on the Explore-Exploit Tradeoff in Reward-Guided Decision Making of Mice

Authors: *D. MUELLER, C. CHEN, A. BANO, E. WOOD, N. M. GRISSOM;
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Abstract: Stress has been implicated in changes in decision making, but the implementation of such changes via computational processes of reinforcement learning remains unclear. Stress causes a widespread refocusing of cognitive resources, and alters numerous factors playing into decision making. Acute stress increases selection of more valuable options, which has been interpreted as increased reward sensitivity. Acute stressors also increase habit over goal-directed actions, decreasing the flexibility of behaviors. Therefore, altered choices after stress could either be due to an increase in reward sensitivity, or a decrease in willingness to switch from a previously chosen option, or both. We examined the effects of acute saline injection stress as part of a behavioral pharmacology experiment on decision making in mice in a restless bandit task. This translational task involves repeatedly selecting between two illuminated squares on a touchscreen operant chamber, which are rewarded probabilistically. This bandit task is “restless” because the reward probability of each choice changes randomly and independently across trials. This encourages animals to continuously sample the choices and learn about the current best choice. To maximize reward, animals have to balance between exploiting a current high-value option and exploring potential better alternatives. We hypothesized that acute stress would increase reward sensitivity, leading mice to exploit more choices following rewarded trials (win-stay). Thirty-two 129/b6j F1 mice (16 male and 16 female) were tested on restless bandit schedules with and without saline injection prior to testing in a within-subjects design, to habituate animals to injections for future behavioral pharmacology experiments. We are currently examining success at obtaining rewards, win-stay/lose-shift behavior, locomotor activity within the chamber, and reaction times for choices and reward retrieval. Our preliminary results indicate that acute injection stress negatively impacted the performance over chance for both male and female mice across sessions, with cumulative impacts of each injection. Along with this, we found that animals showed reduced locomotor behavior in the chamber after saline injection. As hypothesized, acute injection stress appears to increase win-stay behavior, which may prevent animals from exploring to maximize changing reward values. The repeated nature of the injections are intended to induce adaptation or habituation, which may alter the effect on decision making over time.

Disclosures: D. Mueller: None. **C. Chen:** None. **A. Bano:** None. **E. Wood:** None. **N.M. Grissom:** None.

Poster

P613. Stress and Cognition

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P613.05

Topic: F.04. Stress and the Brain

Title: Sex Differences in the Impact of Prenatal Stress on Spatial Memory

Authors: *T. BUCK[1], K. LOTESTO[1], *M. S. SODHI[2];
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Abstract: Prenatal stress is a risk factor for several psychiatric disorders. Prenatal restraint stress (PRS) alters brain development and has long-term effects on behavior, including increased risk aversion, impaired spatial memory and social interaction deficits. Accumulating data indicate that altered glutamatergic transmission in the hippocampus mediates the long term pathology associated with PRS in mice. A post-transcriptional process known as RNA editing regulates the trafficking and function of AMPA glutamate receptors (AMPARs), which are critical for synaptic plasticity, learning and memory. Altered RNA editing of AMPARs and other synaptic proteins may contribute to stress-induced behavioral impairment. We exposed pregnant C57BL/6J and Swiss-Webster mice to restraint stress from GD7 until birth, and evaluated spatial learning, locomotor activity and risk aversion in the offspring. We also tested metabolic activity using the Phenomaster system in the mice at 80 weeks of age. In contrast with Swiss-Webster mice, C57BL/6J mice did not display social interaction deficits after exposure to PRS. Female C57BL/6J adult mice exposed to PRS had improved performance in spatial reversal in the Morris water maze ($p<0.05$), while PRS males showed persistent spatial memory in the reversal task ($p<0.05$), indicating a reduced ability to adapt their behavior in response to a change in the environment. Altered spatial memory was not observed in these mice later in life (80 weeks). Males and females exposed to PRS showed similar increases in risk aversion in the light/dark box and open field tests ($p<0.05$) at 80 weeks, with no accompanying changes in locomotor activity ($p>0.1$). No alterations in metabolic activity were observed with PRS. Analyses of gene expression within the corticolimbic regions of the brain are ongoing to identify molecular pathways impacted by PRS that produce long-term impairments in spatial learning and risk aversion. Moreover, we report improved resilience to prenatal stress in C57BL/6J mice relative to Swiss-Webster mice. Future analyses of genomic differences between inbred strains of mice may reveal pathways that confer relative resilience to the detrimental effects of PRS.

Disclosures: T. Buck: None. **K. Lotesto:** None. **M.S. Sodhi:** None.

Poster

P613. Stress and Cognition

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Program #/Poster #: P613.06

Topic: F.04. Stress and the Brain

Support: Campbell Mental Health Research Institute of CAMH

Title: GABAA receptor positive allosteric modulation has anti-depressant effects, pro-cognitive effects and reverses neuronal atrophy in a mouse model of chronic stress

Authors: *A. BERNARDO[1], P. LEE[2], M. MARCOTTE[1], Y. MIAN[3], Z. A. KHAN[3], D. SHARMIN[3], J. M. COOK[3], E. SIBILLE[1,2], T. PREVOT[1,2];
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Abstract: Chronic stress is a recognized risk factor for developing anxiety and depression. Each of these is linked to reduced cognitive performance and neuronal atrophy, further contributing to the complexity of the pathologies. Both anxiety and depression display a reduced number of GABAergic neurons, reduced GABA release and altered GABAA receptor (GABAAR) functioning. Functionality of GABAARs are essentially related to which α subunits are present within the GABAAR: α1 subunit potentiation is associated with sedation, α2/α3 potentiation with anxiolytic effects and α5 potentiation with cognition. Current GABAergic drugs, such as benzodiazepines, target GABAAR α subunits indiscriminately resulting in several side effects, limited anxiolytic effects and little cognitive benefit. Here we hypothesize that a positive allosteric therapy targeted to α2/α3-GABAAR and α5-GABAAR devoid of α1-GABAAR activity will overcome benzodiazepine limitations. This approach will be clinically relevant and address unmet cognitive impairment therapy needs, and reverse neuronal atrophy which contributes to overall symptomatology. We investigated two enantiomers GL-I-54 and GL-II-73, and their combined use as a racemic mixture (termed GL-RM) because of the desirable positive allosteric modulation profile when combined (α2/3/5-GABAAR and α5-GABAAR respectively). Using the unpredictable chronic mild stress (UCMS) model in C57BL6 mice (50% female; N=48 per study) we assessed anxiolytic (using elevated plus maze, novelty suppressed feeding and phenotyper test), anti-depressant (using sucrose preference and forced swim test) and pro-cognitive effects (Y maze) of GL-RM with acute or chronic administration. Neurotrophic effects were investigated in the chronic treatment study using Golgi Staining and Neurolucida for quantification to view neurons in the prefrontal cortex and hippocampus (CA1 region). Results found GL-RM has anti-depressant and pro-cognitive effects in both acute and chronic studies. Golgi staining found dendritic spine density reduced by UCMS was recovered with chronic GL-RM treatment demonstrating a neurotrophic effect of chronic GL-RM. Results support the value of a therapy with a α2/3/5-GABAAR selective profile to overcome chronic stress-induced mood symptoms, cognitive deficits, and detriments in neuronal morphology. These studies overall demonstrate the usefulness of targeting the GABAergic system as a treatment avenue for stress-related disorders, with symptomatic and disease-modifying effects.

Disclosures: A. Bernardo: None. **P. Lee:** None. **M. Marcotte:** None. **Y. Mian:** None. **Z.A. Khan:** None. **D. Sharmin:** None. **J.M. Cook:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor. **E. Sibille:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor. **T. Prevot:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor.

Poster

P613. Stress and Cognition

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Program #/Poster #: P613.07

Topic: F.04. Stress and the Brain

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Title: Mitochondria-associated CB1 receptors regulate cognitive effects of stress

Authors: *U. SKUPIO, R. SERRAT, A. ERASO PICHOT, A. C. PAGANO ZOTTOLA, F. JULIO KALAJZIC, A. CANNICH, J. WELTE, L. BELLOCCHIO, F. CHAOULOFF, G. MARSICANO; INSERM U1215, Bordeaux Cedex, France

Abstract: Behavioral and cognitive response to stress requires high cellular activity in the brain, which depends on energetic support provided by mitochondria. The endocannabinoid system, which is implicated in stress response, has been reported to directly regulate mitochondrial energetic activity and memory via the type-1 cannabinoid receptors (CB1) associated with the brain mitochondria membranes (mtCB1, Hebert-Chatelain et al., 2016). In the present study, we aimed to evaluate the involvement of the endocannabinoid system in the regulation of cognitive stress effects in adult male mice. We used the novel object-recognition (NOR) task as a model of non-aversive memory to investigate the underlying mechanism of the deleterious effect of stress (single 0.5 mA foot-shock for 2 s) or corticosterone administration (10 mg/kg, sc) on memory consolidation and retrieval. To examine the role of different CB1 pools in this effect, we used a combination of transgenic mouse models (based on C57BL6/J strain) and viral approaches *in vivo* to specifically delete or re-express CB1 in different neuronal populations and subcellular compartments (9-16 mice per experimental group). Our results show that both stress and corticosterone induce impairment of NOR memory consolidation and retrieval and that these alterations are mediated by mtCB1 receptors in specific populations of noradrenergic and GABA-ergic cells, respectively. Interestingly, we found that CB1 receptors present in other neuronal populations are not involved. Overall, by underlying the key involvement of mitochondria-associated CB1 receptors, this work provides a novel outlook on the mechanisms linking stress to cognitive impairment. Thus, these data might pave the way for the development of new therapeutic strategies for the treatment of detrimental effects of stress on cognition.

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Poster

P641. Sleep: Behavior

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Program #/Poster #: P641.01

Topic: F.08. Biological Rhythms and Sleep

Support: CONACYT-254264

Title: Sleep restriction on sweeteners consumption and delta Fos expression

Authors: *F. GARCÍA-GARCÍA[1], **L. A. LOPEZ-MUCIÑO**[2], M. E. ACOSTA-HERNANDEZ[2], A. VENEBRA-MUÑOZ[3];
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Abstract: Adolescence is a critical period in development because it enhances vulnerability towards reward-driven behaviors, and a voluntary sleep restriction occurs (SR). Different studies suggested that SR is a factor that elicits drug consumption, although the neuronal basis remains poorly understood. Additionally, SR favors the preference for palatable foods. For example, sweeteners are known to have a high preference value due to their high sweetness. The present study's objective was to determine whether SR enhances sweeteners consumption and the association with ΔFosB expression in the brain reward circuit. Adolescent Wistar rats (30-60 PND) were housed in individual cages and divided into two groups; control (Ctrl) and SR (4 h/7 days by gentle handling method), matched for mean body weight. The free-selection bottle test was used to determine the preference and intake of each solution. Both groups were divided into 3 subgroups of 8 animals as follows: 1) two bottles of plain water, 2) a bottle of plain water and a bottle of sucrose (1%), and 3) a bottle of plain water and a bottle of Stevia extract (0.05%). At the end of each treatment, brain sections were collected and processed for ΔFosB immunohistochemistry. The analyzed brain regions were the prefrontal cortex (PFC), nucleus accumbens (NAc), central amygdala (CaA), and ventral tegmental area (VTA). No differences were found in fluid intake for each solution between the control and SR groups. However, the number of ΔFosB positive cells was increased in the PFC and NAc Core in the SR group exposed to 0.05% Stevia. On the other hand, a reduction in the number of ΔFosB positive cells in NAc Core and NAc Shell of rats with SR exposed to 1% sucrose was found. In conclusion, SR did not enhance the intake of sweeteners. However, there was a differential ΔFosB expression in brain areas involved in decision making, motivation, and evaluation of salient stimuli, depending on the type of sweetener.

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Poster

P641. Sleep: Behavior

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Program #/Poster #: P641.02

Topic: F.08. Biological Rhythms and Sleep

Support: R01NS078410

Title: The ability of sleep deprivation to impair performance on behavioral tasks is altered in mice that overexpress Bmal1 in skeletal muscle

Authors: *A. TUCKER, I. NICHOLS, K. N. PAUL;
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Abstract: Sleep is a phylogenetically conserved behavior necessary for survival. While chronic insufficient sleep has negative effects on health and well-being, acute sleep loss has negative effects on memory and cognition. In the current study, we use behavioral tests to assess memory function in mice that overexpress the circadian timing gene, *Bmal1*, in skeletal muscle. Recent studies reveal that the overexpression of *Bmal1* in skeletal muscle reduces homeostatic sleep responses to acute sleep loss. In behavioral tests in mice, sleep deprivation immediately after memory acquisition has been shown to negatively impact memory consolidation. Thus, we hypothesized that if *Bmal1* muscle overexpression mice require less recovery after sleep deprivation, they also would not experience the negative cognitive impacts of this sleep deprivation. We examined memory via two behavioral tests — the Novel Object Recognition Test, which measures recognition memory, and the Novel Location Recognition test, which measures spatial memory. In the Novel Object Recognition test, we found that 6 hours of sleep deprivation was unable to disrupt novel object recognition in either *Bmal1* muscle overexpression mice or wild-type littermates (two-way ANOVA: 'Condition' $F_{(1, 18)} = 0.01781$, p=0.8953; 'Genotype' $F_{(3, 18)} = 0.1545$, p=0.9254, 'Condition * Genotype' $F_{(3, 18)} = 0.2354$, p= 0.8705). However, we found that 12 hours of sleep restriction immediately after memory acquisition disrupted novel object recognition during the testing phase in wild-types (paired t-test: p=0.0278/ t=2.886, df=6), but significantly improved novel objection recognition in Bmal1 muscle overexpression mice (paired t-test: p=0.0352, t=2.708, df=6) (two-way ANOVA: 'Condition' $F_{(1, 12)} = 0.01995$, p=0.8900; 'Genotype' $F_{(1, 12)} = 0.5189$, p=0.4851 ; 'Condition x Genotype' $F_{(1, 12)} = 5.529$, p= 0.0366). In the Novel Placement Recognition test, sleep deprivation significantly increased novel location recognition (two-way ANOVA: 'Condition' $F_{(1, 10)} = 9.227$, p=.0125; 'Genotype' $F_{(1, 10)} = 0.02929$, p= .8673 ; 'Condition x Genotype' $F_{(1, 10)} = 0.9798$, p=.3456). Posthoc analysis revealed a significant improvement in sleep-deprived wild-types (t=2.676, df=6, p=0.0367) but not in sleep-deprived *Bmal1* muscle overexpression mice (t=1.881, df=4, p=.1331). These results suggest that skeletal muscle *Bmal1* confers resistance to recognition memory deficits caused by sleep deprivation, but not spatial memory deficits.

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Poster

P641. Sleep: Behavior

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Program #/Poster #: P641.03

Topic: F.08. Biological Rhythms and Sleep

Support: Skidmore Summer Collaborative Research Fellowship

Title: Light has color-dependent effects on sleep in Drosophila melanogaster

Authors: S. M. BOND, D. SIRTALAN, D. A. SKEELE, H. HUANG, D. R. POSSIDENTE, *C. G. VECSEY;
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Abstract: Sleep is a poorly understood, evolutionarily conserved state that has profound health impacts. An emergent cause of human sleep disruption is evening exposure to blue-enriched light from screens on smartphones, computers, and TV. In contrast to blue light's alerting effect, red light may promote sleep. The exact molecular pathways behind light color's impacts on sleep are not fully elucidated. Therefore, we conducted an exploratory study on the sleep effects of blue and red light in the model organism *Drosophila*. To investigate whether blue and red light alter sleep in a time-dependent manner, we examined sleep after light color exposure through all 12 hours of daytime, for 3 hours in the fly's subjective morning, and 3 hours in the evening. Experiments were performed on male and female ($n \geq 24$ for each sex) wild-type Canton-S (CS) flies and ones with a mutation in the *white* gene (w^{1118}) that cannot transport precursors to form screening pigment in the compound eye, resulting in white eyes. Sleep was measured for two full baseline days of 12:12 white light/dark (LD), six experimental days of blue/dark or red/dark exposure, followed by two recovery days of LD. Sleep data from the blue- and red-light days were compared with data from the final baseline day to characterize the sleep effects of these light colors. Here, we show that daytime blue light reduced sleep during exposure in wild-type *Drosophila*, and this effect was consistent with blue exposure in just the morning, evening, or for all 12 hours of daytime. Our data demonstrate that blue light also has nighttime sleep-inhibiting effects in *Drosophila*. Blue light for 12 hours reduced nighttime sleep on the second day of exposure in CS flies. Interestingly, blue light's wake-promoting effects in CS flies were not seen in w^{1118} flies, despite both strains experiencing some common sleep-promoting effects. When flies were exposed to daytime red light, sleep was reduced during exposure, and this was observed in both CS and the w^{1118} flies. Furthermore, red light's daytime sleep-inhibiting effect was specific to the evening and immediately followed by a sleep rebound in both strains. Ultimately, we establish that *Drosophila* sleep, much like human sleep, is altered by light in a wavelength-specific manner, and some of these light color effects on sleep differ based on the time of exposure. Additionally, our differing results between wild-type flies and w^{1118} mutants in response to blue light imply that some of blue light's sleep effects are mediated by a pathway that is altered by the w^{1118} mutation, such as the compound eye. Future studies will show how light color information is detected by the fly brain and transmitted to sleep centers.

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Poster

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Program #/Poster #: P641.04

Topic: F.08. Biological Rhythms and Sleep

Support: F31 NS110273

Title: Mir-190 acts during pupation to regulate sleep behavior in drosophila melanogaster

Authors: *E. J. RIVERA-RODRÍGUEZ, L. C. GRIFFITH;
Brandeis Univ., Waltham, MA

Abstract: Sleep is a widely conserved behavior, known to influence many cognitive and physiological functions. Studies have implicated microRNAs in the regulation of gene expression changes that control sleep behavior. The Griffith lab screened a library of 141 microRNA sponges using the fruit fly *Drosophila melanogaster*, in order to find microRNAs involved in sleep regulation (Goodwin et al., 2018). This screen showed miR-190 to be involved in the regulation of sleep. Flies expressing the miR-190 sponge (*miR-190SP)* in a pan-neuronal manner showed decreased and fragmented sleep, as well as changes in other sleep parameters. Spatial and temporal mapping of its locus of action demonstrates that miR-190 is required during the pupal stage, in a population of neurons that transcribe both glutamatergic and cholinergic genes, but only express glutamatergic proteins (*Glu^{Ach}* cells). Thermogenetic activation of this population of cells by means of dTRPA1 results in a decrease and fragmentation of sleep, phenocopying miR-190 knockdown. At the molecular level, RNA sequencing of both pupal brains and adult heads showed that pan-neuronal expression of *miR-190SP* induces an upregulation of multiple genes, among those *mid*, a T-box transcription factor previously shown to operate as a suppressor of glutamatergic fate. *Glu^{Ach}>mid* overexpression phenocopied miR-190 knockdown with animals showing a decrease in total sleep and sleep fragmentation. Taken together, our results suggest that miR-190 acts during development in *Glu^{Ach}* cells to allow their glutamatergic differentiation and specify the activity of the adult arousal system and adult sleep behavior.

Disclosures: E.J. Rivera-Rodríguez: None. **L.C. Griffith:** None.

Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: CIHR grant MOP 97830

Title: Not all sleep spindles are alike: The onset of clustered spindles is associated with spontaneous reactivation of the task-related network

Authors: *E. GABITOV[1], A. BOUTIN[2,3], B. PINSARD[4], N. CENSOR[5], S. M. FOGEL[6,7], G. ALBOUY[8], B. R. KING[9], H. BENALI[10], J. CARRIER[11], L. G. COHEN[12], A. KARNI[13], J. DOYON[1];
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Abstract: Ample evidence suggests that sleep facilitates the consolidation of newly learned skills. However, the neurophysiological correlates and neural mechanisms underlying the consolidation of new

experiences during sleep are not yet fully understood. One of the leading hypotheses related to this mnemonic process posits that the neural populations involved in encoding the newly acquired knowledge and experiences are repeatedly reactivated during a subsequent sleep period. Such reactivation constitutes an opportunity to reprocess new memories and optimize their storage using the brain network recruited during the initial learning phase. The research in our and other laboratories has shown that the spontaneous reactivation of new memory traces is linked to sleep spindles - bursts of thalamocortical activity at 11-16 Hz occurring during non-REM sleep. Sleep spindles vary in their frequency, amplitude, and duration, and form distinct spatial and temporal patterns. However, there is no unitary view on whether all, or only some types of spindles are associated with memory reactivation processes. Here, we tested our new hypothesis that clustering of spindles into trains (i.e., less than 6 s apart) is crucial for efficient reprocessing of motor memories in humans. To this end, we conducted a sleep study in which we recorded brain activity using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) simultaneously. These simultaneous recordings allowed us to conduct EEG-informed analyses of the fMRI data and estimate changes in activation patterns across the entire brain during spindles. Before the sleep, participants (n=26) were trained on a 5-element sequence of finger movements, tapping it repeatedly on a keyboard with their left hand, and then retested 24 hours later. Spindles were either clustered into trains or occurred in isolation (more than 6 s apart). Our results reveal that the onset of spindle trains, as compared to the isolated spindles, was associated with greater brain activity in key regions involved in motor sequence learning, including the thalamus, sensorimotor cortex, and striatum. Moreover, the onsets of longer trains were associated with a stronger effect, and participants with longer spindle trains exhibited greater activation within the same network; the latter effect being lateralized to the sensorimotor regions contralateral to the performing hand. These findings suggest that reactivation of the newly encoded motor memory is initiated with the first spindle of the trains, whereas spindles followed by longer trains may be more effective in triggering memory reprocessing and consolidation of procedural memories.

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Poster

P641. Sleep: Behavior

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Program #/Poster #: P641.07

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep quality of perimenopausal women in Mongolia

Authors: *B. CHOIJAMTS[1,2], E. TUMURBAATAR[3], O.-E. ARIUNBOLD[4,7], B. LKHAGVASUREN[5,8], T. JADAMBA[6,8];
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Abstract: Objectives: The aim of the study was to determine the quality of sleep and its risk factors in middle-aged Mongolian women. **Materials and methods**: A cross-sectional study were conducted among females aged between 40-65 years in the pre-, peri-, and post-menopausal status. Data was collected using a predesigned questionnaire which included general information, reproductive history, and body measurements along with standardized questionnaires such as the PSQI, Menopause Rating Scale and WHOQOL-BREF. The data analysis was conducted on 351 women. **Results**: Participant's blood pressure (p=0.003) and body mass index (BMI) (p=0.02) was significantly high in perimenopausal women. Average PSQI score in pre-, peri- and post-menopausal women were 6.59, 7.03, and 7.17 respectively. The somato-vegetative (p=0.003) and psychological (p=0.025) symptoms were significantly severe in perimenopausal women. The menopausal symptom severity frequency was significantly higher in perimenopausal women (p=0.017). Most of the participants answered well in both general quality of life and health related quality of life. However, the average of domain scores of WHOQOL-BREF was less than 80% at all menopausal stages. No correlation found to sleep quality either menopausal symptoms or quality of life. The menopausal symptoms (MRS total) (p=0.02) and sexual activity per month (p=0.005) has a significant influence on the overall quality of life. Sexuality had a significantly negative effect on psychological health (p=0.03). The age, occupation, menopausal stage, MRS-somatovegetative symptoms had a significant effect on health-related quality of life ($p<0.05$). **Conclusion**: In conclusion, middle age Mongolian women have poor quality of sleep. However the sleep quality was not the valuable factor for quality of life or menopausal symptoms severity. This however needs confirmation in other, better-designed clinical studies.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01HL148004 to S.B.G.A.

Title: Medullary adrenergic C1 neurons activity oscillates during sleep state transitions and arousal in rats

Authors: *G. M. P. R. SOUZA[1], R. L. STORNETTA[2], D. S. STORNETTA[1], S. B. G. ABBOTT[1]; [2]Pharmacol., [1]Univ. of Virginia, Charlottesville, VA

Abstract: Introduction: Sleep-wake behavior are associated with changes in sympathetic nerve activity (SNA) controlling blood flow to vital organs and muscle. SNA regulating blood pressure (BP) is controlled by adrenergic neurons in the ventrolateral medulla (RVLM), termed C1 neurons. C1 neurons are regulated by inputs from hypothalamic and brainstem regions that control arousal state, such as the orexin/hypocretin neurons. Thus, we hypothesized that C1 neurons mediate changes in SNA that accompany changes in sleep-wake state and vigilance. **Methods:** To test this hypothesis, we recorded the real-time activity from C1 neurons using fiber photometry in freely behaving rats while monitoring the

vigilance states. C1 neurons were targeted with GCaMP7s by microinjection of AAV_1-syn-FLEX-jGCaMP7s in the RVLM of Tyrosine Hydroxylase-Cre transgenic rats and an optical fiber was implanted above the injection site. Rats were fitted with a EEG/EMG head stage to monitor sleep-wake state and a radio telemetry probe to record BP. Normalized fluorescence changes are expressed as Z-score (mean ± SD), paired t-test were used to determine statistically significant differences. **Results:** In all cases, C1 activity as measured by GCaMP7s florescence was increased by acute isovolemic hypotension induced by sodium nitroprusside (2.1 ± 0.5 *vs.* -0.92 ± 0.4, $p<0.0001$, n=5). Similar to SNA in different stages of sleep and wake, C1 neuron activity increased during transitions from NREM to wake (-0.60 ± 0.1 *vs.* 0.59 ± 0.2, $p<0.0001$, n=6) while their activity decreased during transitions from wake to NREM (0.34 ± 0.2 vs. -0.32 ± 0.2, $p<0.0001$, n=6). C1 neurons activity increased during transitions from NREM to REM sleep (-0.74 ± 0.1 *vs.* 0.77 ± 0.1, $p<0.0001$, n=6) and decreased in transitions from REM to wake (0.58 ± 0.2 vs. -0.59 ± 0.2, $p<0.0001$, n=5). Arousal induced by air-puff delivered during NREM sleep caused a significantly greater change in C1 neuron activity than during spontaneous NREM-to-wake transitions (-0.78 ± 0.1 *vs.* 1.56 ± 0.4). **Conclusion:** C1 activity exhibit a pattern of activity that is similar to SNA during changes in sleep-wake state and in response to a stressful stimulus, consistent with the hypothesis that these neurons are responsible for arousal-related changes in SNA. The magnitude of the change in C1 activity during transitions to wakefulness appears to be associated with arousal intensity.

Disclosures: G.M.P.R. Souza: None. **R.L. Stornetta:** None. **D.S. Stornetta:** None. **S.B.G. Abbott:** None.

Poster

P641. Sleep: Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P641.09

Topic: F.08. Biological Rhythms and Sleep

Title: Peripartum estradiol fluctuations impact sleep actigraphy and neural plasticity during a hormone-simulated pseudopregnancy in female Syrian hamsters

Authors: J. E. CORBIN*, C. MERRILL*, K. C. HARRIS, M. A. HORTON, H. C. MORRIS, E. K. HAUGHEE, L. E. BEEN;
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Abstract: During the peripartum period, hormone levels fluctuate dramatically. Estradiol, in particular, increases throughout pregnancy, peaking in the third trimester; after birth and the expulsion of the placenta, however, estradiol levels quickly drop to pregravid levels and remain suppressed until ovulation resumes. Pregnant and postpartum people report clinically-significant disruptions in their sleep, and high levels of estradiol have been reported to suppress sleep in other contexts. However, it is unknown how peripartum estradiol fluctuations impact sleep. We therefore used a hormone-simulated pseudopregnancy model in female Syrian hamsters to test the impact of peripartum estradiol fluctuations on sleep actigraphy and neural plasticity. Adult female Syrian hamsters (n = 24) were ovariectomized and given daily hormone injections to approximate estradiol and progesterone levels during the peripartum period. Following this simulated pregnancy, one group of females was withdrawn from estradiol to simulate the

rapid decline in estradiol during the postpartum period, while one group continued to receive estradiol injections. Both groups were compared to a “no hormone” control that was ovariectomized and received vehicle injections throughout the simulated pregnancy and postpartum period. 24-hour video recordings of subjects in their home cages were taken at seven timepoints: twice prior to the initiation of hormone injections, twice during the early pregnancy stage, twice during the late pregnancy stage, and once during the postpartum period. At the conclusion of the experiment, hamsters were euthanized via intracardial perfusion and brains were processed for immunohistochemical localization of cFos, a marker of neural activation. High levels of estradiol during “late pregnancy” decreased total sleep time and sleep efficiency, and increased locomotion during the white light period. These differences persisted into the postpartum period for females who continued to receive estradiol, but not in females who were withdrawn from estradiol. cFos counts are still in progress, but preliminary results suggest that activation of dorsal raphe neurons may vary by hormone condition. Together, these results suggest that high estrogen levels in late pregnancy disrupt sleep, but postpartum estrogen withdrawal may ameliorate these disruptions, possibly via estradiol-mediated plasticity in dorsal raphe neurons.

Disclosures: J.E. Corbin*: None. **C. Merrill*:** None. **K.C. Harris:** None. **M.A. Horton:** None. **H.C. Morris:** None. **E.K. Haughee:** None. **L.E. Been:** None.

Poster

P641. Sleep: Behavior

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P641.10

Topic: F.08. Biological Rhythms and Sleep

Title: Psychometric properties of the PSQI in the Mongolian general population, prevalence of sleep quality, and nonorganic sleep disorders

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Abstract: There has been no report on sleep disorders and no validated tool for the screening of sleep quality in Mongolia. The aim of this study was to determine the prevalence of nonorganic sleep disorders and sleep quality among the general population using the Pittsburgh Sleep Quality Index (PSQI) followed by a structured psychiatric interview for low sleep quality individuals. This nationwide population-based cross-sectional study was carried out between August and October 2020 and consisted of 964 participants (74% women, mean age: 40.72±14.34) who were randomly selected from 64 clusters in 10 sites of Mongolia. 27.9% of the study participants were evaluated as having nonorganic sleep disorders based on the diagnostic guidelines of the International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10). The prevalence of nonorganic sleep disorders differed in age ($p < 0.001$).

Nonorganic sleep disorders were related to age, employment, diastolic blood pressure, sleep quality, and quality of life. The mean PSQI total score was 5.61±3.36 and 42.2% of the participants were classified as poor sleepers by a cut-off point of 5. An overall Cronbach's α was 0.73. Both exploratory and confirmatory factor analyses of PSQI indicated a two-factor solution. The results suggest that the prevalence of nonorganic sleep disorders in the general population of Mongolia was 27.9%, while the prevalence rate of poor sleep quality was 42.2% in the general population. The Mongolian version of the PSQI provides an important tool for screening of sleep quality and demonstrated good construct validity for use in the general population of Mongolia.

	Characteristics	Nonorganic sleep disorders (n=964)				Sleep Quality (n=1276)			
		All	Yes	No	P value*	All	Poor Sleeper	Good Sleeper	P value *
	Total, n (%)	964	269 (27.9)	695 (72.1)		1276	538 (42.2)	738 (57.8)	
Gender									
	Male	251 (26.0)	65 (25.9)	186 (74.1)	0.140	328 (25.7)	128 (39.0)	200 (61.0)	0.182
	Female	713 (74.0)	204 (28.6)	509 (71.4)		948 (74.3)	410 (43.2)	538 (56.8)	
Age groups									
	< 18	81 (8.4)	9 (11.1)	72 (88.9)	< 0.001	124 (9.7)	43 (34.7)	81 (65.3)	0.219
	18–29	147 (15.2)	26 (17.6)	121 (82.3)		212 (16.6)	93 (43.9)	119 (56.1)	
	30–44	331 (34.3)	96 (29.1)	235 (70.9)		419 (32.8)	171 (40.8)	248 (59.2)	
	45<	405 (42.1)	138 (34.1)	267 (65.9)		521 (40.9)	231 (44.3)	290 (55.7)	
Marital status									
	Never married	194 (20.1)	38 (19.6)	156 (80.4)	0.014	269 (21.1)	108 (40.1)	161 (59.9)	0.158
	Others*	120 (12.5)	38 (31.7)	82 (68.3)		148 (11.6)	73 (49.3)	75 (50.7)	
	Married	650 (67.4)	193 (29.7)	457 (70.3)		859 (67.3)	357 (41.6)	502 (58.4)	
Education									
	Below middle school	437 (45.3)	113 (25.9)	324 (74.1)	0.532	596 (46.7)	244 (40.9)	352 (59.1)	0.744
	Associate's degree	246 (25.5)	74 (30.1)	172 (69.9)		323 (25.3)	144 (44.6)	179 (55.4)	
	Bachelor's degree	249 (25.9)	71 (28.5)	178 (71.5)		314 (24.6)	131 (41.7)	183 (58.3)	
	Above master's degree	32 (3.3)	11 (34.4)	21 (65.6)		43 (3.4)	19 (44.2)	24 (55.8)	
Employment									
	Unemployed	129 (13.5)	44 (34.1)	85 (65.9)	0.003	157 (12.3)	72 (45.9)	85 (54.1)	0.444
	Student	118 (12.2)	17 (14.4)	101 (85.5)		175 (13.7)	66 (37.7)	109 (62.3)	
	Pensioner	224 (23.2)	66 (29.5)	158 (70.5)		286 (22.4)	117 (40.9)	169 (59.1)	
	Employed	493 (51.1)	142 (28.8)	351 (71.2)		658 (51.6)	283 (43.0)	375 (57.0)	
Income									
	<175$	607 (63.0)	182 (30.0)	425 (70.0)	0.169	811 (63.6)	340 (41.9)	471 (58.1)	0.259
	175-525	342 (35.5)	83 (24.3)	259 (75.7)		445 (34.9)	193 (43.4)	252 (56.7)	
	>525$	15 (1.5)	4 (26.7)	11 (73.3)		20 (1.5)	5 (25.0)	15 (75.0)	
Living condition									
	Ger	319 (33.1)	101 (31.7)	281 (68.3)	0.034	411 (32.2)	162 (39.4)	249 (60.6)	0.409
	House	310 (32.1)	93 (30.0)	217(70.0)		420 (33.0)	185 (44.0)	235 (56.0)	
	Dormitory	26 (2.7)	4 (15.4)	22(84.6)		40 (3.1)	20 (50.0)	20 (50.0)	
	Apartment	309 (32.1)	71 (23.0)	238 (70.0)		405 (31.7)	171 (42.2)	234 (57.8)	
Residence location									
	Ulaanbaatar	480 (49.8)	141 (29.4)	339 (70.6)	0.311	621 (46.6)	285 (45.9)	336 (54.1)	0.009
	Rural areas	484 (50.2)	128 (26.4)	356 (73.6)		655 (53.4)	254 (38.6)	402 (61.4)	

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Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.01

Topic: F.09. Food and Water Intake and Energy Balance

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Title: High fat diet feeding blunts AgRP neuron response to cold

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Abstract: To defend energy homeostasis in the cold requires energy expenditure (to support thermogenesis) and energy intake increase, enabling core temperature to be maintained with no change to body fat stores. When acutely housed at a mild cold (14°C), mice increase both food intake and heat production rapidly (~minutes), and these responses occur in parallel. We hypothesized a role for Agouti-related peptide (AgRP) neurons in this response and find their activity is regulated by thermal sensory input, and they increase activity, measured by Fos induction and fiber photometry, upon cold sensation. By inhibiting AgRP neurons during acute cold exposure, we also find this increase in AgRP neuron activity is required for the hyperphagic response to cold. Recent evidence found high-fat diet (HFD) feeding reduced AgRP neuron responsiveness to gastric hormones and standard chow diet presentation, and we hypothesized that their response to cold might also be blunted. We find that although 12-week HFD-fed mice exhibit intact thermogenic responses to cold and defend a normal core body temperature, they fail to increase energy intake (12.43±0.48 for 22°C vs. 13.49±1.54 kcal for 14°C; p=ns) and consequently experience weight loss not observed in chow-fed controls (body weight change: 0.16±0.15g for chow vs. -0.49±0.23g for HFD; p=0.05). This effect is present even after a shorter, 2-week exposure to HFD-feeding, implying a role for diet separate from obesity in the phenotype. To investigate whether HFD-feeding disrupts thermal regulation of AgRP neuron activity, using *Agrp*-Cre/GFP marker mice, we find acute cold exposure rapidly induces Fos (a marker of neuronal activation) in chow-fed mice, but this response is lacking in HFD-fed mice. This effect correlates with a failure to increase hypothalamic *Agrp* mRNA even after five days of mild cold exposure (22°C vs. 14°C; 0.19±0.07 vs. 0.24±0.09; p=ns). Further testing will determine how the food intake response to cold has become uncoupled from other thermoregulatory responses following HFD. Therapeutic strategies that block compensatory hyperphagia in this setting may be an effective way to achieve and maintain weight loss.

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Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.02

Topic: F.09. Food and Water Intake and Energy Balance

Title: A single dose of the probiotic Enterococcus faecium selectively activates c-Fos along the gut-brain axis

Authors: *E. E. BAUER, A. SHOEMAN, A. FRESE, V. TAPPA, J. LABRADOR, G. RUMMEL, A. NIGG, K. HALFHILL, T. J. BUHR, M. LYTE, P. J. CLARK;
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Abstract: Probiotics can exert a wide range of effects on the host, including altering brain function and behavior, via modulation of the microbiome-gut brain axis. The mechanisms of actions by which probiotics influence the gut-brain axis are still incompletely understood. As such, we chose to examine the effects of probiotics on the brain and gut shortly after administration. Indeed, certain probiotics can broadly, yet selectively, elevate neural activity in a within minutes of introduction via the vagus nerve. The present study aimed to examine the possible short-term effects of acute exposure of the probiotic *Enterococcus faecium* on neural activity in both the brain and gut. Adult male CF-1 mice were divided into three groups (n=18): Probiotic Gavage (10^9 CFUs *Enterococcus faecium* in PBS/ mouse), Vehicle Gavage (PBS/ mouse), and Control (handling only) group. To evaluate the acute temporal effects of a single dose of probiotic, these three groups were sampled at 3, 5, and 7 hours (n=6) proximate to the gavage time point. c-Fos immunohistochemistry on gut and brain sections was used as a marker of neural activity and c-Fos/tyrosine hydroxylase co-labeling revealed dopaminergic or noradrenergic activity. Preliminary results suggest that that a single dose *E. faecium* had very little effect on c-Fos most regions of interest in the brain or gut. However, in the gut, cecal crypt c-Fos was elevated at 3 and 5 hours after probiotic administration. In the brain, c-Fos/tyrosine hydroxylase co-labeling was elevated in the locus coeruleus 7 hours after probiotic administration. These preliminary data suggest that a single oral gavage of *E. faecium* selectively alters c-Fos along structures of the gut-brain axis. Results of this study may collectively provide insight for future mechanistic work regarding the elucidation of the pathways by which probiotics can influence brain function and behavior via the microbiome-gut brain axis.

Disclosures: E.E. Bauer: None. **A. Shoeman:** None. **A. Frese:** None. **V. Tappa:** None. **J. Labrador:** None. **G. Rummel:** None. **A. Nigg:** None. **K. Halfhill:** None. **T.J. Buhr:** None. **M. Lyte:** None. **P.J. Clark:** None.

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.03

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIDDK

Title: Fats and Sugars Recruit Distinct Gut-Brain Circuits To Control Food Intake And Reward

Authors: M. MCDOUGLE, A. DE ARAUJO, M. VERGARA, M. YANG, G. DE LARTIGUE;
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Abstract: The high-fat high-sugar food environment has been implicated as a driver of the obesity epidemic. Nodose ganglia (NG) neurons transmit post-ingestive signals, including fat and sugar intake, from the gut to the brain. Previous data revealed distinct vagal circuits are required for post-ingestive fat and sugar reinforcement, but whether these signals converge onto overlapping reward circuits is unclear. **Methods**: To address this, we used FosTRAP mice to genetically label whole-brain neuronal responses to discreet time-restricted stimuli. Using genetic-encoded reporter (tdTom) expression and cFos immunolabeling we compared neural responses to intragastric stimuli at two separate timepoints in the same animal. **Results**: Repeated intragastric infusion of the same macronutrient resulted in high colocalization between tdTom and cFos labeling (>70%) in neurons of a previously identified gut-reward circuit (NTS, PBN, SNc, dorsal striatum). Equicaloric infusion of fat or sugar at two separate timepoints significantly reduced colocalization of tdTom and cFos labeling (<30%), suggesting that fat and sugar recruit parallel but largely distinct reward circuits. Viral-mediated caspase ablation of sugar-sensing NG neurons abolished activation of the reward circuitry for sugar, but not fat; confirming this is a vagally-mediated mechanism. Optogenetic stimulation of fat-sensing NG neurons is sufficient to condition operant behavior. Microdialysis in response to equicaloric intragastric infusions of fat or sugar resulted in similar dopamine efflux in the dorsal striatum. To obtain the same level of dopamine efflux, more calories of an equicaloric fat-sugar combination are required, correlating with compensatory increased intake of fat-sugar solution. **Conclusion**: There are labeled lines for vagally-mediated fat or sugar reward. Reduced reward in response to fat-sugar combinations may explain the inclination to overindulge in high-fat high-sugar foods, and have broad implications for the pathogenesis of obesity.

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Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

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Program #/Poster #: P645.04

Topic: F.09. Food and Water Intake and Energy Balance

Support: FAPESP Grant to ACIK (2019/01306-2)
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Title: Exposure to a highly palatable diet changes maternal feeding pattern of hyperglycemic rats

Authors: G. P. OLIVEIRA[1,2], A. G. CRUZ[1,2], G. V. SILVA[1], M. G. MARTINS[1,2], B. C. WOODSIDE[3], ***A. C. I. KISS**[1,2];
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Abstract: Maternal metabolic and nutritional balance are key factors for a healthy pregnancy and lactation. Diabetes, a common disorder of maternal metabolism, results in a marked change in energy balance, leading to adaptations that may have long-lasting consequences for both the maternal and fetal organisms. Plus, the metabolic impairment caused by maternal diabetes may be aggravated by inadequate eating habits. However, the effects of their combination have not been fully explored yet. In previous studies, we demonstrated that maternal snack intake aggravates the glucose intolerance of hyperglycemic rats. However, it remains a question whether their pattern of food intake is related to this outcome. Therefore, our aim was to evaluate the effects of maternal mild hyperglycemia associated with snack intake during pregnancy and lactation on maternal feeding pattern. In order to achieve this goal, female Sprague-Dawley rats were mated and assigned on pregnancy day (PD) 0 either to standard chow (n=27) or standard chow plus snacks (n=25) (potato chips and 1,5% sucrose solution) from PD 0 to lactation day 14. Mild hyperglycemia was induced through the administration of streptozotocin (STZ, 35 mg/kg, i.p. diluted on citrate buffer 0.1M pH 4,5) on PD 7. Thus, 4 experimental groups were formed: Control (n=14), Control-snack (n=13), STZ (n=13), and STZ-snack (n=12). An oral glucose tolerance test was performed on PD 15. Dams gave birth naturally and litters were culled to 8 pups (4 males, 4 females). Food intake and body weight were measured daily throughout pregnancy and lactation and dams weight gain was calculated. Data on daily food consumption was used to calculate total caloric intake, as well as the percentage of calories coming from each diet component: chow, potato chips, and sucrose solution. The proportion of calories from specific macronutrients and feed efficiency were also calculated. All experimental procedures were approved by the local ethics committee (Protocol 1134). As expected, snack intake aggravated maternal glucose intolerance of hyperglycemic dams. Snack-fed rats, regardless of metabolic state, presented higher caloric intake and reduced chow intake, which was associated with a significant decrease in the proportion of calories coming from carbohydrates and protein, and an increase in the proportion of calories from fat intake. Hyperglycemic dams fed with snacks presented a different feeding pattern, eating more calories from chow than normoglycemic dams. In conclusion, snack intake during pregnancy and lactation changed the feeding pattern of hyperglycemic rats, which might have contributed to the aggravated glucose intolerance in those dams.

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Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

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Program #/Poster #: P645.05

Topic: F.09. Food and Water Intake and Energy Balance

Support: A*STAR Investigatorship Biomedical Research Council (BMRC) of A*STAR (1530700142 to Y.F.)
SINGA A*STAR Graduate Academy

Title: Hypothalamic orexigenic neuronal populations in regulation of high fat food intake

Authors: *E. SENOL[1,2], Y. FU[1,2,3];
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Abstract: Global epidemic of obesity is mainly resulted from over-consumption of high-caloric food, which is rewarding and reinforcing. High-caloric food is preferentially chosen over regular food, and is also used for generating conditioned place preference (CPP). Although several major hypothalamic orexigenic neurons have been identified, how they differentially participate in behavioural outputs related with consuming high fat food is still unclear. By staining for cfos after letting mice consuming either normal chow or high fat diet (HFD) after overnight fasting, we found that tuberal nucleus somatostatin (^{TN}SST) neurons, but not lateral hypothalamus GABAergic (^{LH}VGAT) neurons or zona incerta GABAergic (^{ZI}VGAT) neurons or ^{ARC}AgRP neurons, showed specific higher cfos-positive population after consuming HFD. Subsequently, to understand the effect of the post-ingestive mechanisms on ^{TN}SST activity, we designed an experiment where different caloric content liquids have been administered to the mice by gavaging and quantification of cfos positive SST neurons in TN region showed no significant difference. This result suggested that the caloric content of the infused liquid did not affect ^{TN}SST activity and the response to HFD mainly through pre-ingestive or consummatory mechanisms, not post-ingestive mechanisms. Further in vivo microendoscopy imaging of ^{TN}SST neurons showed that the majority of them showed preferential response to HFD without consuming it. The preferential response of ^{TN}SST neurons did not dictate preferential choice of HFD in hungry mice, because chemogenetically inhibiting ^{TN}SST or ^{LH}VGAT or ^{ARC}AgRP neurons all resulted in less consumption of HFD in hungry mice, and activating either of these four neuronal populations in sated mice all led to preferential consumption of HFD. Interestingly, only inhibiting ^{TN}SST neurons, but not other two neuronal populations, abolished CPP resulted by HFD, suggesting an unique role of ^{TN}SST neurons in associative learning related with HFD food. Therefore, we revealed an unique HFD-specific response of ^{TN}SST neurons, and suggest that choosing HFD is not dictated by a specific hypothalamic orexigenic neuronal population, but reinforcing effect of HFD specifically requires ^{TN}SST neurons.

Disclosures: E. Senol: None. **Y. Fu:** None.

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.06

Topic: F.09. Food and Water Intake and Energy Balance

Title: Effect of metformin on spontaneous activity in rats with metabolic syndrome

Authors: *A. VAZQUEZ-ALVAREZ, G. FERNANDEZ-SAAVEDRA, C. REYES-VAZQUEZ, D. BARRERA-OVIEDO;
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Abstract: Metabolic syndrome is a condition where there are at least three diseases (insulin resistance, diabetes, hypertension, central obesity, hypercholesterolemia or hypertriglycemia) that increase the risk of cardiovascular disease. Metformin is a biguanide used in the treatment of type 2 diabetes and it also has antineoplasic properties. The objective of this work was to determine spontaneous activity in a model of metabolic syndrome. Adult male Wistar rats that were fed a hypercaloric diet enriched with 15% lard and water with 15% sucrose, were used and streptozotocin (35 mg/kg) was administered intraperitonealy. Control rats ingested a normal diet (Laboratory Chow Purina). Rats with metabolic syndrome had insulin resistance, hyperglycemia, hypercholesterolemia, and hypertriglycemia. Metformin (100 mg / kg) was administered orally to a group of rats with metabolic syndrome. The spontaneous activity was assessed in an AccuScan Open Field Locomotor Activity equipment, for one hour between 10 am and 2 pm. An increase in horizontal activity, number of movements, time in movement, stereotyped activity and displacement was observed in rats with metabolic syndrome relative to control rats and a decrease in activity in rats with metabolic syndrome who were administered metformin ($P < 0.05$). This indicates that metformin helps control hyperactivity associated with metabolic syndrome.

Disclosures: A. Vazquez-Alvarez: None. **G. Fernandez-Saavedra:** None. **C. Reyes-Vazquez:** None. **D. Barrera-Oviedo:** None.

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

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Program #/Poster #: P645.07

Topic: F.09. Food and Water Intake and Energy Balance

Support: PO1 DK088761
RO1 DK118725

Title: Fatty acid synthase expression in POMC neurons is necessary for glucose homeostasis and insulin release

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Abstract: Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus are necessary to coordinate satiety signals, energy expenditure and glucose homeostasis. The alteration of energy sensing mechanisms in POMC neurons can lead to dysregulation of food intake, body weight, and nutrient availability and uptake. Previous evidence suggests that central fatty acid metabolism is involved in the regulation of food intake and glucose homeostasis. Fatty Acid Synthase (FASN) has been proposed as an energy sensor, since central FASN inhibition causes loss of bodyweight, acute anorexia, increased energy expenditure and alterations in glucose homeostasis. However, the specific hypothalamic neuronal populations underlying the metabolic effects of FASN inhibition are not fully defined. We hypothesized that FASN acts in POMC neurons to sense nutrient availability and adjust food intake and glucose homeostasis in response to metabolic challenges. For this purpose, we took advantage of our constitutive

and adult tamoxifen induced POMC-Cre mouse models to delete FASN from this neuronal population. We found that FASN deletion in POMC neurons reduced fat depots and impaired food intake. Furthermore, these animals had impaired glucose tolerance and altered carbohydrate metabolism that was accompanied by deficiencies in glucose-induced insulin release, further changing fat metabolism and leptin release. Together, our data indicates that FASN expression in POMC neurons serves as a nutrient sensing mechanism to precisely control glucose homeostasis through the autonomic nervous system and contributes to the understanding of the link between lipid metabolism in POMC neurons and glucose-induced insulin release

Disclosures: L.A. Leon-Mercado: None. **C. Lord:** None. **C. Liu:** None. **C. Lee:** None. **K.W. Williams:** None. **Z. He:** None. **A. Tinajero:** None. **C. Limboy:** None. **S. Lee:** None. **J.K. Elmquist:** None.

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.08

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH Grant DK119498
NIH Grant L30 DK1149978

Title: Cholinergic neurotransmission controls biosynthesis of small-intestinal endocannabinoids in obesity

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Abstract: Rationale: The endocannabinoid (eCB) system is an endogenous lipid signaling system that controls food intake and energy balance. In diet-induced obesity (DIO), the eCB system becomes dysregulated in the brain and peripheral organs and contributes to overeating. For example, we reported that the eCB 2-arachidonoyl-*sn*-glycerol (2-AG) is elevated in the small-intestinal epithelium of mice fed a high-fat/high-sucrose western-style diet (WD) when compared to control mice fed a standard rodent diet (SD). Overactive 2-AG signaling drives hyperphagia in DIO animals by activating local cannabinoid receptor subtype-1 (CB_1R). Moreover, efferent vagal cholinergic neurotransmission controls 2-AG production in the small intestine in rats, which drives overeating after a fast. We now tested the hypothesis that cholinergic signaling at muscarinic acetylcholine receptors (mAChRs) leads to increased biosynthesis of 2-AG in the small-intestinal epithelium, which may drive hyperphagia in DIO. **Methods:** Male 8-week-old C57BL/6 mice were maintained on WD for 60 days. Littermates maintained on SD served as controls. Animals received IP injections of DAU5884 (a selective m_3 mAChR antagonist), pirenzepine (a selective m_1 mAChR antagonist), or vehicle 30 minutes prior to harvest. Levels of 2-AG in the small intestinal epithelium were quantitated by ultra-performance liquid-chromatography/tandem mass spectrometry (UPLC-MS/MS). The activity of biosynthetic and degradative enzymes for 2-AG, diacylglycerol lipase (DGL) and monoacylglycerol lipase (MGL), respectively, were analyzed via UPLC-MS/MS-based assays of enzyme activity. **Results:** WD-fed mice exhibited elevated levels of 2-AG and

DGL activity in the small-intestinal epithelium, which was blocked in mice pre-treated with DAU 5884 or pirenzepine. There were no significant differences in activity of MGL between groups. **Conclusions:** These results suggest that in DIO, excessive cholinergic activity at m_3 and m_1 mAChRs in the intestinal epithelium drives increases in biosynthesis of 2-AG. Activation of these G_q-coupled mAChRs initiates the PLC-dependent generation of 1-stearoyl-2-arachidonoyl-*sn*-glycerol (SAG), which is subsequently converted to 2-AG by DGL. The functional consequences of this heightened signaling on feeding behavior in DIO and roles for the efferent vagus nerve in these processes are currently under investigation.

Disclosures:

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P645.09

Topic: F.09. Food and Water Intake and Energy Balance

Title: Effects of herpes simplex virus I inoculation on feeding behavior in C57BL/6 mice

Authors: *J. E. HASSELL, Jr[1], C. S. NIEMEYER[1], L. MERLE[2], A. N. BUBAK[1], D. RESTREPO[2], M. A. NAGEL[1];
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Abstract: Herpes simplex virus type 1 (HSV-1) is the most common cause of viral encephalitis that presents with seizures, alterations in consciousness, and focal neurological deficits; brain imaging shows inflammation of the temporal lobe(s) and viral DNA is present in cerebrospinal fluid. Prolonged sequelae include cognitive deficits, as well as changes in mood, sleep, and energy levels that do not localize to the temporal lobe. Murine studies of HSV-1 infection show that multiple brain regions beyond the temporal lobe are infected; however, these studies did not characterize nuanced behavioral changes associated with these other infected brain regions. Our preliminary studies show that intranasal HSV-1 infection of mice leads to a striking localization of HSV-1 antigen in the bilateral dorsomedial hypothalamus and lateral hypothalamus, associated with microglial activation. Because these regions are associated with feeding behaviors, we hypothesized that these infected mice would have altered motivation to feed and decreased food intake. Furthermore, because neuroinflammation can contribute to alterations in these behaviors and persistent CNS inflammation has been observed up to 60 days after HSV-1 infection, we expect to see long-term feeding behavior deficits well after productive HSV-1 infection has resolved. To test this hypothesis, we mock- or HSV-1-infected mice intranasally. We examined food intake using feeding experimental device 3 (FED3) automated feeders continuously prior to infection, during acute infection, and 30-60 days after infection when HSV-1 has established latency. Specifically, we assessed meal size, meal intervals, and circadian patterns of eating. Additionally, we examined HSV-1 induced sickness behavior as demonstrated with conditioned flavor taste preference changes. Overall, the results of the current study would corroborate alterations in feeding behavior with the neuroanatomical sites of HSV-1 infection and inflammation, broadening the spectrum of postviral sequelae.

Disclosures: J.E. Hassell: None. **C.S. Niemeyer:** None. **L. Merle:** None. **A.N. Bubak:** None. **D. Restrepo:** None. **M.A. Nagel:** None.

Poster

P645. Ingestive Behavior: Effects of Diet and Metabolic Syndrome

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Program #/Poster #: P645.10

Topic: F.09. Food and Water Intake and Energy Balance

Support: JPB Grant JPBF-184517-03

Title: Control of feeding behavior by delivery of modified retroAAV to the gastrointestinal tract to specifically target vagus nerve afferents.

Authors: *R. MARONGIU[1], J. WANG[1], S. UNDA[1], J. BARBERA[1], L. VELAZQUEZ[1], N. DE SILVA[1], W. TOWER[1], R. LI[2], M. JIMENEZ-GONZALES[2], S. STANLEY[2,3], M. G. KAPLITT[1]; [1]Neurolog. Surgery, Weill Cornell Med., New York, NY; [2]Diabetes, Obesity and Metabolism Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY, New York, NY; [3]Nash Family Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Appetite is tightly regulated in order to ensure appropriate levels of nutrients in the body. The gut mediates short-term feedbacks to satiety circuits in the central nervous system (CNS), including the nucleus of solitary tract (NTS) and the hypothalamus, through the gastrointestinal branches of the vagus nerve to regulate food intake. However, preclinical and clinical reports employing external vagal nerve and gastric electric stimulation to modulate vagal neuron control of appetite generated inconsistent results and the pathways regulating these feedbacks are not fully understood.To address some of the limitations in these studies, we used our expertise in AAV-mediated gene delivery to access the CNS through the vagus nerve and assess if chemogenetic activation of vagal neurons is sufficient to regulate food intake and neuronal activity in CNS satiety nuclei in wild type (wt) mice. We injected retrograde AAV vectors (AAVrg) carrying the chemogenetic hM3Dq transgene (for neuronal activation), or mCherry as a control, under the chicken beta-actin promoter into the corpus of the stomach ($2x10^{12}$ vg/ml). Interestingly, our AAVrg exclusively transduces vagal sensory afferent neurons, which have their cell bodies in the nodose ganglion (NG) and project one axonal branch to the visceral organs and the other one to the NTS in the brainstem. Activation of afferent vagal neurons by hM3Dq following acute CNO injection (1 mg/Kg, i.p.) significantly reduces feeding behavior in normally fed or overnight fasted wt mice compared to control mice injected with mCherry or AAVrg.hM3Dq mice treated with saline. Additionally, chronic chemogenetic activation of transduced vagal sensory neurons reduces body weight gain in wt mice fed with high fat diet, indicating that regulation of satiety pathways can significantly be achieved by our AAVrg approach.Next, we tested if chemogenetic activation following single CNO injection of vagal sensory neurons regulates the neuronal activity in the NTS and indirectly in specific hypothalamic nuclei. We found that acute activation of vagal afferent neurons significantly increases c-Fos expression in the NTS, in the dorsal-medial and ventral-lateral nuclei of the ventral-medial hypothalamus (VMH) and the arcuate segments (ARC) of the hypothalamus compared to control mice.In conclusion, our AAV-mediated specific activation of vagal afferent neurons in the stomach is sufficient to significantly reduce

food intake and weight gain and to activate the NG, NTS, VMH and ARC nuclei in wt mice. Our study also suggests that the macro-circuit gut-NTS-VMH is linked to the VMH-ARC microcircuit.

Disclosures: R. Marongiu: None. **J. Wang:** None. **S. Unda:** None. **J. Barbera:** None. **L. Velazquez:** None. **N. de Silva:** None. **W. Tower:** None. **R. Li:** None. **M. Jimenez-Gonzales:** None. **S. Stanley:** None. **M.G. Kaplitt:** None.

Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P702.01

Topic: G.05. Mood Disorders

Support: NIMH R01MH121350

Title: Effort-related motivational effects of the vmat-2 inhibitor tetrabenazine and the da transport inhibitor methylphenidate on male and female rats.

Authors: *A. ECEVITOGLU[1], R. A. ROTOLO[1], R. E. PRESBY[1], N. REN[1], E. ZORDA[1], S. M. SRINATH[1], N. M. MEKA[1], C. CARRATALA-ROS[2], E. ARIAS-SANDOVAL[2], J. CHROBAK[1], I. STEVENSON[1], M. CORREA[2], J. D. SALAMONE[1];
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Abstract: Motivational symptoms such as fatigue, anergia, and amotivation are seen in many disorders including depression, multiple sclerosis, Parkinson's disease, schizophrenia, and chronic fatigue syndrome. Animal studies of effort-based choice behavior have been used to provide models for effort-related aspects of motivation in humans. One way of assessing effort-based choice is using progressive ratio (PROG) tasks, which are useful in exploring activational aspects of motivation and exertion of effort. Previous studies showed that a low effort bias can be induced in rodents by injecting the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ), which can be reversed by drugs that are known as dopamine transport (DAT) inhibitors, including methylphenidate, lisdexamfetamine, GBR-12909, and PRX-14040. Although methylphenidate has been shown to reverse the effort-related effects of TBZ in several fixed-ratio (FR) schedules, its influence on both male and female rats performing on other schedules remains unknown. Rats were assessed using a modified PROG which was developed to study the effects of altering ratio requirements of PROG tasks. The modified PROG schedule had a gradually increasing the ratio increment (e.g., FR1, FR5, FR9, etc.) as a way of increasing the work requirement. In the present study, the ability of methylphenidate to reverse the effort-related motivational effects of TBZ was assessed using the modified PROG. TBZ (1.0 mg/kg) decreased lever pressing in both males and females. Methylphenidate was co-administered at doses ranging from 1.0-4.0 mg/kg, and it successfully reversed the effects of TBZ at the highest dose for males but at the lowest dose for females, which suggests a sex difference in the dose/response function for methylphenidate. When methylphenidate was administered alone at doses ranging from 0.5-4.0 mg/kg, strong sex differences were observed. There was a substantial increase in lever pressing in males at the highest doses, however, variable effects were found

in females. Future studies are focused on obtaining electrophysiological markers of the exertion of effort during instrumental tasks, and the effects of drugs on these biomarkers.

Disclosures: A. Ecevitoglu: None. **R.A. Rotolo:** None. **R.E. Presby:** None. **N. Ren:** None. **E. Zorda:** None. **S.M. Srinath:** None. **N.M. Meka:** None. **C. Carratala-Ros:** None. **E. Arias-Sandoval:** None. **J. Chrobak:** None. **I. Stevenson:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Program #/Poster #: P702.02

Topic: G.05. Mood Disorders

Support: FPI BES-2016-077177
PRE2019-090163
PROMETEO/2020/032

Title: Mild maternal separation in mice of both sexes affects the dopaminergic system and has an impact in adulthood on vigor to approach or to escape motivational stimuli

Authors: *C. CARRATALÁ-ROS[1], P. MATAS-NAVARRO[1], A. MARTÍNEZ-VERDÚ[1], E. ARIAS-SANDOVAL[1], R. OLIVARES-GARCÍA[1], J. D. SALAMONE[2], M. CORREA[1];
[1]Area de Psicobiologia, Univ. Jaume I, Castellon DE LA Plana/Castello DE LA Pla, Spain; [2]Dept Psychological Sci., Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Early-life stress affects brain development and induces long-lasting effects that can lead to psychiatric disorders such as depression. Little is known about the effect of early-life stress on motivational processes such as effort-based decision-making, which often is impaired in people with depression. Mesolimbic dopamine (DA) regulates behavioral activation and effort in motivated behaviors. Stress can produce opposite effects on DA release depending on its intensity and duration. Maternal Separation (MS) is as an early-life stressor that can alter brain function permanently. Using CD1 male and female mice, we evaluate the impact of early and mild MS (PND3 to 5, 90 min each day), on selection of effortful responses in adulthood under positive or aversive experimental conditions. In a three-choice-T-maze, the preference of mice for active reinforcers such as a running wheel (RW) versus sedentary ones was evaluated, and in a forced swim task (FST), time dedicated to vigorously escape or passively floating was measured. In addition, we studied if MS interacts with DA depletion in adulthood, administering tetrabenazine (TBZ), a VMAT-2 inhibitor that induces fatigue and anergia in rodents and humans. We also assessed the impact of MS on DA-related markers such as the cerebral dopamine neurotrophic factor (CDNF) on nucleus accumbens core (Nac), shell (NacSh) and anterior cingulate (Cg). Both males and females spend more time in the RW and less time eating or sniffing a neutral odor in the T-maze, independently of separation. However, separated mice of both sexes spent more time in the RW, and climbing in the FST compared to non-separated mice. Only among males, TBZ reduced time in RW, increased time eating, reduced climbing and increased immobility. Females were not affected by DA depletion. MS produced an increased in a CDNF marker in female separated mice both in Nac and

NacSh, suggesting that this neurotrophic factor may protect functions regulated by mesolimbic DA. We did not observe any effect of MS on CDNF in male mice. These results highlight the importance of early-life experiences, specifically MS, on establishing patterns of behavioral activation in different contexts, and the role of the DA system. Further studies should explore different times and durations of MS in order to better characterize this phenomenon and also to improve its translational potential.

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Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Program #/Poster #: P702.03

Topic: G.05. Mood Disorders

Support: NIMH (R01MH121350)

Title: Behavioral and EEG effects of dopaminergic drugs that alter effort-related aspects of motivation: Implications for avolition and anergia

Authors: *J. D. SALAMONE[1], *R. A. ROTOLO[1], A. ECEVITOGLU[1], N. REN[1], R. E. PRESBY[1], C. CARRATALA-ROS[2,1], N. M. MEKA[1], S. M. SRINATH[1], E. ARIAS-SANDOVAL[2], A. YU[1], D. CANFIELD[1], M. CORREA[2], I. H. STEVENSON[1], J. J. CHROBAK[1];
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Abstract: People with neuropsychiatric disorders such as depression, schizophrenia, and Parkinson's disease suffer from fatigue, anergia, apathy, and other motivational dysfunctions, which can be treatment resistant. To assess these motivational dysfunctions in animal models, tasks have been developed to measure effort-related choice, offering the option of high effort actions leading to more valued reinforcers vs. low effort/low reward activities. Such tasks are useful for preclinical studies related to drug development. A low effort bias can be induced in male and female rats by injection of the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ), which induces depressive symptoms in people. By virtue of blocking vesicular storage, TBZ depletes DA and suppresses high-effort instrumental behaviors across multiple tasks. Suppression of lever pressing is also induced by injections of pro-inflammatory cytokines, which provide an inflammatory challenge. These deficits can be reversed by drugs that are dopamine transport (DAT) inhibitors. Because many drugs that block DAT act as major stimulants and produce undesirable side effects, there is a need to develop and characterize novel atypical DAT inhibitors with unique neurochemical profiles. Recent studies have shown that novel atypical DAT inhibitors, including modafinil analogs, also can restore motivational function, and increase selection of high-effort activity. Drugs that selectively stimulate serotonin and norepinephrine transmission are not effective in this regard. Other strategies being investigated involve the development of potential physiological biomarkers of the effects of drugs or other conditions that alter effort-related functions. Recent studies in our laboratory have focused on the electroencephalographic (EEG) and local field

potential (LFP) effects of TBZ and other drugs that affect DA transmission. In rats, there is a predominant peak in the alpha/theta frequency range (6-9 Hz) in medial prefrontal cortex that is suppressed by TBZ in male rats, but less so in females. It is possible that this research will identify new avenues for drug treatment of effort-related motivational symptoms in humans, including apathy, avolition, anergia, and COVID-related fatigue.

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Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P702.04

Topic: G.05. Mood Disorders

Title: The antidepressant bupropion enhances behavioral activation in a mouse model of effort-based decision-making: assessment of individual differences between choice and non-choice operant tasks and its relation with the cdnf-related marker

Authors: *E. ARIAS-SANDOVAL[1], G. D'ALOISIO[1], C. CARRATALÁ-ROS[1], A. MARTINEZ-VERDU[1], P. MATAS-NAVARRO[1], R. OLIVARES-GARCÍA[1], J. D. SALAMONE[2], M. CORREA[1]; [1]Univ. Jaume I, Castellon de la Plana, Spain; [2]Dept Psychological Sci., Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Vigor, persistence, and work output are fundamental features of normal motivation. Nucleus Accumbens (Nacb) dopamine (DA) regulates behavioral activation and effort-related decision-making in motivated behavior. Impairments in DA transmission lead to symptoms such as fatigue, anergia and apathy. These motivational symptoms are seen in pathologies such as depression and are highly resistant to treatment. In the present study, we administered Bupropion (BUP; 0, 5.0, 10.0 and 15.0 mg/kg, IP) a DA uptake blocker used as an antidepressant, to enhance DA function in CD1 male adult mice. To evaluate the effect of BUP not only on effortful behaviors, but specifically on effort-based decision making, mice were split into two groups: the first group was trained in an operant chamber under a high effort progressive ratio schedule that, during 5 seconds, made available a bottle with a 10% sucrose solution (no-choice condition). The second group of animals was also trained in the same progressive ratio schedule for 10% sucrose, but additionally they concurrently had in the operant box a bottle with a 3% sucrose solution (choice condition). The presence of the free 3% sucrose solution led to a much lower baseline lever pressing in the choice condition, and mice consumed the same volume of both solutions (a total volume of fluid similar to the non-choice group). In a previous free-drinking choice test with no operant work required, all mice strongly preferred and consumed significantly more of the 10% sucrose vs the 3% sucrose solution. We further assessed individual differences in behavior (high and low responders) and on DA-related markers such as the cerebral dopamine neurotrophic factor (CDNF) on several brain areas. The dose of 10.0 mg/kg BUP significantly increased lever pressing for the high and low responders in the no-choice group, while for the choice group the effect of BUP depended on baseline

performance; high responders increased at 15.0 mg/kg, and low responders at 5.0 mg/kg. CDNF immunoreativity differences were found between high and low responders of both operant conditions in accumbens core and shell, and medial and lateral dorsal striatum, but not in anterior cingulate. These results indicate that individual differences in willingness to work are related to DA-related neurotrophic factors in ventral and dorsal striatum, and also that drugs acting on DA transmission may be effective for improving depressive symptoms related to amotivation and anergia

Disclosures: E. Arias-Sandoval: None. **G. D'Aloisio:** None. **C. Carratalá-Ros:** None. **A. Martinez-Verdu:** None. **P. Matas-Navarro:** None. **R. Olivares-García:** None. **J.D. Salamone:** None. **M. Correa:** None.

Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Program #/Poster #: P702.05

Topic: G.05. Mood Disorders

Support: NIH Grant R00DA043572-03

Title: Evaluating Common Behavioral Factors Underlying Chronic Pain and Depression that Contribute to Opioid Abuse

Authors: *C. O'BRIEN, U. MOHAMMED, R. VEMIREDDY, C. PIZZANO, J. MEJAES, D. BARKER;
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Abstract: Chronic pain and depression are highly comorbid conditions with overlapping symptomologies. To determine which behavioral features best predict this overlap in mice, we modeled chronic pain using a spared nerve injury (SNI) model and depression using a learned helplessness paradigm. Mice in both groups were then subjected to the same battery of behavioral tests that measure depression-like behaviors, anxiety-like behaviors, mechanical pain responses, and thermal pain responses. Our results show that SNI and learned helplessness mice both exhibit anhedonic responses in the two-bottle choice, as compared to controls, but performed similarly in the elevated plus maze and open field tasks. Similarly, we found mechanical hypersensitivity in both SNI and learned helplessness mice, as compared to controls. However, thermal sensitivity was only observed in SNI mice. Next, to determine the common features of pain and depression that contribute to opioid abuse, we used a principal component analysis to determine which specific behavioral features best predicted the susceptibility to oral fentanyl consumption. Surprisingly, the principal component analysis revealed that a combination of heightened anxiety-like responses and hypersensitivity to pain best predicted increased opioid intake, whereas levels of anhedonia and behavioral despair carried less weight. These data show individual markers that may be key indicators of opioid abuse susceptibility. The combination of these behavioral features across painful and depressive-like states could help predict fentanyl consumption by highlighting individual phenotypic differences.

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Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Topic: G.05. Mood Disorders

Support: This study was supported by the Intramural Research Program of the National Institute on Drug Abuse
R00DA043572

Title: Lateral preoptic area glutamate neurons relay nociceptive information to the ventral tegmental area

Authors: *D. BARKER[1], S. ZHANG[2], D. J. ESTRIN[3], J. A. MIRANDA-BARRIENTOS[4], R. J. JUZA[5], B. LIU[6], S. MONGIA[7], M. F. MORALES[8];
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Abstract: The Ventral tegmental area (VTA) has been proposed to play a role in pain, but the brain structures modulating VTA activity in response to nociceptive stimuli remain unclear. One unexamined route by which nociceptive information might reach and influence the VTA is through the lateral preoptic area (LPO). The LPO provides strong projections to VTA and receives direct inputs from the dorsal horn of the spinal cord. In the present study, we used anatomical, behavioral, and electrophysiological approaches to examine a possible role of projections from the LPO to the VTA in relaying nociceptive information to the VTA. By anatomical approaches, we that around 40% of LPO neurons innervating the VTA expressed the vesicular glutamate transporter 2 (VGluT2) and around 60% expressed the vesicular GABA transporter (VGaT). By fiber photometry calcium imaging, we characterized the responses of VTA-projecting LPO-VGluT2 and LPO-VGaT neurons in response to the optogenetic stimulation of peripheral nociceptors. We found that LPO-VGluT2 neurons synapsing on VTA neurons responded to nociceptive stimulation and conditioned stimuli predicting nociceptive stimulation. By independent optogenetic stimulation of VTA inputs from LPO-VGluT2 or LPO-VGaT, we found that VTA activation of inputs from LPO-VGluT2 neurons drove aversion, while VTA activation of inputs from LPO-VGaT neurons drove reward. By ex vivo electrophysiology, we observed that LPO inputs evoked EPSCs and IPSCs in VTA-dopamine, VTA-VGluT2 and VTA-VGaT neurons, with the strongest responses from both LPO-VGluT2 and LPO-VGaT neurons on VTA VGaT neurons. By ultrastructural analysis, we found that within the medial and lateral VTA, LPO-VGluT2 and LPO-VGaT neurons differentially established synapses on the cell bodies or dendrites of VTA-dopamine, VTA-VGluT2 or VTA-VGaT neurons. In summary, we found that (a) there is a complex circuitry between LPO glutamatergic and GABAergic neurons and the different subclasses of VTA neurons, and (b) the LPO-glutamatergic neurons synapsing on VTA neurons responded to nociceptive stimulation and conditioned stimuli predicting this

stimulation. We concluded that the pathway from LPO to VTA represents an important, yet previously undefined, interface between peripheral nociceptive information and the limbic system.

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Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Topic: G.05. Mood Disorders

Support: Rutgers Brain Health Institute Pilot Grant
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NIH Grant R01NS112390

Title: The effect of the synaptojanin1 gene mutation on motivational behavior & cocaine seeking in mice

Authors: *J. I. MEJAES[1], J. SAENZ[2], S. V. ROZARIO[1], C. PIZZANO[1], C. O'BRIEN[1], S. BRYANT[1], P.-Y. PAN[2], D. J. BARKER[1];
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Abstract: The synaptojanin1 *(SYNJ1)* gene plays important roles in several dopamine-related disorders, such as bipolar disorder, schizophrenia, and parkinsonism. Recent evidence has demonstrated that Synj1 deficient mice (*Synj1+/-*), unlike their littermate controls (*Synj1+/+*), have reduced levels of striatal dopamine (DA), dystrophic changes in DAergic axons, and impairments in DAergic synaptic recycling. Despite these clear links to midbrain DA systems, the effect of *Synj1* mutations on motivation and rewarding behaviors has not been examined. Our objective was therefore to assess the role of the *Synj1* gene in a variety of behavioral tasks associated with mood, motivation, learning and reward. We subjected *Synj1+/-* male and female mice (n= 18) and their littermate controls (n=17), to a battery of behavioral tests used to assess specific features of these behaviors. Our results indicate that *Synj1+/-* mice exhibited normal anxiety like behaviors in the Elevated Plus Maze and Open Field Test. Additionally, *Synj1+/-* mice also displayed normal hedonic responses and reward seeking behaviors to sucrose in the Sucrose Preference Test, Operant Conditioning Paradigm and Progressive Ratio-Schedule Task. However, during the cocaine Conditioned Place Preference Paradigm (CPP), the *Synj1+/-* male mice did not develop the typical behaviors associated with cocaine-seeking. Moreover, unlike their littermate controls, *Synj1+/-* male mice did not exhibit a cocaine-induced increase in dopamine transporter (DAT) levels in the striatum and midbrain. Overall, these results suggest that the *SYNJ1* gene may affect specific types of reward processing via altering DAT-regulated DA signaling.

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Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

Location: Virtual Only

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Topic: G.05. Mood Disorders

Support: R01DA050454

Title: L-type calcium channels mediate mood-related behavioral phenotypes in rats exposed to chronic unpredictable stress.

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Abstract: Exposure to chronic daily stressors can induce symptoms of depression and anxiety in susceptible individuals. In preclinical rodent models, chronic unpredictable stress (CUS) has been demonstrated to promote depression and anxiety-like behavioral phenotypes. The ventral tegmental area (VTA) to nucleus accumbens (NAc) dopaminergic pathway has been implicated in the neurobiological response to stress. Prior work has demonstrated a role of VTA L-type calcium channels (LTCCs) in regulating depression and anxiety-like behavior in rodents. Furthermore, VTA LTCCs have been shown to regulate dopamine (DA) signaling in the NAc. However, it is unknown whether LTCCs regulate behavioral responses to CUS exposure. Therefore, we tested the hypothesis that LTCC blockade would attenuate CUS induced pro-depressive and anxiogenic behavioral responses in female and male rats. Following 21 days of CUS exposure, female and male rats were tested on the sucrose preference test (SPT), elevated plus maze (EPM), and the forced swim test (FST). CUS exposure produced pro-depressive and anxiogenic-like behavior as demonstrated by decreased sucrose preference in the SPT, decreased time spent in the open arm on the EPM, and increased immobility time in the FST. Systemic administration of the LTCC blocker, isradipine, (0, 0.4, 1.2mg/kg, intraperitoneally (I.P.), 15 min prior) attenuated CUS induced pro-depressive and anxiogenic behavioral responses on the SPT, EPM and FST in both female and male rats. In contrast, in female and male control rats that had no CUS exposure, isradipine did not alter behavioral responses on the SPT or EPM, suggesting an interaction between CUS exposure and the ability of LTCCs to regulate pro-depressive and anxiogenic behavioral responses. In the FST, however, isradipine decreased immobility time in both CUS and control rats, suggesting that the FST may be a sufficient acute stressor to unmask LTCCs' ability to mediate responses to both acute and chronic stress. In ongoing experiments, we are investigating the effect of LTCC blockade via systemic isradipine (0, 1.2mg/kg, I.P.) on NAc DA release using fast-scan cyclic voltammetry (FSCV) in CUS and non-CUS exposed female and male rats.

Disclosures: N. Kebede: None. **E.J. Nunes:** None. **N.A. Addy:** None. **A.M. Rajadhyaksha:** None.

Poster

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Program #/Poster #: P702.09

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH120131-01A1

Title: Balance of GABA and glutamate co-release in the lateral habenula mediates reward sensitivity

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Abstract: More than 300 million people in the world suffer from Major Depressive Disorder (MDD). For better treatment, we need an understanding of the circuits and mechanisms that underlie the disorder. Many brain regions contribute to the pathology of depression, but the lateral habenula (LHb) stands out because, in contrast to other regions, its activity increases during negative affective states. Additionally, hyper-activation of the LHb has been implicated in depression in humans. Significant input to this region comes from the internal globus pallidus (GPi), which is thought to drive LHb activity during negative feedback (aversive stimuli) and reduce its activity during positive feedback (reward). Interestingly, although GPi-LHb projections are predominantly excitatory, they co-release GABA with glutamate. GABA co-release from GPi is inhibitory and one of the few known sources of GABA in the LHb. In a rat model of depression, the ratio of GABA-to-glutamate in GPi-LHb is reduced. In contrast, antidepressant treatment increased the ratio in mice. I hypothesized that the ratio of GABA-to-glutamate released from the GPi regulates neuronal activity in the LHb, and the inability to increase the ratio during excessive excitatory input results in LHb hyperactivity and increases in depressive symptoms. To test this hypothesis, I determined if reduced GABA co-release from GPi-LHb projections increases depression-related behavior. Preliminary results suggest that reducing GABA co-release by knocking down the vesicular GABA transporter (VGAT) causes anhedonia in mice but has no effect on other depression-related behaviors. To test for a more specific role of GABA co-release in regulating behavioral sensitivity to positive and negative feedback, I tested the same mice in a risky decision-making task. VGAT knockdown mice were risk averse, consistent with altered sensitivity to positive and/or negative feedback. In combination with future experiments**,** I expect to identify the GPi-LHb circuit as a strong candidate for the development of new therapeutics for anhedonia and advance our knowledge of activity regulation in the reward system.

Disclosures: N. Rodriguez Sosa: None. **S. Shabel:** None.

Poster

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NIDA P30 DA048736 (SRON and SAG)
NARSAD Young Investigator Award 27082 (SAG)
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Title: Validation of brain-wide PHP.eB infectivity across outbred hybrid transgenic mouse lines for the study of appetitive aggression and complex social behaviors

Authors: *J. NAVARRETE[1], E. SZELENYI[1], A. ABANTO[2], V. TSAI[1], N. GOODWIN[1], S. A. GOLDEN[1];
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Abstract: Background
Neuropsychiatric disorders, such as depression and post-traumatic stress disorder, are commonly associated with maladaptive or inappropriate aggression that is demarcated as either reactive (defensive) or appetitive (rewarding). We have developed several behavioral procedures to examine appetitive aggression in outbred mice, which limits the use of common genetic tools that require inbred transgenic strains. To overcome this caveat, we recently established Cre x CD-1 F1 generation hybrids as a model system for studying complex social behaviors that allow genetic access to select cell types and circuits. Here, we assess and validate the use of systemic PHP.eB viral infections - initially optimized with inbred mice - using a new genetic tool and automated cell segmentation in outbred hybrid lines.

Methods
We created an optimized nuclear localization (oNLS) tag that shows enhanced nuclear restriction for brain-wide cellular segmentation. We packaged oNLS-PHP.eB and validated the brain-wide infectivity across outbred hybrid lines. Quantification of infectivity 3 weeks post-retroorbital infection was assessed on coronal brain sections ranging from 2.00 to -4.00 AP. Brain registration, anatomical annotation, and cell segmentation were performed using SMART (semi-manual alignment to reference templates) and QuPath, respectively.

Results
Preliminary results suggest subtle, but significant, differences in PHP.eB infectivity across hybrid lines.

Conclusion
Based on our preliminary results, careful assessment of PHP.eB infectivity across outbred and hybrid transgenic lines are required prior to use.

Disclosures: J. Navarrete: None. **E. Szelenyi:** None. **A. Abanto:** None. **V. Tsai:** None. **N. Goodwin:** None. **S.A. Golden:** None.

Poster

P702. Animal Models of Motivated Behavior, Emotional Reactivity, and Pain

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Idex

Title: Contribution of the amygdalo-cingulate pathway in depression, pain and their comorbidity

Authors: *L. J. BECKER, C. FILLINGER, R. WAEGAERT, P. HENER, B. AYAZGÖK, S. H. JOURNÉE, M. BARROT, P. VEINANTE, S. HUGEL, P.-E. LUTZ, I. YALCIN;
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Abstract: Major Depressive Disorder (MDD) is a chronic and debilitating disease with poor treatment outcomes. It is often comorbid with chronic pain, resulting in an increased disability and poorer prognosis than either condition alone. Evidence from animal models and human studies suggest a crucial role of the anterior cingulate cortex (ACC) and the anterior part of the basolateral amygdaloid nucleus (BLA) in the development of MDD and in its comorbidity with chronic pain. Our team showed that lesion or inhibition of the ACC in mice alleviates anxiodepressive-like symptoms in chronic pain-induced depression model and that its repeated activation triggers these behaviors in naive mice. We highlighted a strong reciprocal connection between the ACC and the BLA, making this pathway a good candidate to begin the dissection of the ACC connectome in mood disorders and their comorbidity with chronic pain. First, we tested if the inhibition of the BLA-ACC connection could alleviate the anxiodepressive-like behaviors in our model of peripheral neuropathy. To inhibit the BLA-ACC connection, we injected an AAV5 coding for the archaerhodopsin in the BLA of C57BL6/J neuropathic mice and we delivered green light in the ACC during behavioral testing. While mechanical hypersensitivity and anxiety stayed unchanged, this manipulation improved the depressive-like behaviors induced by chronic pain. Conversely, we activated the BLA-ACC pathway to determine if its hyperactivity was sufficient to trigger depressive-like behaviors in naive mice. We injected an AAV5 coding for the channelrhodopsin in the BLA and delivered repeated blue light pulses in the ACC to activate the pathway. We showed that chronic activation of the BLA-ACC pathway selectively induces depressive-like behaviors. The need for a repetitive activation strongly suggest the involvement of plastic changes within the ACC. To test this, we conducted high-throughput RNA-sequencing in the ACC of the optogenetic-induced depression model. To uncover transcriptomic alterations relevant to the human pathology the results were compared with those obtained in severely depressed patients (Rank-Rank Hypergeometry Overlap method). We constructed gene network for both species (Weighted Gene Co-expression Network Analysis) and calculated their conservation rate. Our data highlight strong similarities in transcriptomic profile between optogenetic-induced depression in mice and MDD patients

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Poster

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Topic: G.05. Mood Disorders

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Title: Examining the role of specific touch neurons in reward and stress resilience

Authors: *M. SCHAFFLER[1], J. ARNOLD[1], I. ABDUS-SABOOR[2];
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Abstract: Social touch is rewarding, motivating social interactions and relationships, and can act as a stress buffer, regulating physiological and behavioral responses to short-term challenges. However, the skin-to-brain neuronal circuits by which touch is rewarding and promotes stress resilience remain unknown. Discovery of the specific peripheral neurons that play a role in the rewarding and/or anxiolytic nature of touch would be the first step in elucidating such a circuit. Social behaviors like hugging, huddling, and allo -grooming activate a wide variety of peripheral sensory neurons, but only a subset govern the pleasant nature of touch. Here, we focus on Mas-related G-protein coupled receptor B4 (MrgprB4) -positive sensory neurons in mice, as they project exclusively to the hairy skin (areas predominantly involved in social touch behaviors like allo-grooming), activate an affective touch pathway in the central nervous system, and share many functional and anatomical features with theorized affective touch neurons in humans.
We assessed the effects of optogenetic activation and genetic ablation of these MrgprB4+ neurons on stress- and reward-related behaviors in mice. Using transdermal optogenetics in a novel place preference paradigm, we found that activation of MrgprB4+ neurons promotes conditioned place preference, suggesting that activation of these neurons is rewarding. We also found that after 3 days of variable stress, mice with MrgprB4+ neurons ablated spent less time grooming in the sucrose splash test, indicating decreased self-care behavior, and had increased immobile time in the forced swim test, indicating increased helplessness in response to an aversive stimulus, relative to controls. These data suggest that MrgprB4 neurons are required for promoting resilience to stress.
Overall, our results indicate that activation of MrgprB4+ neurons is rewarding, and ablation of the same population increases stress susceptibility. These results further our understanding of the relationship between the peripheral nervous system and reward and stress, and could provide new therapeutic targets for treatment of mood disorders. We are currently testing whether specific activation of these neurons can rescue or prevent a stress-induced phenotype.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

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Title: Adaptive versus maladaptive forms of regret after chronic social stress

Authors: R. DURAND-DE CUTTOLI[1], F. MARTÍNEZ-RIVERA[1], L. LI[1], A. MINIER-TORIBIO[1], F. CATHOMAS[1], L. HOLT[1], F. YASMIN[1], S. O. ELHASSA[1], J. F. SHAIKH[1], S. AHMED[1], S. J. RUSSO[1], E. J. NESTLER[1,2], ***B. M. SWEIS**[1,2];
[1]Neurosci., [2]Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Regret describes the phenomenon in which an individual recognizes that an alternative action could have led to a better outcome. The neurobiology of regret in mood disorders such as depression, and whether or not regret represents an adaptive or maladaptive process, remain poorly understood. By characterizing mice exposed to chronic social defeat stress (CSDS) on a novel neuroeconomic decision-making paradigm termed "Restaurant Row" (RRow), we demonstrate fundamentally distinct forms of regret between stress-resilient (RES) versus stress-susceptible (SUS) phenotypes, and establish a region-specific role for CREB, a key transcription factor implicated in chronic stress action. We subjected C57BL/6J male mice to CSDS and identified SUS and RES mice based on a rapid social interaction screen. We then characterized SUS, RES, and non-stressed control (CON) mice longitudinally on RRow. Mice have a limited time period each day to forage for their sole source of food by navigating a maze with four uniquely flavored and contextualized feeding sites, or "restaurants." Each restaurant has a separate offer zone (OZ) and wait zone (WZ). Upon entry into the OZ, a tone sounds whose pitch indicates how long of a delay mice will have to wait in a cued countdown should they choose to enter the WZ. We found that SUS mice were uniquely sensitive to regret type I: missed opportunities when rejecting high-value offers followed by encountering low-value offers. These scenarios capture risky decisions with poor outcomes to which neither RES nor CON mice were sensitive. Conversely, RES mice were more sensitive to regret type II: placing more weight on change-of-mind quit decisions in the WZ when correcting previous mistakes that followed accepting low-value offers in the OZ. SUS mice lost sensitivity to regret type II. Furthermore, RES mice were more sensitive to valuing past investments in the form of time already waited, or sunk costs, during these change-of-mind decisions. Overexpressing a dominant-negative form of CREB in the medial prefrontal cortex versus nucleus accumbens, a molecular manipulation known to promote SUS or RES respectively, differentially perturbed these distinct forms of regret. These data reveal new insights into how adaptive versus maladaptive stress responses are related to distinct forms of counterfactual thinking. The study provides a novel framework for understanding pathological versus healthy forms of regret that hinge on the framing of mistakes. This work can guide not only the development of new diagnostic tools or interventions for depression but can also steer psychotherapy toward unveiling distinct computations through decision narratives.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

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Hope for Depression Research Foundation

Title: Expression of the Astrocyte-Specific Extracellular Matrix Gene Htra1 Regulates Susceptibility to Stress in a Sex-Specific Manner

Authors: *E. M. PARISE[1], T. GYLES[1], O. K. SIAL[2], A. GODINO[1], C. J. BROWNE[1], L. F. PARISE[1], A. TORRES-BERRÍO[1], M. SALERY[1], R. DURAND-DE CUTTOLI[1], L. HOLT[1], Y. VAN DER ZEE[1], Z. S. LORSCH[1], F. CATHOMAS[1], J. B. GARON[1], C. TEAGUE[1], O. ISSLER[1], P. J. HAMILTON[3], C. A. BOLANOS-GUZMAN[2], S. J. RUSSO[1], E. J. NESTLER[1];
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Abstract: While the underlying pathophysiology of major depressive disorder (MDD) is poorly understood, convergent evidence from preclinical and clinical research supports the notion that MDD is related to impaired structural and synaptic plasticity in key limbic regions. The extracellular matrix (ECM) of the brain represents a novel domain for study as it not only provides structural support, but also is intimately involved in regulating synaptic plasticity and remodeling. We analyzed transcriptional profiles of ECM-related genes from the nucleus accumbens (NAc) in postmortem brain tissue of humans with MDD as well as in mice exhibiting a depression-like behavioral abnormalities after exposure to chronic variable stress (CVS). We identified *Htra1*, an astrocyte-enriched secreted serine protease, as being significantly down-regulated in the NAc of males and up-regulated in females across both species. We found that selective manipulation of the *Htra1* gene in astrocytes within the mouse NAc bidirectionally controls susceptibility to stress in a sex-specific manner. Furthermore, direct manipulation of *Htra1* in astrocytes of the NAc, in conjunction with sub-threshold stress, influences medium spiny neuronal signaling. Our findings reveal a pivotal role of astroglia as well as the brain's ECM in mediating stress vulnerability that is impacted in a sex-specific manner and set the stage for novel therapeutic approaches for MDD.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

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Topic: G.05. Mood Disorders

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Hope for Depression Research Foundation

Title: Characterizing Approach-Avoidance Biases After Chronic Social Defeat Stress

Authors: A. M. MINIER-TORIBIO, F. J. MARTINEZ, S. TOFANI, C. J. BROWNE, L. ROYCHOWDHURY, A. TORRES-BERRIO, E. J. NESTLER;
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Abstract: Under approach-avoidance scenarios, healthy individuals balance their decisions towards the most favorable outcomes. However, individuals with major depressive disorder (MDD) display blunted approach towards rewards and excessive avoidance. Here, we combined the platform-mediated avoidance (PMA) task (Bravo-Rivera et al. 2014) and chronic social defeat stress (CSDS), a well-validated model used to study MDD, to assess the impact of social stress on decision-making under approach-avoidance conflict in mice. Following CSDS, mice were classified as resilient (RES) or susceptible (SUS) based on a rapid social interaction screening test. Next, along with a control group (not receiving CSDS), RES and SUS mice were trained in the PMA task whereby they learn to avoid a tone signaling a footshock by losing access to pressing a lever for a saccharine-water reward. Lever presses and time on platform were recorded as approach and active avoidance learning, respectively. After ten days of acquisition, mice received four days of extinction, where the tones are not contingent with footshocks. While we did not observe significant differences in the acquisition of avoidance ($F_{(2,61)}$=0.2, p=0.86) or approach ($F_{(2,61)}$=1.7, p=0.19) among groups, SUS mice displayed elevated levels of freezing to the tone ($F_{(2,61)}$=4.2, p=0.02). Conversely, during extinction, RES mice showed reduced platform avoidance ($F_{(2,61)}$=3.1, p=0.05) and increased lever pressing ($F_{(2, 61)}$=6.5, p=0.003), suggesting facilitation of extinction learning. In contrast, SUS mice exhibited elevated avoidance and blunted lever pressing. Together, our results indicate that RES mice bias their behavior towards approach when contingencies change (i.e., extinction), whereas SUS mice bias their behavior towards avoidance. Ongoing experiments combining whole brain-wide mapping of neural activity and cell-type-specific chemogenetics aim to reveal the brain regions and cell types that signal these behavioral biases in SUS or RES phenotypes. This work provides a neurobehavioral profile of maladaptive decision-making after social stress, revealing novel neurobiological targets to treat MDD and other stress-related syndromes.

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Poster

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Topic: G.05. Mood Disorders

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Title: FEDORA Long Noncoding RNA is a Cell-Type- and Sex-Specific Regulator of Mood

Authors: *O. ISSLER[1], Y. Y. VAN DER ZEE[1], S. XIA[2], A. K. ZINSMAIER[2], A. RAMAKRISHNAN[1], C. TAN[3], W. LI[3], M. SALERY[1], C. BROWNE[1], R. FUTAMURA[1], B. LABONTE[1], J. L. DUPREE[4], C. A. TAMMINGA[3], Y. DONG[2], J. MURROUGH[1], L. SHEN[1], E. J. NESTLER[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]UT Southwestern, Dallas, TX; [4]Virginia Commonwealth Univ., Richmond, VA

Abstract: Major depressive disorder, the leading cause of disability worldwide, strikes women twice as often as men, yet the molecular mechanisms contributing to this sex difference are poorly understood. There is an urgent need for novel sex-specific molecular targets, which can aid the development of new diagnostics and therapeutics for depression. To gain insight into molecular processes associated with sex differences in depression, we explored the regulation of long noncoding RNAs (lncRNAs), a class of regulatory transcripts, in our postmortem brain RNA-sequencing dataset from depressed subjects compared to healthy controls. We found a robust baseline sex difference in lncRNA expression patterns across multiple brain regions in healthy controls, which was profoundly reverted in depressed subjects. Here we highlight one such lncRNA, which is expressed in lower levels in healthy women compared to men but is upregulated in depressed women only in multiple brain regions. Therefore, we named this lncRNA FEDORA (FEmale DepressiOn lncRnA). FEDORA arose in the primate lineage and is expressed primarily in oligodendrocytes and to a lower extent in neurons. To test if FEDORA has a sex-specific causal role in depression, we utilized a cell-type-specific viral approach to express it in the prefrontal cortex (PFC) of mice of both sexes. We found that expressing FEDORA exclusively in neurons promoted anxiety- and depression-like behaviors in females only, which mirrored the human sex-specific phenotype. These behavioral changes were associated with transcriptional changes that resemble the sex-specific transcriptional signature of chronic stress and were associated with changes in PFC pyramidal neuron electrophysiological properties. Expression of FEDORA in oligodendrocytes again had a female-specific effect on motivational behavior, which was associated with decreased myelin thickness and altered gene expression. Interestingly, we found that expressing FEDORA in oligodendrocytes had opposing effects on the transcriptome compared to its expression in neurons. Finally, we found that circulating FEDORA levels are elevated in depressed women only and that these levels are associated with response to the rapidly-acting antidepressant ketamine. Together, these findings offer further evidence that lncRNAs play key roles in shaping the sex-specific landscape of the brain and contribute to sex differences in depression. Our studies of FEDORA and other lncRNAs may lead to the identification of novel targets for the diagnosis and treatment of depression.

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Poster

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Title: Role of Histone 3.3 Lysine 27 Methylation and SUZ-12 in Conferring Enduring Stress Susceptibility

Authors: *A. TORRES-BERRIO[1], A. RAMAKRISHNAN[1], A. MINIER-TORIBIO[1], E. M. PARISE[1], F. J. MARTINEZ-RIVERA[1], C. J. BROWNE[1], O. ISSLER[1], Y. Y. VAN DER ZEE[1], O. SIAL[1], B. A. GARCIA[2], K. HELIN[3], S. SIDOLI[4], L. SHEN[5], E. J. NESTLER[1];
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Abstract: Depression is a prevalent psychiatric disorder characterized by symptoms such as feelings of sadness, lack of interest or pleasure, and suicidal ideation. Many of these symptoms can last a lifetime and remain even after several courses of antidepressant treatments. Vulnerability to depression is associated with long-lasting changes in the transcriptional signatures of the nucleus accumbens (NAc), a brain region involved in reward and mood regulation, however, the molecular mechanisms underlying these alterations are not fully understood. Here, we characterized the enduring changes in histone modifications in the NAc of mice exposed to chronic social defeat stress (CSDS), a validated model for the study of depression-like behaviors that separate mouse populations into susceptible (SUS) and resilient (RES) based on a social interaction test (SIT), which is highly predictive of numerous other behavioral abnormalities. Tissue from the NAc of control (CON), SUS, and RES mice was collected either 24 hr or 4 weeks after the SIT and processed for histone profiling via mass spectrometry. In parallel, we mapped the genome-wide enrichment of the most changed histone modifications using Cleavage Under Targets & Release Using Nuclease (CUT&RUN). We found that CSDS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3—the predominant form of H3 present in adult brain neurons. Specifically, we observed an increase in the abundance of H3.3K27me1 (which preliminary data suggest is selective for D1-type medium spiny neurons) and a decrease in the abundance of H3.3K27me2 in the NAc of SUS mice. Genomic distribution shows that H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, suggesting its crucial role in determining stress-induced transcriptional profiles. In contrast, H3.3K27me2 is weakly deposited across intergenic regions. Changes in H3.3K27me1 and H3.3K27me2 are associated with increased expression of SUZ-12, a protein that controls H3K27 methylation in cultured cells by guiding the polycomb repressive complex 2 to precise genomic sites. We are currently manipulating SUZ-12 expression, and several mutant forms of the protein, in NAc in a cell-type-specific manner to assess their impact on H3.3K27 methylation and on CSDS-induced persistent behavioral alterations. Together, our results suggest that H3.3K27me1 and H3.3K27me2 are important chromatin “scars”. Understanding the molecular basis of these adaptations, including a possible role for SUZ-12, and identifying the genomic regions affected will shed new light on persisting forms of stress-induced pathology.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P707.06

Topic: G.05. Mood Disorders

Support: NIH P50MH096890
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Hope for Depression Research Foundation

Title: Persistent transmission of paternal stress phenotypes to offspring are associated with brain transcriptomic alterations

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Abstract: Depression risk has long been known to be highly influenced by both genetic and environmental factors. More recently, it has been proposed that epigenetic mechanisms may also contribute, representing a third basis of risk. Previous studies on intergenerational trauma in rodents from our lab have shown that resilient and susceptible fathers exposed to chronic social defeat stress (CSDS) have different patterns of behavioral transmission and transcriptional changes in sperm. However, no studies to date have examined the persistent transmission of stress phenotypes to multiple litters and how these patterns may differ between resilient and susceptible lineages. To study this, male mice were exposed to 10 days of CSDS and subjected to social interaction testing to assess paternal phenotype. Males identified as resilient or susceptible to CSDS, as well as control F0 males, were allowed to mate 30 days after the stress. After F1 litter 1 was born, the same paternal paired were mated again to produce F1 litter 2. We found that while both resilient and susceptible fathers persistently transmitted altered stress phenotypes to female F1 offspring, only susceptible fathers persistently transmitted altered stress phenotypes to male offspring. To better understand how the brain transcriptome is altered by both paternal exposure to CSDS and offspring stress exposure we conducted RNA-sequencing of the prefrontal cortex and nucleus accumbens. We found a number of distinct transcriptomic profiles in resilient and susceptible lineages. Taken together, these studies advance our understanding of intergenerational epigenetic transmission of behavioral experience.

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Poster

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Topic: G.05. Mood Disorders

Support: Brain and Behavior Research Foundation
JPB
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Title: Neuron-glia interactions regulate the onset of the antidepressant response

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Abstract: Commonly prescribed antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) take weeks to achieve therapeutic benefits. The underlying mechanisms of why antidepressants take so long to reverse depressed mood are not understood. Using a single cell sequencing approach, we analyzed gene expression changes in mice subjected to stress-induced depression and determined their temporal response to antidepressant treatment in the cerebral cortex. We discovered that both glial and neuronal cell populations elicited gene expression changes in response to stress, and that these changes are reversed upon treatment with fluoxetine (Prozac), a widely prescribed selective serotonin reuptake inhibitor (SSRI). We reproduced the molecular signaling events regulated by fluoxetine in a cortical culture system and reveal that these signaling events are serotonin-dependent and require reciprocal neuron-glia communication. We demonstrate that chronic treatment with extracellular serotonin regulates temporal and activation of consequent FGF2 and BDNF signaling and show that autoregulation and cross-regulation between the two pathways are essential for the response. Mainly, FGF2 signaling directly regulates *Bdnf* synthesis in a neuron-glia dependent manner, which upon activation of BDNF-TrkB signaling contributes to long-term neuronal adaptations, through the expression of neuronal remodeling genes such as *S100a10*, eventually leading to improved mood. Thus, we show evidence that glial cells work in concert with neurons in a serotonin-dependent manner to facilitate response onset, shaping the subsequent neuronal response. Our studies provide molecular insight into the early phase of the antidepressant response, highlighting a fundamental role for neuron-glia reciprocal signaling, thus providing a novel avenue to mitigate delayed onset of antidepressant therapies.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

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Topic: G.05. Mood Disorders

Support: NCCR SYNAPSY (The synaptic bases of mental diseases)
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Title: Role of adult hippocampal neurogenesis in the antidepressant effects of lactate

Authors: *A. CARRARD[1], F. CASSÉ[1], C. CARRON[1], S. BURLET-GODINOT[1], N. TONI[1], P. J. MAGISTRETTI[2], J.-L. MARTIN[1];
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Abstract: Astrocytes are key players in energy metabolism and glutamate transport. In addition, growing evidence suggests that astrocytes are involved in the pathophysiology and treatment of depression. For instance, SSRIs stimulate lactate release from cortical astrocytes. Recently, we showed that acute lactate administration increased lactate concentration in the hippocampus and reduced immobility in the forced swim test (Carrard et al, Mol Psychiatry 2018). Further investigation of the antidepressant behavioral effects of lactate revealed that chronic administration of lactate improved depressive-like behavior in the corticosterone model of depression and in the open-space forced swim test. The antidepressant effects of lactate are associated with changes in the expression of specific target genes among which Hes5 and p11 are involved in adult hippocampal neurogenesis. These findings led us to investigate the role of adult hippocampal neurogenesis in the antidepressant effects of lactate.The involvement of adult hippocampal neurogenesis in the antidepressant effects of lactate was examined in the corticosterone model of depression. We found that chronic peripheral injection of lactate counteracted the decreased neural progenitor proliferation and survival induced by corticosterone treatment (Carrard et al., Mol Psychiatry 2021). In contrast, chronic administration of pyruvate did not produce antidepressant-like effects and did not prevent the inhibition of neural progenitor proliferation and survival induced by chronic corticosterone injection. Importantly, depletion of adult hippocampal neurogenesis by administration of the antimitotic drug temozolomide suppressed the antidepressant-like effects of lactate on behavioral despair and anhedonia in animals chronically treated with corticosterone.*In vitro* studies on hippocampal stem cell cultures revealed that corticosterone decreased cell proliferation and increased ROS production. Consistent with our *in vivo* observations, lactate but not pyruvate suppressed the effect of corticosterone on ROS production and partially counteracted the effect of corticosterone on stem cell proliferation. Similarly to lactate, NADH prevented ROS production elicited by corticosterone and partially reversed the inhibition of stem cell proliferation induced by corticosterone. Therefore, our data suggest that conversion of lactate to pyruvate with the concomitant production of NADH is necessary for the neurogenic and antidepressant effects of lactate. Collectively, these data emphasize the importance of adult hippocampal neurogenesis in the antidepressant effects of lactate.

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Poster

P707. Neural Mechanisms of Relevance to Stress and Depression

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Program #/Poster #: P707.09

Topic: G.05. Mood Disorders

Support: NARSAD Young Investigator Award (GEH)

Title: Effects of Pro- and Anti-Inflammatory Microglial Activation on Behavior in Female Mice

Authors: *M. TSYGLAKOVA, E. H. HURST, N. L. STOREY, J. R. RAINVILLE, G. E. HODES; Virginia Tech., Blacksburg, VA

Abstract: Depression and anxiety are common and debilitating mood disorders, that are more prevalent in females than males. Stress is a trigger for many mood disorders and has effects on plasticity in the brain's reward circuitry, including nucleus accumbens (NAc). We previously demonstrated that 6 days of variable stress sex specifically regulates glutamatergic pre-synaptic components in the NAc, and induces depression-associated behavior only in female mice.
Microglia become activated in response to injury or stress. Interestingly, in patients with MDD, microglial activation in response to stress has been observed in brain regions associated with MDD, including the reward circuitry. Such region-specific microglia activation suggests a potential microglial involvement in stress susceptibility. To investigate microglia activation and its effects on stress susceptibility, we conducted a series of experiments, combining a variable stress paradigm with pharmacological means of manipulating activation of microglia in female mice. Variable stress consisted of three different stressors: foot shock, restraint tube and tail suspension. Each stressor was administered for one hour, and stressors alternated each day for either 3 or 6 days. In the first experiment, we blocked pro-inflammatory activation of microglia with minocycline administered in the drinking water to female mice, which underwent 6 days of stress. Next, we administered rosiglitazone, PPARs-γ agonist, in the drinking water to promote anti-inflammatory microglia activation in female mice, which underwent 6 days of stress. Lastly, to promote pro-inflammatory microglia activation, i.p. injections of LPS were administered to female mice, followed by three days of stress. To access behavioral effects of pharmacological treatments, we conducted a series of behavioral tests, including novelty suppressed feeding, social interaction, forced swim test and splash test. Our results indicate that each pharmacological treatment had behavior specific effects in female mice. To investigate the effects of pharmacological treatments along with variable stress on microglial population in the NAc of female mice, we used IHC analysis for expression of ionized calcium binding adaptor molecule 1 (Iba1) and CD68 in the NAc. We calculated the area of CD68 inside microglia and the area of microglial cells; and performed skeleton and sholl analysis to access the complexity profile of microglial cells. Our preliminary results indicate that minocycline combined with stress decreased the total area of CD68 inside microglia. Microglial analysis from the brains of mice treated with rosiglitazone and LPS is ongoing.

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Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

Location: Virtual Only

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Program #/Poster #: P718.01

Topic: G.08. Other Psychiatric Disorders

Title: Neural Progenitor Cells derived from Lithium Responsive and Non-responsive Bipolar Disorder Patients Exhibit Differential Neurotoxic Responses to Methamphetamine

Authors: *H. MISHRA[1], **A. MANDYAM**[1], M. MCCARTHY[2];
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Abstract: Bipolar disorder (BD) is a genetically inherited mood disorder that affects around 1-2% of the population. BD is characterized by two states: mania and depression. Lithium is a mood stabilizer commonly used to treat BD, and often controls symptoms. However, 33% of patients do not respond to lithium and psychiatrists must often test different doses of lithium and other drugs to determine an effective treatment. Given that death by suicide is 10-30 times higher in BD patients, determining lithium responsiveness more quickly would aid psychiatrists to treat BD more efficiently. There are no reliable biomarkers for predicting lithium response. In order to discover biomarkers, recent studies have developed a novel biological model for BD by using induced pluripotent stem-cell (iPSC) technology. This study used neural progenitor cells (NPCs) derived from iPSCs from lithium responsive (Li-Rs) and lithium nonresponsive (Li-NRs) BD patients and age-matched control subjects. Methamphetamine is a drug that upregulates the neurotransmitter dopamine and produces cell death at high concentrations. A similar upregulation of dopamine is observed in the manic phase of BD, therefore, we used methamphetamine to model neuronal damage associated with mania and determine whether cell death varied between Li-R, Li-NR and control NPCs. NPCs from each group were incubated with methamphetamine (1 mM) or saline for 24 hours. Afterwards, digital images were collected under standardized conditions using a brightfield stereomicroscope. NPC counts were quantified with ImageJ in a blinded fashion. Analysis showed that the number of NPCs from control subjects and Li-NR was significantly reduced after exposure to methamphetamine ($p<0.05$). However, the number of NPCs from Li-R did not differ between saline and methamphetamine conditions ($p>0.05$), suggesting that Li-R NPCs were resistant to methamphetamine-induced cell death. Therefore, our study reveals a difference in cell death in the context of increased dopamine induced by methamphetamine, a model for mania in NPCs from Li-R and Li-NR BD patients. Understanding the mechanisms underlying reduced cell death by methamphetamine in Li-R NPCs could help identify biomarkers for lithium responsiveness. Pharmacogenomic markers for lithium responsiveness are unavailable and incompletely investigated, therefore the current *in-vitro* system can be further researched to eventually implement a more efficient screening process for identifying lithium responsiveness.

Disclosures: H. Mishra: None. **A. Mandyam:** None. **M. McCarthy:** None.

Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

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Program #/Poster #: P718.02

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant R61MH119291

Title: Relationship between judgment of social interactions in virtual reality and neural responses to self and other pain images in children with disruptive behavior disorders

Authors: J. BRICKMAN[1], R. MCCARTHY[1], G. RODRIGUEZ[1], Z. WOOD[3], K. MILLER[3], D. NEUMANN[2], W. KRONENBERGER[1], T. A. HUMMER[1];
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Abstract: Virtual reality (VR) technology has potential for clinical use in the assessment and treatment of children with disruptive behavior disorders (DBD). Previous research indicates that children with DBD experience deficits in empathy and social perspective taking that lead to attributing hostile motivations to others' behavior. In the brain, children with DBD have shown decreased sensitivity to others' pain. This study investigates whether the neural response to self and other physical pain is related to the attribution of more hostile intentions by virtual characters. Nineteen children (ages 9-12; 14 males, 5 females) with a diagnosed DBD underwent fMRI while viewing blocks of images depicting pain-inducing and non-pain activities. Images were accompanied by instructions to imagine the image happening to oneself (Self Pain) or to a novel VR character (Other Pain). Subsequently, participants were asked to complete a task in a virtual school cafeteria. During this scene, a virtual counterpart interfered with their goal (e.g., by bumping into them). Participants then completed ratings of the counterpart's intentions and the usability of the VR task and headset. On a 1-100 rating scale, participants rated the VR as highly enjoyable (mean=99.2, SD=2.9) and easy to use (mean=90.8, SD = 19.1). Ratings of "meanness" of the virtual counterpart were highly variable across the sample (mean=71.3; SD=36.7). During fMRI, participants had strong responses to both Self and Other pain in visual and emotional regions. Higher meanness ratings of the virtual counterpart were associated with greater activation in response to Self Pain in several clusters in the anterior cingulate cortex ($p<.01$, $k>1000$ voxels). However, no such relationship was present in the Other Pain condition. Additional fMRI and VR analysis is ongoing. These results indicate that, in children with DBD, neural sensitivity to their own imagined physical pain is associated with a greater likelihood to infer that others are inflicting intentional social pain. Further, combining VR and fMRI methods holds promise for understanding the neural circuitry underlying social-cognitive and behavioral deficits. The next avenue in this ongoing research aims to determine whether experiencing VR scenes from the counterpart's point of view can improve social perspective-taking abilities in children with DBD.

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Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

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Topic: G.08. Other Psychiatric Disorders

Support: NIH NINDS BRAIN Initiative via contract UH3NS100549
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Title: Effects of deep brain stimulation treatment for refractory obsessive-compulsive disorder on ventral striatal field potentials

Authors: *A. S. WAITE[1,2], N. PROVENZA[1,2], Y. FAN[1], E. DASTIN-VAN RIJN[1,2], W. K. GOODMAN[3], S. A. SHETH[3], D. BORTON[1,2,4];
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Abstract: About 10-20% of patients with obsessive-compulsive disorder (OCD) have treatment refractory illness. For these patients, deep brain stimulation (DBS) therapy is a viable treatment option. The current DBS therapy framework is primarily open-loop, in which the clinician episodically titrates stimulation parameters based on behavioral responses. This limits titration to only being available in the clinic, whereas a quantitative measure would enable titration to occur continuously. Investigation of the precise effects of DBS on neural oscillatory activity during DBS may yield insight into control signals (e.g. neural signatures of therapeutic effectiveness or adverse effects) and inform a closed-loop neuromodulation framework. Here, we identify trends in relative power for specified frequency bands as a result of changes to DBS delivery parameters in patients with refractory OCD, in order to identify frequency bands that could be used in a closed-loop DBS feedback system. Three participants were implanted with the Medtronic Summit RC+S device enabling the delivery of therapeutic stimulation while simultaneously sensing local field potentials (LFPs) on neighboring contacts. In-clinic programming sessions were used to compare changes in LFP data as a result of DBS amplitude changes. Relative power was calculated offline using windowing and a moving average filter throughout the session. Additionally, a single median value was calculated for LFP relative power at each DBS amplitude. Short term amplification of DBS amplitude resulted in suppression of the delta and theta band relative power, as well as enhancement in the gamma band relative power in two participants. Relative power changes between two participants followed similar trends in the previously mentioned frequency bands, however different stimulation amplitudes caused significant changes for each patient. Relative power at different stimulation amplitudes were compared with 0 mA stimulation amplitude acting as a baseline. Delta, theta, and gamma band LFP oscillations displayed significant changes in oscillatory patterns in the short term that could be used as an input for an initial closed-loop DBS paradigm. Future experiments will continue to explore these relative power changes coupled with clinical measures of OCD.

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Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

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Support: NWO VIDI grant to I.W. (864.14.010, 2015/06367/ALW)
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Project grant from the Foundation for OCD research (FFOR) to I.W.

Title: Characterization of the effects of deep-brain stimulation of the mouse internal capsule on brain-wide neural circuits and compulsive behavior

Authors: *B. J. G. VAN DEN BOOM[1,2], A. ELHAZAZ FERNANDEZ[1], P. RASMUSSEN[1], E. H. VAN BEEST[1], A. PARTHASARATHY[1,2], D. DENYS[1,2], I. WILLUHN[1,2];
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Abstract: Deep-brain stimulation (DBS) of the internal capsule (IC) is an effective treatment for otherwise therapy-resistant patients suffering from different psychiatric disorders, most notably for patients with severe obsessive-compulsive disorder (OCD). IC-DBS is thought to recruit cortico-striatal circuits, but understanding of the specific mechanisms of action of DBS is insufficient. Here, we systematically examined the effects of different IC-DBS parameters on brain-wide neuron-population activity in mice (wide-field calcium imaging of GCaMP6 in dorsal cortex). Furthermore, we investigated DBS effects on neural-circuit activity (one-photon calcium imaging using miniaturized fluorescence microscopes) and compulsive-like behavior in SAPAP3 mutant mice ($SAPAP3^{-/-}$), a versatile model for OCD, that, similar to patients, exhibit compulsive behavior (excessive grooming) and functional deficits in cortico-striatal circuits. Single-cell analyses of cortico-striatal circuits revealed distinct differences in spontaneous activity between $SAPAP3^{-/-}$ and wild-type mice, potentially responsible for compulsive grooming. IC-DBS immediately and selectively reduced compulsive grooming in $SAPAP3^{-/-}$ in an intensity-dependent manner and, similar to OCD patients, compulsive behavior reinstated promptly after cessation of DBS. IC-DBS induced instant homogeneous activity patterns in neuron-populations across the dorsal cortex, while single-cell analyses of cortico-striatal circuits revealed complex heterogeneous responses in the spatiotemporal domain. Overall, we identified several functional principles: Increasing current intensity 1) dose-dependently recruited neurons, both by exciting and inhibiting cells, 2) recruited overlapping but not identical ensembles of neurons, and 3) substantially modulated cortico-striatal activity but maintained an excitation/inhibition (E/I) balance. 4) A neuron's recruitment directionality (excited or inhibited) remained consistent across current intensities, and 5) neurons were recruited either briefly upon DBS onset or throughout the DBS period. Our findings demonstrate that IC-DBS reduces excessive grooming in $SAPAP3^{-/-}$, and indicate recruitment of cortico-striatal circuits as a mechanism for it. We identified general functional principles of IC-DBS, which suggest that anti-compulsive effects of IC-DBS may manifest by means of modulating impaired prefrontal cortex activity, while maintaining E/I balance. Although IC-DBS is an effective therapy, understanding its underlying mechanisms has the potential to significantly improve its efficacy.

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Poster

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Program #/Poster #: P718.05

Topic: G.08. Other Psychiatric Disorders

Title: Characterization of the gut microbiota among Veterans with unique military-related exposures and high prevalence of chronic health conditions: A United States-Veteran Microbiome Project (US-VMP) Study

Authors: *L. A. BRENNER[1,2], **C. E. STAMPER**[1,2], M. A. STANISLAWSKI[3], K. A. STEARNS-YODER[1,2], A. J. HOISINGTON[4], D. P. BROSTOW[1,2], J. E. FORSTER[1,2], T. T. POSTOLACHE[5], C. A. LOWRY[6];
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Abstract: The gut microbiome is impacted by environmental exposures and has been implicated in many health conditions. United States (US) military Veterans are a unique population in that their military-related exposures can have consequences for both physical and mental health. Nevertheless, the gut microbiome of this population has been understudied. In this study, we describe the exposures, health conditions, and medication use of Veterans in the US-Veteran Microbiome Project (US-VMP), and examine the associations between these characteristics and the gut microbiota. This cohort included 331 US Veterans seeking care in the Veterans Health Administration that were 83% male with an average age of 47.6 ± 13.4 years. The cohort displayed a high prevalence of posttraumatic stress disorder (49.8%), traumatic brain injuries (76.1%), multiple chronic diseases, and high use of prescription medications (74.9%). We report significant associations between the gut microbiota composition and gastroenteritis, peripheral vascular disease (PVD), bipolar disorders, beta-blockers, serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressants, diabetes medications, opioids, and proton pump inhibitors. Many of the Veteran characteristics examined were also associated with shifts in specific taxa. We also found that PVD and cardiovascular disease (CVD) were associated with lower gut microbiota α-diversity, while vitamin use was associated with higher α-diversity. Our study contributes novel insights into how the unique exposures of Veterans correlate with the gut microbiome and, in line with previous findings with other population-level studies of the microbiome, confirms that medication use has important effects that should be considered in studies of the human gut microbiome.

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Poster

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Support: NIH Grant: AA026421 (RS)
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Title: Effects of age and sex on behavioral measures of sensation/novelty seeking in rats

Authors: *K. ISHIWARI, M. C. TURK, H. M. BOOL, R.-Y. SHEN, S. HAJ-DAHMANE, J. B. RICHARDS;
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Abstract: Sensation/novelty seeking (SNS) is associated with elevated risk for drug abuse, especially in adolescents and young adults. In humans, SNS peaks in mid- to late adolescence and subsequently declines into adulthood and is generally higher in men than in women. However, relatively few studies have examined age- and sex-related differences in SNS in rodents, and such studies, using various behavioral paradigms, have yielded mixed findings. The present study examined the effects of age and sex on two behavioral measures of SNS in rats, locomotor response to novelty and operant responding for a sensory reinforcer, which have previously shown to measure overlapping but different aspects of SNS. Male and female Sprague Dawley rats were tested in the two behavioral tasks in sequence, starting at postnatal day [PND] 32 (periadolescence, male: n=15, female: n=15), PND 72 (young adulthood, male: n=13, female: n=12), or 6 months of age (adulthood, male: n=15, female: n=14). In the locomotor response to novelty test (1 session), rats were tested for locomotor activity for 18 min in novel plastic chambers equipped with an infrared motion-sensor system. In the light reinforcement test, which measured operant responding for a light stimulus, animals were placed in dark operant chambers with poke holes in the left and right walls for 18 min per session. In the initial habituation phase (6 sessions), rats' snout-poke responses had no consequences. During the following light reinforcement phase (6 sessions), snout-pokes into one of the holes, designated active, produced a 5-sec illuminance of the lights in the ceiling and the back wall of the chamber according to a variable-interval 1 min schedule of reinforcement, while pokes into the other inactive hole had no consequences. Contrary to our expectations, the results of the locomotor response to novelty test found no significant differences in the total distance traveled among the three age groups or between the sexes. However, the results of the light reinforcement test showed that rats' operant responding for light was influenced by both sex and age. Females made more responses for light than males overall, while no significant effect of sex was found on preference for light (active - inactive responses). In addition, in both sexes, both the number of active responses and preference for light peaked in young adulthood and declined in adulthood, although this age-related change reached statistical significance in males only. Thus, our results indicate that, in rats, aspects of SNS measured by operant responding for purely sensory stimuli peak in young adulthood and decline in adulthood, while this decline may be slower in females.

Disclosures: K. Ishiwari: None. **M.C. Turk:** None. **H.M. Bool:** None. **R. Shen:** None. **S. Haj-Dahmane:** None. **J.B. Richards:** None.

Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P718.07

Topic: H.03. Decision Making

Title: Electrophysiological Correlates of BIS/BAS: A Systematic Review

Authors: *M. L. DARWIN, D. B. DAVALOS;
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Abstract: The Behavioral Inhibition System/Behavioral Activation System scale (BIS/BAS scale; Carver & White, 1994) is a self-report measure of personality that has evolved into a widely-used assessment tool extending over various domains of neurobehavioral research. The BIS and BAS characterize individual differences in threat and reward-mediated behavioral responses to environmental cues, respectively. As the literature currently stands, reports of electroencephalographic (EEG) indices of BIS and BAS in association with the BIS/BAS scale are mixed. EEG indices appear to differ depending on a number of methodological factors and are periodically inconsistent within similar study designs. The wide-spanning methodological incongruences across studies that seek to relate self-reported levels of BIS and BAS with EEG outcomes presents a challenge in interpreting results on a study by study basis. The importance of investigating the electrophysiological correlates of the BIS/BAS scale lies in the need for a standardized, empirically-supported methodology that elicits a strong relation between self-report, electrophysiological, and behavioral manipulations, and the need to further determine the ability of the scale to adequately predict behavioral outcomes in differing situational contexts. The current systematic review provides a report of the assorted findings throughout the literature regarding scores on the BIS/BAS scale and related EEG correlates. Results from twenty empirical studies are included in this review. Measuring the EEG correlates of BIS may be most practical when either investigating the interaction between perceived threat, arousal, and negative stimuli, or the subsystem's sensitivity to the detection of behavioral outcomes that are incongruent with what was expected. High BAS is consistently predicative of higher alpha activity in the absence of a behavioral task. Within a task-based design, measurement may be most practical when aiming to bridge EEG indices of BAS with situational factors that allow for positive reinforcement of behavioral outcomes and within the context of positive emotional stimuli. Further discussion arranges the findings to best determine the behavioral conditions that are associated with each electrophysiological correlate and provides recommendations for subsequent uses of the BIS/BAS scale in light of these conclusions.

Disclosures: M.L. Darwin: None. **D.B. Davalos:** None.

Poster

P718. Preclinical Models, Human Studies, and Therapeutic Approaches

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P718.08

Topic: G.08. Other Psychiatric Disorders

Support: BRAINS'LABORATORY S.A.S.
NIMES UNIVERSITY

Title: From breath to the brain: biomolecules detection

Authors: *V. COMPAN[1], A. HACHACHE[2], S. CHOQUART[3];
[1]BRAINS'LABORATORY, NIMES UNIVERSITY, Nimes, France; [2]NIMES UNIVERSITY, NIMES, France; [3]BRAINS'LABORATORY, NIMES, France

Abstract: Integrating nanobiology into wearables could introduce new pathways for extending actual noninvasive and nonintrusive monitoring of physiological states, treatment effects and pathogens or toxins impact. However, sophisticated procedures with the use of large equipment, and different technologies, generally make difficult real time detection of these “nano-agents” of air in freely moving individuals. Here, we describe our e-connected lightweight wearable device, that detects at room and outside temperature in breath of humans, SARS-CoV-2 within 3 min, requiring no user intervention other than turn on the device and breath. Series of biomarkers are currently tested and related to the brain.

Disclosures: V. Compan: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BRAINS'LABORATORY S.A.S. **A. Hachache:** F. Consulting Fees (e.g., advisory boards); BRAINS'LABORATORY S.A.S. **S. Choquart:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BRAINS'LABORATORY S.A.S..

Poster

P730. Neural Mechanisms of Addictive Drugs I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant
CIHR Grant

Title: A taste for blood: chemosensing in the oral cavity-choroid plexus circuit regulates the addictive properties of systemic nicotine

Authors: *S. CALIGIURI[1], P. J. KENNY[2];
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Abstract: The gustatory system guides ingestive behaviors to ensure survival, ie: reinforcing intake of sweet, salty, & umami flavors, which represent carbohydrates, electrolytes, & protein respectively, while avoiding strongly sour & bitter tastes which through evolution often represented spoiled or poisonous compounds. Intriguingly, the majority of addictive drugs are classified as bitter tasting alkaloids. The relevance of the gustatory system to substance use is supported by the recent discovery of taste receptor expression outside the oral cavity; this suggests that the taste receptors may respond to circulating drugs consumed via different routes. As such, the gustatory system may not only apply to ingestive behaviors, but general consummatory behaviors which include substances of abuse. We propose that the bitter taste receptor chemosensory network facilitates the satiety/aversion response to alkaloid drugs like nicotine, as part of the evolutionary defense mechanism. Here, we provide evidence that the bitter taste receptors (T2Rs) are targets of alkaloid drugs of abuse; when the G-protein to which the bitter taste receptors (T2Rs) couple, α-gustducin (Gnat3), is knocked down via CRISPR in STC-1 cells, intracellular calcium was lower versus eGFP knockdown cells ($p<0.05$). In mice (n=120), pharmacological antagonism of T2Rs, global KO or CRISPR mediated knockdown of Gnat3, the valence of an otherwise aversive dose of nicotine became preferable in a conditioned place aversion protocol (+12%), enhanced oral nicotine intake (>2-fold), & elevated intravenous self-administration of nicotine (>2-fold). The location of the T2Rs that may regulate this phenotype is the oral cavity-ventricular connection. AAVs injected into the 4th ventricle of the brain resulted in robust expression in the oral cavity; likewise, PRV tracing indicated a connection of the tongue to the nearby nucleus of the tractus solitarius (NTS). This suggests direct communication & connection of the oral cavity to this hindbrain region known to regulate nicotine aversion/satiety. When Gnat3 was knocked down in this specific oral-4th ventricle connection using CRISPR technology (n=40), the increase in nicotine taking behaviors was again observed. These behavioral findings were accompanied by reduced neuronal recruitment in bitter responsive cells of the NTS as well as altered cholinergic subunit expression in the choroid plexus of the 4th ventricle. These data highlight a new chemosensory system consisting of the T2Rs that may modulate nicotine taking behavior & moreover that the gustatory system may not only guide ingestive behavior, but consumption of substances via different routes.

Disclosures: S. Caligiuri: None. **P.J. Kenny:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA039658 to CDF

Title: Defining the role of purinergic signaling in the medial habenula

Authors: *Y.-C. CHEN[1], D. J. RINDNER[2], T. S. HNASKO[3], G. LUR[4], C. D. FOWLER[5]; [1]Neurobio. and Behavior, Univ. Of California, Irvine, Irvine, CA; [2]Neurobio. and Behavior, Univ. of California, Irvine, CA; [3]Neurosciences, Univ. of California San Diego, La Jolla, CA; [4]Neurobio. and

Behavior, Univ. of California, Irvine, Irvine, CA; [5]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Tobacco smoking is one of leading causes of preventable death worldwide, and nicotine is considered to be the primary reinforcer of tobacco dependence. In these studies, we sought to assess the role of purinergic signaling on neuronal activity in the medial habenula. Brain sections from male and female wildtype mice were sectioned, and neurons in the medial habenula were examined with patch clamp electrophysiology. Initial studies characterized the baseline firing rates and the effects of a receptor agonist on cholinergic habenular neurons. Next, since the medial habenula has been highly implicated in mediating symptomology associated with nicotine withdrawal, we then examined the effects of purinergic receptor activation on neuronal firing during a state of nicotine withdrawal in both sexes. We found that purinergic signaling mediates neuronal activity of the medial habenula, with differential effects occurring during nicotine withdrawal. Together, these data contribute to our understanding of the factors mitigating withdrawal effects that may underlie the nicotine dependence state.
This work was supported by funding from the NIH National Institute on Drug Abuse (DP1 DA039658 to CDF).

Disclosures: Y. Chen: None. **D.J. Rindner:** None. **T.S. Hnasko:** None. **G. Lur:** None. **C.D. Fowler:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.03

Topic: G.09. Drugs of Abuse and Addiction

Support: DA039253
DA051450

Title: Intrinsic excitability of indirect pathway spiny projection neurons in the dorsomedial striatum is increased at early and decreased at protracted abstinence from repeated methamphetamine administration

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Abstract: Methamphetamine (meth) is a potent psychostimulant and the number of persons suffering from a meth use disorder is increasing in the US (NSDUH 2018; Winkelman *et al., JAMA Netw Open* 1:e183758). The dorsal striatum is an important component of the basal ganglia that is predominantly composed of GABAergic direct pathway spiny projection neurons (dSPNs) which express D1 dopamine receptors and indirect pathway spiny projection neurons (iSPNs) which express D2 dopamine receptors (Gerfen and Surmeier, *Annu Rev Neurosci* 34:441 2011). The dorsomedial striatum (DMS) in particular is associated with goal-directed behavior; optogenetic stimulation of dSPNs in this region is reinforcing whereas optogenetic stimulation of iSPNs is aversive (Kravitz *et al., Nat Neuro* 15:816 2012). In a self-administration model both D1 and D2 receptor antagonism attenuate meth-seeking behavior after 21 days of abstinence (Caprioli et. al, *J Neurosci* 37:1014 2017) and chemogenetic inhibition of DMS dSPNs

decreases cocaine-seeking in rats exhibiting a 'high risk' phenotype (Yager *et al.*, *Addict Biol* 24:251 2019). These data indicate that the DMS is involved in reinforcement and maladaptive behaviors associated with addiction; however, stimulant-induced dysfunction of DMS SPNs is understudied. To begin to address this knowledge gap mice expressing eGFP and tdTomato under control of the *Drd2* and *Drd1a* receptor regulatory element, respectively, were administered saline or meth (2 mg/kg; i.p.) for 10 consecutive days in their homecage and *ex vivo* brain slices prepared after 1 or 21 days of abstinence; iSPNs and dSPNs were patched in whole-cell configuration and intrinsic excitability assessed by depolarizing current injection. After 1 day of abstinence DMS iSPN intrinsic excitability was increased resulting in more action potentials generated in response to depolarizing current injections whereas after 21 days of abstinence intrinsic excitability was decreased. In contrast to the changes in DMS iSPNs, DMS dSPN intrinsic excitability was unchanged at both abstinence time points. Further study is needed to determine the behavioral consequences associated with the observed changes. Nonetheless, our results indicate that meth-induced DMS striatal dysfunction, with respect to intrinsic excitability, is specific to iSPNs with opposite effects at early *versus* protracted abstinence.

Disclosures: S. Choi: None. **Y. Du:** None. **S.M. Graves:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Program #/Poster #: P730.04

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA CEBRA R21 DA048633
NIDA R21 DA050821

Title: Manipulating brain activity to rescue drug-induced cognitive deficits.

Authors: *M. PRATELLI[1,2], N. C. SPITZER[1,2];
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Abstract: Drugs of abuse share the ability to induce widespread neuroplastic changes upon repeated intake. This affects the functionality of brain circuits, induces behavioral alterations and can lead to addiction. Since drug intake alters neuronal activity, we asked if prolonged drug exposure induces a form of activity-driven neuroplasticity called neurotransmitter switching (NTS). NTS occurs when a group of neurons loses the neurotransmitter it was expressing and gains a new one, and has been shown to affect behavior. We used two drugs known to increase the activity of prelimbic cortex (PrL) glutamatergic neurons upon acute intake: phencyclidine (PCP), a NMDA receptor antagonist, and methamphetamine (METH), a DAT blocker that increases extracellular monoamines. Repeated administration of PCP or METH for 10 or 7 consecutive days respectively, causes ~600 PrL glutamatergic neurons to express the inhibitory transmitter GABA, its synthetic enzyme and its vesicular transporter. These neurons show decreased expression of the vesicular glutamate transporter, indicating that neurotransmitter switching has occurred. We then used an RNA interference strategy to prevent PrL glutamatergic neurons from gaining

GABA upon PCP exposure. This intervention prevented the appearance PCP-induced deficits in the novel object recognition test and spontaneous alternation task, indicating a causal link between NTS and cognitive deficits. Since NTS is driven by changes in neuronal activity, we asked if it can be prevented by counteracting PCP- and METH-induced increases in PrL pyramidal neuron activity. We used a chemogenetic strategy to selectively increase the activity of parvalbumin-positive (PV+) interneurons *during* drug exposure. PV+ neurons can suppress glutamatergic neurons' hyperactivity, as they provide feed-forward inhibition of pyramidal cells. This strategy prevented the appearance of both NTS and drug-induced cognitive deficits. We then tested whether the same strategy can be used *after* drug exposure to reverse the switch and the cognitive deficits. Two days after the end of drug treatment, mice were started on a protocol of daily chemogenetic stimulation for an additional 10 days. Remarkably, this approach reversed both NTS and cognitive deficits in mice previously treated with either PCP or METH. We next tested the effect of clozapine, a pharmaceutical known to block the PCP-induced increase in PrL activity. Treating mice with clozapine for 14 days *after* the end of PCP exposure also reversed both the NTS and cognitive deficits. These results suggest that targeted manipulation of electrical activity can reverse drug-induced cognitive deficits by reversing NTS.

Disclosures: M. Pratelli: None. **N.C. Spitzer:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Program #/Poster #: P730.05

Topic: G.09. Drugs of Abuse and Addiction

Support: DA044468
DA037327
DA054370

Title: Cellular and Molecular adaptations in D2-MSNs of the Nucleus accumbens associated with individual differences in cocaine-seeking behavior.

Authors: *J. PARRILLA-CARRERO[1], M. EID[1], Y. S. CHAO[2], A. THOMAS[1], O. P. CULVER[1], R. CHANDRA[3], M. LOBO[4], T. C. JHOU[1];
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Abstract: Of all individuals who experiment with cocaine, only a fraction subsequently progress toward developing cocaine addiction. Although it is clear that vulnerability to cocaine addiction results from predisposing factors, it remains unclear how these influence cocaine addiction. A major challenge in differentiating these possibilities is our limited knowledge of the cellular/molecular changes associated with individual differences in brain circuitries related to motivated behavior. Using the runway model of cocaine self-administration, here we demonstrated that cocaine seeking varies significantly among rats. To further determine why the motivation to seek cocaine may be much more robust in some individuals than in others, we then evaluated D2 medium spiny neurons (D2-MSNs) excitability in the medial

nucleus accumbens shell (mNACshell) in ex vivo preparations. Notably, we found that low- but not high-seeker rats displayed increased excitability in D2-MSNs, which manifest as a greater basal firing rate, higher glutamatergic synaptic drive, and decreased long-term depression (LTD). Besides, we found that in the mNACshell, low-seeker rats showed greater levels of RhoA activity, whereas high-seeker rats showed lower levels of RhoA activity relative to saline-control rats. Further characterization of this cellular alteration revealed that cell-type-specific up or down-regulation of RhoA activity in NACshell D2-MSNs decreases or increases cocaine-seeking behavior, respectively, by altering D2-MSNs excitability. Altogether, these results identified RhoA as a critical mediator of D2-MSN excitability and suggest that enhanced RhoA signaling in this cell population decreases cocaine-seeking behavior.

Disclosures: J. Parrilla-Carrero: None. **M. Eid:** None. **Y.S. Chao:** None. **A. Thomas:** None. **O.P. Culver:** None. **R. Chandra:** None. **M. Lobo:** None. **T.C. Jhou:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.06

Topic: G.09. Drugs of Abuse and Addiction

Support: Medical research Council: MR/NO2530X/1

Title: The basolateral amygdala influences the activity of dorsolateral striatum medium spiny neurons via direct projections to the nucleus accumbens core

Authors: *A. BELIN-RAUSCENT, B. J. EVERITT, D. J. BELIN;
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Abstract: Although the basolateral amygdala (BLA) does not project directly to the anterior dorsolateral striatum (aDLS), it bidirectionally gates the response of subpopulations of medium spiny neurons (MSNs) in the aDLS to their major glutamatergic input from the cortex. The remote control whereby associative information processed in the amygdala can influence the neural locus of control of habits may be a mechanism by which the amygdala gates the progressive devolution of control over the aDLS during the development of drug seeking habits characteristic of addictive behaviour. Our recent investigations of the neural mechanisms underlying this functional control have shown that, in drug-naive rats, electrical stimulation of the BLA applied 100 to 300 milliseconds before that of the motor cortex 1 (M1) elicits a bidirectional regulation of spike probability of the aDLS MSNs. While the control exerted by the BLA over aDLS MSNs has been shown to depend on a polysynaptic functional network that involves antecedent glutamatergic mechanisms in the core of the nucleus accumbens (AcbC), the nature of the amygdalo-striatal circuit by which this control is mediated has not been defined. Here we used projection-specific expression of channelrhodopsin to investigate the role of the BLA -AcbC pathway in mediating the control by the BLA of aDLS MSNs activity.In anaesthetised rats, optogenetic stimulation of terminals of the AcbC-projecting BLA neurons was combined with extracellular *in vivo* recordings of the activity of the MSNs in the aDLS evoked by electrical stimulation of M1. Photostimulation of the terminals of BLA neurons in the AcbC was sufficient to induce bidirectional modulation of the activity of aDLS MSNs:

aDLS MSNs were shown either to up or down regulate their spike probability following photostimulation of the BLA-AcbC pathway.These data demonstrate that the BLA can exert control over the physiology of the aDLS indirectly through its direct projections to the AcbC. Further experiments will establish whether the AcbC mediates this influence on the aDLS via its connectivity with the ascending dopamine-dependent spiralling circuitry shown to be necessary for the functional recruitment of aDLS dopamine dependent drug seeking habits.

Disclosures: A. Belin-Rauscent: None. **B.J. Everitt:** None. **D.J. Belin:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.07

Topic: G.09. Drugs of Abuse and Addiction

Support: AA020919
DA035958

Title: Effects of catharanthine on the mesolimbic dopamine system

Authors: *B. M. WILLIAMS[1], J. A. SAUNDERS[1], N. D. STEED[1], E. K. BALDWIN[1], S. LEE[1], E. Y. JANG[2], H. R. ARIAS[3], S. C. STEFFENSEN[1];
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Abstract: Ibogaine is one of several indole alkaloids compounds that are found in the *Catharanthus roseus* plant, or commonly known as the Madagascar periwinkle. Ibogaine reduces opioid and alcohol withdrawal symptoms and decreases drug self-administration in both animal and human models. However, ibogaine has also been shown to induce heart arrhythmias and has hallucinogenic properties, which has resulted in ibogaine being classified as a Schedule 1 substance by the DEA in the United States. Catharanthine, an ibogaine analog, could be an alternative pharmacological treatment for addiction without the adverse side effects. The objective of this study was to evaluate the effects of catharanthine on dopamine (DA) transmission in the mesolimbic DA system implicated in drug reward. To accomplish these studies, we used fast scan cyclic voltammetry (FSCV) and microdialysis/HPLC in C57 mice. Superfusion of catharanthine (1-100 µM) inhibited evoked DA release in brain slices from the nucleus accumbens (NAc) of the striatum with an IC_{50} of 30 µM, as measured by voltammetry. Based on our previous studies, we hypothesized that catharanthine acts through inhibiting nicotinic acetylcholine receptors (nAChRs) or voltage-sensitive calcium channels, which we confirmed through testing the effects of dihydro-β-erythroidine hydrobromide (DHBE), an α4β2 nAChR antagonist, mecamylamine, a non-selective nAChR antagonist, α-conotoxin MII, a selective α6-nAChR antagonist, and cadmium, a voltage-gated calcium channel antagonist. Although mecamylamine did block catharanthine-induced inhibition of evoked DA release, the greatest effect was seen with DHBE, suggesting that catharanthine is more selective for α4β2/α4β4 nAChRs. Superfusion of MII and cadmium failed to significantly inhibit

catharanthine activity, suggesting that catharanthine is less selective for α6-nAChRs or voltage-gated calcium channels. Intraperitoneal administration of catharanthine into mice at 10 mg/kg increased basal DA in the NAc, as measured by microdialysis. These findings suggest that catharanthine may be a suitable pharmacological treatment for substance use disorders.

Disclosures: B.M. Williams: None. **J.A. Saunders:** None. **N.D. Steed:** None. **E.K. Baldwin:** None. **S. Lee:** None. **E.Y. Jang:** None. **H.R. Arias:** None. **S.C. Steffensen:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Program #/Poster #: P730.08

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA-IRP, NIH, Z1A-DA000611

Title: Exploring novel therapeutic options for psychostimulant use disorder: an FSCV study on accumbens dopamine dynamics in rats

Authors: *M. HERSEY, A. H. NEWMAN, G. TANDA;
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Abstract: Psychostimulant use disorder (PSUD) is an increasingly prevalent condition with significant medical and public health consequences worldwide. While misuse of illicit and prescribed stimulants is becoming increasingly common, there remains no FDA approved treatments for PSUD. Modafinil (MOD), a pharmaceutical agent currently approved for the treatment of narcolepsy and sleep disorders, has been suggested as a potential PSUD medication. However, in clinical trials its efficacy appears limited to subjects with PSUD diagnosis without comorbid alcohol use disorder. To broaden its efficacy, analogs of MOD with higher affinities for the dopamine transporter (DAT) than the parent compound and varying behavioral profiles have been synthesized as potential therapeutic options for PSUD. Like MOD, some of these novel compounds produce behavioral and neurochemical effects inconsistent with those elicited by typical abused psychostimulants. In this study, we explored the neurochemical underpinnings of psychostimulant actions by employing fast scan cyclic voltammetry (FSCV) for real-time investigation of evoked dopamine release and clearance in the nucleus accumbens shell (NAS) of Sprague Dawley rats. Preliminary FSCV data shows that pretreatments with the MOD-analogs JJC8-088 and JJC8-091 may produce divergent effects on NAS dopamine dynamics elicited by i.v. cocaine administration (0.1, 0.3, and 1.0 mg/kg). The MOD analog JJC8-088, demonstrates behaviors in rodents that resemble those of a typical, cocaine-like DAT inhibitor, and enhanced cocaine-induced increases in evoked dopamine release suggesting an additive effect of these compounds. JJC8-088 pretreatment also produced a modest effect on dopamine clearance. In contrast, the MOD analog JJC8-091, an atypical DAT inhibitor that elicits limited, if any, cocaine-like stimulant effects, produced mild reductions in cocaine-induced stimulation of evoked dopamine release. These findings, showing a reduction in cocaine neurochemical effects by pretreatments with JJC8-091, provide insight into the potential efficacy of atypical DAT inhibitors as therapeutic agents for PSUD. This work was supported by NIDA-IRP/NIH.

Disclosures: M. Hersey: None. **A.H. Newman:** None. **G. Tanda:** None.

Poster

P730. Neural Mechanisms of Addictive Drugs I

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P730.09

Topic: G.09. Drugs of Abuse and Addiction

Support: President's Council of Cornell Women Affinito-Stewart Grant

Title: Cocaine intake and craving is enhanced by presynaptic alpha-synuclein upregulation that regulates synaptic vesicle release onto VTA dopamine neurons.

Authors: J. F. HALE[1], A. E. LANE[2], ***D. LANE**[2];
[1]Pathology, Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA; [2]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: The activity of ventral tegmental area (VTA) dopamine neurons is a balance of excitatory and inhibitory inputs that is disrupted with repeated drug use, causing a shift to increased glutamate activation of these cells. Dopamine neurons receive inputs from a large number of cortical and subcortical structures that control various aspects of motivated behavior including reward, aversion, compulsion, and association to environmental cues. We recently reported that drugs of abuse (both stimulants and opiates) amplify presynaptic alpha-synuclein levels in axon terminals making synaptic contacts with VTA dopamine neurons. Alpha-synuclein expression changes in response to neuronal activity and is highest in brain regions undergoing synaptic plasticity. Consistent with these ideas, we found dynamic shifts in alpha-synuclein levels within VTA axon terminals matching previously reported changes in cocaine mediated glutamate activity in this region. Repeated cocaine administration increased alpha-synuclein immunolabeling in glutamatergic axon terminals in the VTA when cocaine is systemically present. When mice were in withdrawal, alpha-synuclein levels decreased in glutamate, but increased in GABA axon terminals in the VTA. Our rationale is that dynamic expression of alpha-synuclein in specific VTA axon terminals after drug exposure positions it to fine-tune the complex afferent circuitry controlling dopamine activity, making alpha-synuclein a prime mediator for the progressive changes in behavior occurring with chronic drug use. To examine this further *in vitro* and *in vivo* glutamate release and cocaine intake was assessed using viral biosensors. VTA axon terminals with increased alpha-synuclein levels show greater glutamate release than in the absence of alpha-synuclein but only after cocaine treatment. The relationship between alpha-synuclein levels and glutamate release was not observed in vehicle controls. The effects of VTA alpha-synuclein on hedonic stimuli, including cocaine and sweetened condensed milk, showed that deletion of alpha-synuclein significantly decreased intake of both substances. Together the data suggest that cocaine-induced alpha-synuclein upregulation critically modulates motivated behavior by control of afferent input to VTA dopamine neurons.

Disclosures: J.F. Hale: None. **A.E. Lane:** None. **D. Lane:** None.

Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Topic: G.09. Drugs of Abuse and Addiction

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TCU SERC GR 200409
Psi Chi 23728

Title: Blood alcohol concentration, open field activity, and c-Fos expression after oral exposure to 66% alcohol: Pharmacological or sensation-seeking effect?

Authors: *C. HAGEN, S. GUARINO, M. R. PAPINI;
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Abstract: While rodents generally reject high concentrations of alcohol, recent experiments have demonstrated that alcohol at high concentrations can reinforce operant behavior. This suggests that alcohol even at high concentrations has rewarding properties. However, given the relatively small amounts consumed the mechanism underlying this rewarding effect is unclear. To further characterize this understudied phenomenon, Wistar rats were given access to either 66% alcohol or water in their home cages for one hour over the course of several sessions. The measured liquid displacement after alcohol sessions was similar to that after water sessions indicating that rats did not reject the 66% alcohol solution. In addition, exposure to an open field for 5 min after access to 66% alcohol resulted in increased activity relative to activity after access to water. Moreover, this increase was solely concentrated to the periphery of the field, suggesting that any amount of alcohol consumed did not cause motor impairment or anxiolysis, but instead promoted locomotor activity. This effect was also positively correlated with blood alcohol concentration indicating that it was a direct result of alcohol exposure. Finally, c-Fos immunoreactivity after exposure to 66% alcohol vs. water showed increased activation in the anterior cingulate cortex, insular cortex, and nucleus accumbens shell. These results further contextualize research showing that 66% alcohol can reinforce operant licking responses in rats and support the claim that higher concentrations of alcohol can be rewarding. The amounts consumed and the blood alcohol concentrations observed suggest that the reinforcing effect of 66% alcohol is probably more related to sensation seeking than to a pharmacological effect.

Disclosures: C. Hagen: None. **S. Guarino:** None. **M.R. Papini:** None.

Poster

P737. Alcohol Intake and Preference: Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P737.02

Topic: G.09. Drugs of Abuse and Addiction

Support: AA006420
AA026999
AA028549
T32 AA007456
M-AES

Title: Evaluation of endocannabinoid concentrations in alcohol-dependent rats.

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Abstract: Alcohol is one of the most widely used psychoactive drugs worldwide. In the United States alone, alcohol use disorder (AUD) affects 14.1 million adults, and problems associated with AUD cost the US economy several billion dollars annually. Chronic and heavy alcohol consumption affect the reward system function, promoting a dependent state. Several studies have shown alterations of endocannabinoid (eCB) levels across various brain regions as a result of alcohol exposure. The present study examined concentrations of anandamide (AEA), palmitoylethanolamide (PEA), oleoylethanolamide (OEA), 2-arachidonoylglycerol (2-AG), and 1-AG in plasma in animals with a history of alcohol dependence. Male Wistar rats were trained to orally self-administer alcohol (10% w/v) daily in 21 consecutive sessions (30 min/day) and then made dependent via chronic intermittent alcohol vapor exposure (14 h vapor ON/10 h vapor OFF per day). A control nondependent group was kept in the vivarium and exposed to air only for the remainder of the study. At the end of the experiment, the animals were sacrificed at an acute abstinence point (8 h after the vapor turned OFF). Trunk blood was collected, and plasma was analyzed by liquid chromatography-dual mass spectrometry to determine eCB concentrations. The results showed lower levels of 2-AG and 1-AG and higher levels of AEA, PEA, and OEA in dependent rats compared with nondependent rats. These findings demonstrate that alcohol dependence results in alterations of the eCB system and suggest that targeting the eCB system could be beneficial for the treatment of AUD.

Disclosures: F. Di Ottavio: None. **L. Sanchez-Marin:** None. **F.J. Flores-Ramirez:** None. **A. Matzeu:** None. **R. Martin-Fardon:** None.

Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Topic: G.09. Drugs of Abuse and Addiction

Support: 1R01AA024798

Title: FGF2/FGFR1 system in embryonic hypothalamus: Involvement in sexually dimorphic stimulatory effects of prenatal alcohol exposure on peptide-expressing neurons linked to alcohol consumption

Authors: N. YASMIN, G.-Q. CHANG, O. KARATAYEV, A. D. COLLIER, M. FAM, A. ONOICHENCO, N. KHALIZOVA, A. ALBEG, S. CAMPBELL, *S. F. LEIBOWITZ;
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Abstract: Prenatal alcohol exposure (PAE) is known to stimulate alcohol consumption in rat offspring and increase the risk for alcohol use disorder in humans. This phenomenon is believed to involve the stimulatory effect of PAE on neurogenesis and density of neurons in the lateral hypothalamus (LH) expressing orexigenic neuropeptides, including melanin-concentrating hormone (MCH) and orexin, which are known to stimulate alcohol intake. In rats, PAE increases the expression and density of these peptide neurons and alcohol drinking in a sexually dimorphic manner, consistently stronger in female than male offspring. With fibroblast growth factor 2 (FGF2) through its receptor FGFR1 known to stimulate neurogenesis, promote alcohol intake, and have sexually dimorphic properties, we investigated here the involvement of this FGF2/FGFR1 system in mediating this PAE-induced increase in density of these peptide neurons. Using qRT-PCR and RNAscope, we examined MCH-expressing neurons in the LH of female and male postnatal offspring of pregnant rats gavaged with a moderate dose of alcohol (2 g/kg/day) compared to vehicle from embryonic day 10 (E10) to E15 during peak neurogenesis. Our results show that: 1) PAE stimulates mRNA levels of FGF2 and FGFR1 along with MCH, the density of MCH neurons expressing FGF2 or FGFR1 transcripts, and the number of FGF2 or FGFR1 transcripts per MCH neuron; 2) these effects on FGF2 are sexually dimorphic, occurring in females but not males, while those on FGFR1 are similar in females and males; 3) these stimulatory effects of PAE on MCH neurons are mimicked by peripheral injection of FGF2 (80 µg/kg/day) in pregnant rats; 4) more detailed analyses of individual MCH neurons and their intracellular FGF2 and FGFR1 transcripts reveal specific sexually dimorphic changes, with PAE inducing in females but not males a strong, positive correlation between the number of FGF2 and of FGFR1 transcripts and PAE increasing in females but not males their number in the nucleus as well as cytoplasm, with males affected only in the cytoplasm; and 5) further analyses of the PAE-induced increase in density of MCH neurons and their number of FGF2 and FGFR1 transcripts reveal sex differences in their anatomical location, with females showing effects in both the dorsal and ventral areas of the LH while males respond only in the dorsal LH. We conclude that the FGF2/FGFR1 system is involved in mediating the PAE-induced increase in density of MCH neurons in females more than males and the sexually dimorphic nature of this phenomenon is attributed, in part, to sex differences in their ligand-receptor relationship, intracellular distribution of transcripts, and anatomical location of neurons.

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Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Program #/Poster #: P737.04

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Support: F31 AA029292

P50 AA26117
R37 AA17531
R01 AA26551
R21 26455

Title: Sexually dimorphic behavior of Long-Evans rats on a novel task of maladaptive alcohol self-administration

Authors: *H. N. CARLSON, J. L. WEINER;
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Abstract: The progression of recreational drinking to alcohol use disorder is characterized by loss of control over seeking, which involves continued use of alcohol despite a variety of negative consequences. However, due to a paucity of translational models for this aspect of alcohol use disorder, little is known about the circuitry underlying maladaptive alcohol seeking, which precludes the discovery of therapeutic targets. Though alcohol seeking is a common and important metric of animal models, there have been few efforts to parse this construct into more specific facets of motivated behavior. Increased seeking might result from disinhibition, in which the distinction between appropriate and inappropriate behavior is known but overridden, or discrimination failure, in which the distinction between when it is appropriate or inappropriate to drink becomes unclear. The present study proposes a novel maladaptive alcohol self-administration task (MAST), which will be used to assess motivation and inhibitory control across several dimensions of seeking behavior. Furthermore, despite rising rates of alcoholism among women in the human population, translational research endeavors on sex differences in alcohol-related behavior remain sparse. In the present study, we compare cohorts of male and female Long-Evans rats on a novel model of alcohol seeking, the maladaptive alcohol-seeking task (MAST). Two cohorts, one male and one female, (n=8) were brought in at approximately five weeks of age. Behavioral procedures were identical between groups and all phases of training, acquisition, maintenance, and experimentation were performed concurrently on the same days to eliminate external variables. To assess the impact of acute stress on MAST performance, we administered counterbalanced doses of saline (control) and yohimbine (2mg/kg) 30 minutes prior to behavioral testing. We discuss sex differences in daily performance as well as in response to a pharmacological manipulation.

Disclosures: H.N. Carlson: None. **J.L. Weiner:** None.

Poster

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Support: Research supported by a Programme grant from the MRC (MR/NO2530X/1) to BJE and DB
LMP is supported by a Leverhulme Trust Early Career (ECF-2018-713) and Isaac Newton Trust fellowship (18.08(g))

Title: Involvement of the kappa opioid receptor system in the vulnerability to develop compulsive alcohol drinking by the use of alcohol as a coping strategy

Authors: *L. MARTI-PRATS, C. GIULIANO, A. BELIN-RAUSCENT, M. FOUYSSAC, C. VELAZQUEZ-SANCHEZ, X. ZHANG, B. J. EVERITT, D. BELIN;
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Abstract: Only some vulnerable individuals who recreationally drink alcohol eventually lose control over their intake and develop compulsive alcohol seeking and drinking, in that it is maintained despite adverse consequences, a core characteristic of alcohol use disorder (AUD). It has been suggested that the initiation of alcohol use for emotion regulation, or as a coping strategy, plays a determining role in the vulnerability to develop AUD. Indeed, the recent increase in problem drinking in some individuals during the COVID-19 pandemic is further evidence that the use of alcohol as a coping mechanism exacerbates the vulnerability to AUD. However, the psychological and neural basis of this increased vulnerability have not been elucidated. Negative emotional states have been associated with a dysregulation of the dynorphin/kappa opioid receptor (KOR) system. We therefore tested the hypothesis that the KOR system plays a role in the engagement in alcohol drinking as a coping mechanism and the associated increased tendency to persist in drinking alcohol despite negative consequences. Sprague-Dawley rats were exposed to a novel procedure, based on Schedule-Induced Polydipsia (SIP), that enables the identification of individual differences in the reliance on alcohol to cope with distress. In SIP procedures, intermittent food delivery triggers a state of internal distress that some rats learn to cope with by developing adjunctive anxiolytic behaviours, such as excessive water intake. Some rats, referred to as water copers, learned to cope with the distress of the SIP procedure by adjunctively drinking water, as evidenced by a decrease in anxiety and corticosterone levels. In contrast, a subpopulation of rats, referred to as alcohol copers, never acquired adjunctive water drinking; they only developed an adjunctive, anxiolytic, polydipsic response when they had access to alcohol instead of water. While water and alcohol copers did not differ in their overall intake of alcohol, the latter specifically developed compulsivity in that they persisted in drinking alcohol when adulterated with quinine. Furthermore, alcohol intake was decreased only in alcohol copers by systemic administration of the KOR antagonist norbinaltorphimine, suggesting involvement of the dynorphin/KOR system in the use of alcohol to self-medicate distress. These results suggest that the acquisition of alcohol drinking through negative reinforcement-based self-medication is mediated by the dynorphin/KOR system and is a gateway to the development of compulsive drinking in vulnerable individuals.

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Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Title: Neural circuits for low and moderate alcohol responses in Drosophila melanogaster

Authors: S. L. SONG[1], V. SANKAR[1], N. T. SAVORY[1], T. L. RAUFF[2], T. M. A. NGUYEN[2], S. D. POLLACK[2], K. R. KAUN[1], ***K. M. SCAPLEN**[2,1,3];
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Abstract: Drugs of abuse such as alcohol disrupt dopaminergic reward pathways, leading to maladaptive goal-directed behaviors. In both mammals and *Drosophila*, evidence suggests that dopamine also mediates ethanol-induced locomotor activity, however, the underlying neural circuitry remains poorly understood. Using flyGrAM, an automated group activity monitor, we investigated whether distinct populations of dopamine neurons are differentially recruited to support ethanol-induced activity in a dose-dependent manner. We then performed high-content behavior analysis using FlyTracker and Ctrax. We found that both the PAM and PPL1 subsets of dopamine neurons are involved in the ethanol response and have ethanol-dependent modulatory activity. Additionally, we discovered neuronal subsets with dynamic roles in modulating ethanol-induced activity. Specifically, increased dopamine neuronal involvement occurred at higher doses of ethanol, suggesting that more dopamine neurons are recruited at higher doses to counter the sedating effects of ethanol. Overall, this study clarifies our understanding of the dose-dependent activity of specific subsets of dopamine neurons and serves as a starting point for more detailed circuit analyses.

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Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Topic: G.09. Drugs of Abuse and Addiction

Support: R01AA026347

Title: Adolescent binge ethanol-induced dysregulation of histone marks may underlie myelin deficits

Authors: E. R. BROCATO[1], *J. WOLSTENHOLME[2];
[1]Pharmacol. and Toxicology, [2]Virginia Commonwealth Univ., Richmond, VA

Abstract: The prefrontal cortex (PFC) undergoes significant changes during adolescence, and alcohol exposure during this time is particularly damaging. Consuming alcohol, especially in binges, has been shown to negatively impact the adolescent brain, resulting in brain structural changes, decreased myelin, and memory deficits. Previously, we have shown that adolescent mice exposed to binge ethanol had

memory deficits that lasted into adulthood. Gene expression changes in the PFC were measured by microarray to uncover the mechanisms in which ethanol induces these behavioral changes, and results showed that binge ethanol decreased myelin-related gene expression as well as the expression of chromatin remodeling genes responsible for the methylation of histone 3 lysine 9 (H3K9). H3K9me3 is a repressive histone mark that results in transcriptional silence, and is needed for the differentiation of oligodendrocyte progenitor cells to mature oligodendrocytes. Specifically, H3K9me3 must be present at certain synaptic transmission-related genes to repress gene expression and allow oligodendrocyte differentiation to occur. Ethanol-induced dysregulation of H3K9me3 could result in decreased oligodendrocyte differentiation, leading to deficits in PFC myelin, which could ultimately underlie the persistent memory deficits of adolescents exposed to binge ethanol. To investigate this potential mechanism, binge levels of ethanol (4g/kg) or water were administered to adolescent mice. Twenty-four hours after the last dose of ethanol, RNA-sequencing was performed and showed that expression of genes required for oligodendrocyte differentiation and proliferation were impacted by adolescent binge ethanol. Chromatin immunoprecipitation coupled to sequencing (ChIP-seq) was also performed on the same PFC tissue to further investigate the link between ethanol-induced H3K9 dysregulation and myelin deficits. Here, I discuss how our lab is taking steps to understand how this epigenetic mechanism may underlie persistent memory deficits associated with adolescent binge ethanol. Supported by NIAAA R01AA026347 to JTW.

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: NCN Grant 2016/21/N/NZ4/03807

Title: Alcohol sensitization results in long-lasting changes in motivation to drink and altered dendritic spines morphology in central amygdala

Authors: *A. CALY[1], M. SLIWINSKA[2], M. ZIOLKOWSKA[1], J. FRACZEK[1], A. BEROUN[3], K. RADWANSKA[1];
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Abstract: Regular alcohol abuse lead to physical and mental dependency described like an alcohol addiction. The neuronal basis of this process are still poorly understood, thus, we investigated the behavioral and molecular consequences of the alcohol treatment. Mice injected (i.p) with ethanol (2 g/kg) for 7 days, developed context-independent sensitization of locomotor response observed after 7-day withdrawal; and it was further enhanced after 30-day incubation. Interestingly, this short protocol resulted in higher motivation for alcohol and increased alcohol seeking during withdrawal measured close-to-ethologic conditions in the IntelliCages. Alcohol sensitization was accompanied by structural (analyzed

with Serial Block-face scanning Electron Microscopy (SBEM)) and functional (whole-cell patch-clamp) changes of the central nucleus of the amygdala (CeA) glutamatergic synapses and decreased levels of the autophosphorylated form of αCaMKII. In agreement with this observation αCaMKII autophosphorylation-deficient heterozygote mutant mice (αCaMKII-T286A$^{+/-}$) showed enhanced sensitization as well as increased alcohol consumption in the IntelliCages, and surprisingly lower alcohol seeking during withdrawal and cue relapse. Funding: National Science Center, grant Preludium 2016/21/N/NZ4/03807.

Disclosures: A. Caly: None. **M. Sliwinska:** None. **M. Ziolkowska:** None. **J. Fraczek:** None. **A. Beroun:** None. **K. Radwanska:** None.

Poster

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Program #/Poster #: P737.09

Topic: G.09. Drugs of Abuse and Addiction

Support: Indiana Alcohol Research Center

Title: Alcohol exposure enhances neuronal excitability of anterior insular cortex-dorsolateral striatum circuit

Authors: *Y. YIN[1], S. ZHOU[1], D. HAGGERTY[1], B. K. ATWOOD[1,2], P. L. SHEETS[1,2];
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Abstract: Alcohol is the most abused addictive drug in the United States. Unfortunately, our understanding of alcohol-induced alterations to specific brain circuits remains incomplete. Numerous studies show that chronic alcohol exposure alters synaptic plasticity in the dorsolateral striatum (DLS), a subcortical region involved in the development of addiction. However, the effect of alcohol on cortical circuits that send projections to the DLS is poorly investigated. Here, we used intracranial injection of retrograde tracers, the drinking-in-the-dark (DID) paradigm for three weeks to model binge-like alcohol drinking, and whole-cell patch-clamp electrophysiology in acute brain slices to record the intrinsic properties of neurons in the anterior insular cortex (AIC) that send projections to the DLS (AIC-DLS neurons). Our results indicate that AIC-DLS neurons from DID-alcohol mice display a hyperpolarized voltage threshold action potential (AP) firing resulting in an increased frequency of APs in response to depolarizing current steps compared to DID-water mice. Surprisingly, DID had no effect on the excitability of neurons in the motor cortex that send projections to the DLS, suggesting that alcohol differentially alters DLS-projecting neurons based on cortical regions. We are currently exploring the possibility that alcohol induced changes to AIC-DLS neurons is driven by alterations to ascending synaptic inputs. The basolateral amygdala (BLA) is a brain region involved in alcohol use disorder, and our newest data show that the BLA sends direct projections to AIC-DLS neurons. Our goal is to measure changes in the synaptic plasticity of BLA inputs to AIC-DLS neurons in DID-alcohol mice. Moreover, alcohol consumption and pain are strongly comorbid. Measurement of reflexive withdrawal to mechanical

stimuli is frequently used to assess pain behavior. However, these tests do not measure the dynamic behavior of enduring pain to achieve a deliberate goal. Therefore, we tested one week DID animals in a paradigm involving active decision making to obtain reward (alcohol) under aversive temperatures, to quantify the effects of alcohol on motivation and pain tolerance. The results suggested that temperature changes had a main effect on the time they spent on the reward side, but there was no significant differences between DID-alcohol and DID-water mice. Overall, our results show that binge alcohol drinking enhances neuronal excitability of AIC-DLS circuit. However, one week of DID was not sufficient to significantly alter motivation for alcohol under aversive temperatures. We are currently exploring if extending DID to three weeks changes this behavior.

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Poster

P737. Alcohol Intake and Preference: Mechanisms II

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant F30 AA029261
NIH Grant RO1 AA027754-02

Title: Prenatal alcohol exposure differentially affects synaptic activity in striatal projection neurons and GABAergic interneurons in the developing striatum

Authors: *A. R. TOUSLEY, V. FERNANDEZ, P. W. L. YEH, H. H. YEH;
Geisel Sch. of Med. At Dartmouth, Hanover, NH

Abstract: Fetal alcohol spectrum disorders (FASD) are the most common non-genetic cause of neurodevelopmental disability worldwide. Delayed motor development is one of the earliest clinical signs of FASD, but how prenatal alcohol exposure (PAE) effects the neural circuits underlying early motor development is poorly understood. The functional maturation of neurons in the striatum, the input nucleus of the basal ganglia is closely related to the onset of complex motor abilities during development. Imaging studies have found striatal dysmorphology and changes to corticostriate connectivity to be associated with FASD diagnosis and symptom severity. Here we assess the effects of a brief prenatal binge exposure to ethanol on embryonic day (E) 13.5- to E16.5 on two cell populations within the developing mouse striatal microcircuit: striatal projection neurons (SPNs) and striatal GABAergic interneurons (GINs). Previous work indicated that though PAE does not to result in aberrant embryonic migration of Nkx2.1/Cre Ai14 GABAergic interneurons to the developing striatum, it does lead to presynaptic deficits in GABAergic and glutamatergic inputs to striatal GABAergic interneurons during the first two postnatal weeks. Here we show that PAE results in decreased GABAergic, but not glutamatergic synaptic inputs to developing striatal projection neurons (SPNs) during the first two postnatal weeks using whole cell voltage clamp recordings of spontaneous GABAergic and glutamatergic post-synaptic currents. On-going work will assess how these synaptic deficits may be related to changes

dendritic morphology of neurobiotin-filled SPNs, and the embryonic migration of SPNs as determined by alterations in the distribution of CTIP2 immunofluorescence on E16.5. Further work will investigate how changes in synaptic development and neuronal morphology may be associated with the onset of early motor behaviors. We are assessing early motor function using a series of brief behavioral tasks including: surface righting, negative geotaxis, horizontal/vertical screen tests prior electrophysiological recordings during the first two postnatal weeks. All experiments are performed in animals of both sexes, with a sample size of n=3 litters. Our results indicate that the synaptic development subpopulations of cells in the mouse striatum may be differentially affected by PAE. Future experiments will continue to explore the influence of PAE on the functional development of striatal neurons, to characterize the source of synaptic deficits and understand how synaptic deficits may be related to altered early motor development.

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Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P782.01

Topic: H.03. Decision Making

Support: CIHR (PJT-162444)

Title: Sex differentially interacts with multiple dopamine receptor subtypes to modulate cue-guided risk/reward decision making

Authors: *S. SCHOFIELD-LEWIS[1], J. SCHUMACHER[1], E. HU[1], S. B. FLORESCO[2];
[2]Psychology and Djavad Mowafaghian Ctr. for Brain Hlth., [1]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The ability to integrate cues from the environment to make more profitable decisions is a central behavioral adaptation in many organisms. Conditions involving pathophysiology of the dopamine (DA) are associated with suboptimal in risk/reward decision-making. Prior preclinical research on dopaminergic modulation of risk/reward decision making has used rodent assays that require the use of internal representations of reward history to guide optimal decisions (eg probabilistic discounting) rather than gathering information about the profitability of different options from external stimuli. To measure the latter type of decision making, our group has developed a rodent operant assay known as the "Blackjack" task in which rats use external cues to guide decision-making. Rats choose between a small/certain option (1 pellet at 100% probability) and a large/risky option (4 pellets, probabilistically). Different auditory stimuli signal if choice of the large/risky lever has good (50%) or poor (12.5%) odds of delivering the large reward. Well-trained rats show a strong bias toward the large/risky option on good odds trials and vice versa. Here, we investigated the specific contributions of different dopamine receptor subtypes in male and female rats, using systemic treatments with either amphetamine or D1, D2, D3, or D4 antagonists. Previous studies have shown D1 blockade reduces risky choice on a probabilistic discounting task. However, comparable doses of the D1 antagonist SCH23390 (0.001-0.01 mg/kg) did not alter choice on the Blackjack task, although a significantly higher dose (0.1 mg/kg) impaired choice. D2

antagonism reduced risky choice on good odds trials but increased risky choice on poor odds trials. D3 antagonist administration had no effect whereas moderate doses of a D4 antagonist improved decision making by reducing risky choice on poor odds trials. In females, a higher dose of the D4 blocker caused an generalized reduction in risky choice. Amphetamine increased risky choice on poor odds trials and had a more pronounce effect in females. Together these findings clarify how the dopamine system modulates cue-guided risk/reward decision making in a manner that is dependent on the decision making strategy employed, receptor subtype and sex.

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Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Program #/Poster #: P782.02

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Differential effects of distinct forms of acute stress on reward-related decision making and response inhibition involving punishment

Authors: *G. LAINO CHIAVEGATTI[1], J. SCHUMACHER[1], G. L. DALTON[1], S. B. FLORESCO[2]; [2]Psychology and Djavad Mowafaghian Ctr. for Brain Hlth., [1]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Decision making involving choice between different actions that may yield rewards associated with costs or punishments is mediated by distributed circuits within the mesocorticolimbic dopamine system. Stressors can differentially alter how these systems regulate action selection in a manner depended on the type of costs that are being evaluated. Previous work by our group has shown that acute restraint stress does not alter preference for larger, uncertain rewards vs smaller/certain ones, but markedly reduces choice of larger rewards linked to greater physical effort costs. Yet, how stress may alter reward-related action selection in situations involving risk of punishment has yet to be fully explored. Here we examined how acute restraint and pharmacological stress influenced action selection on two tasks involving reward seeking under the risk of punishment in male and female rats. One series of experiments utilized a risky decision-making task involving choice between two levers: choice of a small/safe option always delivered one reward pellet, whereas choosing a large/risky option delivered three pellets but could also deliver foot shock with a probability that increased across blocks of trials (0, 25, 50, 75 and 100%). In well-trained rats, one-hour restraint stress made rats more punishment sensitive, markedly reducing preference for the larger reward associated with shock; an effect comparable across male and female rats. In contrast, the alpha-2 noradrenergic antagonist and pharmacological stressor yohimbine had minimal effects on choice. A second study used a behavior control task assessing ability to inhibit approach towards a readily available reward associated with punishment. Here, a food pellet was delivered in a food cup, and on 30 of 60 trials the rat merely had to approach it to retrieve reward. On the other 30 trials, a 12-s visual/auditory warning cue signaled food retrieval also delivered foot shock and

that approach must be withheld until cue termination. Restraint did not affect performance overall, but revealed subtle sex differences, whereby males were less likely to wait and received more punished rewards compared to baseline, whereas females showed the opposite effect. Yohimbine had no effect on behavioral control, but did increase overall locomotor activity. These findings suggest that restraint stress selectively amplifies how punishment influences cost/benefit decisions involving choice between rewards of different value, while having a minimal effect on inhibiting punished reward seeking. The mechanisms underlying this effect may relate to the increased risk aversion observed in individuals with depression

Disclosures: G. Laino Chiavegatti: None. **J. Schumacher:** None. **G.L. Dalton:** None. **S.B. Floresco:** None.

Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Program #/Poster #: P782.03

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Differential roles for dopamine D1 and D2 receptors across the dorsal and ventral medial prefrontal cortex in cue-guided, risk/reward decision making

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Abstract: Optimal risk/reward decisions often require organisms to synthesize information learned from past-experience as well as information provided by cues in the environment that inform about the likelihood of obtaining reward. Human neuroscience research uses paradigms that capture both these aspects of risk/reward decision making, however, rodent preclinical research has traditionally neglected the latter aspect. Previous studies using rodent behavioral assays such as probabilistic discounting that assess decisions guided by choice-outcome history, have shown that dopamine (DA) transmission within the medial prefrontal cortex (mPFC) differentially modulates optimal decision making via D1 and D2 receptors. The present study assessed the role of PFC DA on cue-guided, risk/reward decision making, using an assay colloquially named the “Blackjack task”. Rats choose between a small/certain option that always delivers 1 reward pellet and a large/risky option that delivers 4 reward pellets probabilistically. The probability associated with the large/risky lever is signaled by two distinct auditory stimuli that indicate good (50%) or poor odds (12.5%) of obtaining the larger reward. Choice on this task is differentially mediated by the prelimbic and infralimbic regions of the mPFC. Male and female rats were trained over several weeks at which point they showed a strong bias towards the large/risky option on good odds trails and the small/safe on poor odds trials. Blockade of D2 receptors in the prelimbic mPFC reduced choice of the large/risky option when the odds were favorable and impaired flexible adaptations to dynamic reward contingencies. In contrast, blockade of infralimbic D2 receptors increased risky choice

on poor odds trials in male rats. Surprisingly, blockade of D1 receptors in either region had no effect on choice. Together these results highlight a subregion and receptor subtype dependent role for DA transmission in the mPFC in modulating cue-guided risk/reward decision making. They further suggest that how mesocortical DA modulates risk/reward decision making can differ depending on whether decisions are guided by internal representations of reward history or by external cues.

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Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P782.04

Topic: H.03. Decision Making

Support: European Union's Horizon 2020 research and innovation programme: ACoDM - Affective Control of Decision Making (867424)

Title: Firing features of basal amygdala neurons projecting to the dorsomedial striatum and prelimbic cortex in decision making under conflict

Authors: *C. PARDO-BELLVER[1], N. SOLARI[2], P. HEGEDÜS[2,3], B. HANGYA[2], N. HÁJOS[1]; [1]Lendület Lab. of Network Neurophysiol., [2]Lendület Lab. of Systems Neurosci., Inst. of Exptl. Med., Budapest, Hungary; [3]János Szentágothai Doctoral Sch. of Neurosciences, Semmelweis Univ., Budapest, Hungary

Abstract: In daily life, animals are faced with innumerable decisions as they interact with the environment. Decisions should be made in unfamiliar situations, without any prior knowledge, or based on previous experience; yet this cognitive process is always influenced by emotional and motivational factors. Thus, decision-making requires the interplay of multiple neural structures. Recent human studies suggest an important role for the amygdala in guiding more sophisticated action-selection processes underlying decisions. The aim of this research is to understand affective aspects of circuit mechanisms underlying value-based decisions and whether they can be effectively controlled by amygdalar networks, particularly by the amygdalostriatal and amygdalocortical pathways, under risky conditions. To investigate this, we used a combination of optogenetics, electrophysiology and a risk-taking behavioural paradigm. The identity of the neurons projecting from the basal amygdala (BA) to the dorsomedial striatum (DMS) and from the BA to the prelimbic cortex (PrL) was distinguished by opto-tagging, after injecting mice with retrograde-transported virus in the DMS and PrL, and revelling their presence in the BA. At the same time, we implanted a custom-made microdrive (32 electrodes and a built-in optic fibre) into the BA. We trained mice in a risk-taking gambling task, in which they have to choose between a safe-small reward and a larger reward that might be swapped with a punishment (air-puff). The head-fixed mice chose which side to lick (left or right, as signalled by discriminative auditory cues) knowing that licking to the risky side rewards them with a larger amount of water that sometimes is replaced by a punishment. During the task we recorded the spiking activity in the BA and analysed the data using built-

in and custom-made scripts. Our results so far show that around 30% of the recorded neurons change their firing in relation to the task. The neurons in the BA show a wide range of responses. The most common is the inhibition upon reward delivery, but we also found neurons that increase their firing and, rarely, neurons showing side-specific activity. Additionally, we found neurons activated by sound and punishment. Although we have identified several opto-tagged neurons, their particular contribution to the task is still uncertain. The wide range of responses in the activity of the BA during a risk-taking task suggests that the BA has a critical role in processes underlying decisions. However, further analysis is required in order to understand the actual complexity of the proposed network.

Disclosures: C. Pardo-Bellver: None. **N. Solari:** None. **P. Hegedüs:** None. **B. Hangya:** None. **N. Hájos:** None.

Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Program #/Poster #: P782.05

Topic: H.03. Decision Making

Title: Neurophysiological markers in the corticostriatal network associated with impulsive choice behavior during a delayed discounting task.

Authors: M. J. FRANCOEUR, S. HULYALKAR, J. CRAMER, D. RAMANATHAN; Psychiatry, Univ. of California San Diego, San Diego, CA

Abstract: Impulsivity, acting prematurely without consideration of future consequences, is usually considered maladaptive and is a central feature in brain injury and neurological disorders including attention deficit/hyperactivity disorders, substance abuse, Parkinson's, schizophrenia [(1-3)]. The corticostriatal pathway is critical for reward related behaviors, but little is known about neural correlates of impulsive behavior. We record local field potentials (LFP) from the corticostriatal network during a delayed discounting task and compare to single unit activity recorded from orbitofrontal cortex, anterior cingulate cortex, and nucleus accumbens during the same task to identify neurophysiological signatures associated with impulsive choice. During the delayed discounting task rats must choose between two reward locations: one location immediately leads to a small reward (1x) and another to a delayed (2 or 10s) large reward (3x). The temporal delay is adjusted within-session from 2 to 10s after 75 trials. While rats perform the task, we record LFP from 32 brain areas simultaneously (9 rats) or single units (6 rats per area) and time-lock activity to behavioral events. Overall rats show significant temporal discounting (ANOVA $p<.05$), making 60% (+/- 12) high value choices during 2s delay trials and only 40% (+/- 8) on 10s trials. We found an initial burst of theta/alpha activity during the choice selection followed by sustained beta activity coinciding with reward in the corticostriatal network (across 80 sessions). Beta activity is stronger for the immediate, low value reward compared to the delayed, high value reward. We collected 900 neurons from each area (~150 per rat) and found activity correlated to choice selection, the length of delay, anticipation, and reward value (high or low). We find evidence that the assigned value of reward is de-valued as delay length increases. Changes in electrophysiology correspond to trial x trial changes in discounting behavior as confirmed by correlational analyses. We have identified

neurophysiological markers in vivo that can be used as assays for pharmacological testing. Studying neural responses during tests of impulsivity will help inform where behavioral inhibition is impaired. [1]Dalley, Everitt, & Robbins (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron.* [2] Pujara & Koenigs (2014). Mechanisms of reward circuit dysfunction in psychiatric illness: Prefrontal-striatal interactions. *Neuroscientist.* [3] Roesch & Bryden (2011). Impact of size and delay on neural activity in the rat limbic corticostriatal system. *Frontiers in Neuroscience.*

Disclosures: M.J. Francoeur: None. **S. Hulyalkar:** None. **J. Cramer:** None. **D. Ramanathan:** None.

Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Program #/Poster #: P782.06

Topic: H.03. Decision Making

Support: NIDA Grant R00DA041493-3

Title: Sex differences in dopaminergic regulation of risky decision making.

Authors: *A.-R. WHEELER[1], L. M. TRUCKENBROD[1], A. M. BOEHNKE[2], E. M. COOPER[3], C. A. ORSINI[3];
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Abstract: Risky decision making reflects the ability to weigh decisions based on risk versus reward. This process is crucial to navigating everyday circumstances, and impairments are implicated in many psychiatric conditions such as substance use disorders. Previous research has shown that dopaminergic neurotransmission modulates risk-based decision making by acting on brain regions within the mesocorticolimbic circuit, such as the basolateral amygdala (BLA). The majority of these studies, however, have only used male subjects. Given that there are sex differences in risk taking and dopaminergic manipulations of risk taking, it is prudent to determine whether similar dopaminergic mechanisms are involved in female risk taking. To do this, male and female rats were trained in the Risky Decision-making Task (RDT) in which rats choose between a small, safe food reward and a large, risky food reward that is accompanied by an increasing risk of mild footshock punishment. In Experiment 1, rats were trained in the RDT and then received systemic injections of the D2 dopamine receptor (D2R) agonist bromocriptine prior to RDT testing. Bromocriptine decreased lever pressing for the large, risky reward in both male and female rats, but affected choice behavior in females at lower doses that were ineffective in males. To determine the neural substrate underlying such sex differences, rats in Experiment 2 were trained in the RDT and then received intra-BLA infusions of the D2R agonist quinpirole prior to RDT testing. Intra-BLA infusions of quinpirole decreased choice of the large, risky reward (decreased risky choice) in females, but had no effect in males. Further, this reduction in risky choice in females was accompanied by an increase in sensitivity to punishment and a decrease in sensitivity to rewards relative to vehicle conditions. In the final experiment, rats received intra-BLA infusions of the D2R antagonist eticlopride prior to being tested in the RDT. Eticlopride had no effect on risky choice in male or female rats. Considered together, these data indicate that sex differences in risk

taking may be due to differential D2R sensitivity in the BLA, with greater sensitivity in females contributing to phenotypical female risk aversion. Future experiments will use a similar experimental design to investigate the role of D1 dopamine receptors in the BLA in risk taking in males and females and evaluate whether sex differences in dopaminergic input to the BLA contributes to differential BLA D2R sensitivity between sexes.

Disclosures: A. Wheeler: None. **L.M. Truckenbrod:** None. **A.M. Boehnke:** None. **E.M. Cooper:** None. **C.A. Orsini:** None.

Poster

P782. Neural Mechanisms of Risk-Taking, Decision-Making, and Impulsive Choice

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Program #/Poster #: P782.07

Topic: H.03. Decision Making

Support: NIH Grant T32DA018926

Title: Cognitive relationships underlying risky decision making in male and female rats

Authors: *L. M. TRUCKENBROD[1], E. M. COOPER[2], A.-R. WHEELER[1], C. A. ORSINI[2];
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Abstract: The ability to properly evaluate the relative potential risk or reward of our actions is a hallmark of healthy cognitive function. Previous work has shown that individual differences in risk-based decision making (risk taking) are associated with cognitive ability in other executive functions, which, collectively, has implications for identifying vulnerabilities that may predispose individuals to develop neuropsychiatric diseases. Notably, the majority of these studies have been conducted in males, despite sex differences in risk taking. To address this, we behaviorally characterized male and female Long-Evans rats in a rodent model of risky decision making ("Risky Decision-making Task"; RDT) in which rats choose between a small, "safe" reward and a large, "risky" reward accompanied by an increasing probability of a mild footshock delivery. After reaching behavioral stability in the RDT, rats were tested in a battery of cognitive tasks to identify relationships between risk taking and several measures of executive function in both males and females. Replicating previous work, females were more risk averse than males in the RDT. There were no sex differences in impulsive choice, risk taking involving uncertainty of reward delivery, working memory ability, or motivation to work for a food reward. Females, however, displayed greater cognitive inflexibility than males in a set-shifting task. Although there were no significant correlations between choice behavior in the RDT and probability discounting, there was a near significant sex-specific correlation with risk taking and impulsive choice in females, such that greater risk aversion was associated with greater impulsive choice. Similarly, greater risk aversion predicted better working memory ability only in females. In contrast, greater risk taking in males was associated with a greater number of errors during set shifting. There was no relationship between risk taking and motivation to work for food in either sex. Overall, our data suggest that distinct underlying cognitive processes mediate risk-based decision making in males and females. Specifically, the ability to make adaptive risk-based decisions in males appears to depend on the ability to flexibly shift behavioral

responses as choice contingencies change. Alternatively, female risk taking may depend on the ability to retain information about past outcomes in working memory to guide future choice behavior. Future studies will examine whether such sex differences in the cognitive mechanisms underlying risk taking are mediated by distinct neural processes in brain regions such as the basolateral amygdala.

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Poster

P821. Cortical Networks III

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Program #/Poster #: P821.01

Topic: H.08. Learning and Memory

Support: R01 AG064247

Title: Regional covariation between relational memory ability and hippocampal resting-state functional connectivity in typically developing periadolescent individuals

Authors: *L. BEHM[1], C. J. PHIPPS[1], J. N. SEXTON[1], M. K. RAMIREZ[1], T. A. DECESARE[1], A. M. HELLER[1], A. C. MAERLENDER[2], V. S. PHATAK[1], J. A. CRAMER[1], J. R. BLAIR[3], D. L. MURMAN[1], D. E. WARREN[1];
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Abstract: The hippocampus (Hc) and its associated functional brain networks are necessary for normal declarative/relational memory. Relational memory has been shown to improve throughout childhood, and these improvements may result from developmental changes to the Hc and its functional networks. However, neurodevelopmental changes to functional brain networks associated with hippocampal memory abilities are not well characterized, particularly in periadolescent individuals. Therefore, we used a cross-sectional approach to explore whether individual differences in hippocampal functional connectivity were associated with enhanced relational memory abilities in periadolescent children. To do so, we utilized preliminary data from our ongoing NIA-funded Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study, which is recruiting healthy periadolescent individuals in order to better understand how brain and cognitive development is affected by polygenic risk for Alzheimer's disease. The present work describes our preliminary findings examining whether individual differences in hippocampal resting-state functional connectivity (RSFC) covary with outcomes on a test of declarative/relational memory ability in periadolescent children. We conducted our analysis on preliminary data from healthy periadolescent participants (N=60; age 8-13 years). To assess declarative/relational memory ability, we used Cambridge Cognition's Paired Associates Learning (PAL) task. Resting-state functional MRI analyses were conducted using a seed-based approach with the bilateral hippocampus as the seed region of interest. Hippocampal RSFC data were then analyzed to determine their covariance with relational memory ability (operationalized as PAL performance). Broadly consistent with prior work, we observed patterns of hippocampal RSFC that overlapped ventral and lateral portions of the default mode network (DMN). In more novel findings, we also observed regional

covariance between hippocampal RSFC and performance on the PAL test of relational memory ability. Here we report preliminary findings of the ongoing PRANK study. Our initial observations are consistent with the perspective that hippocampal RSFC covaries regionally with hippocampal-dependent declarative/relational memory ability among periadolescent children. To understand whether this hippocampal network development is susceptible to genetic risk factors for AD, future work from the PRANK study will utilize participants' AD polygenic risk scores to determine whether those scores are related to individual differences in hippocampal RSFC.

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Poster

P821. Cortical Networks III

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Program #/Poster #: P821.02

Topic: H.08. Learning and Memory

Support: NIA Grant R01AG064247

Title: Connectomic analysis of intrinsic functional brain networks vulnerable to Alzheimer's Disease and covariance with relational memory ability during periadolescent development: preliminary findings from the PRANK study

Authors: *C. PHIPPS[1], J. SEXTON[1], L. BEHM[1], T. DECESARE[1], A. HELLER[1], A. MAERLENDER[2], V. PHATAK[1], J. CRAMER[1], J. R. BLAIR[3], D. MURMAN[1], D. WARREN[1];
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Abstract: Cognitive abilities and the brain's intrinsic functional networks undergo change throughout the lifespan, but pathologies such as Alzheimer's disease (AD) alter normative developmental trends. It is possible that early-life brain and cognitive development modulates vulnerability to neuropathologies in later life. Here, we used a cross-sectional approach to characterize the organization of brain networks and memory abilities in periadolescent children. Data were drawn from the Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study. Our goal is to evaluate whether early-life functional brain development may modulate vulnerability to late-onset AD. To characterize the relationship between network properties of the brain and hippocampal-dependent memory, we studied cognitive and brain measures in a preliminary sample of periadolescent children (N=60) from the PRANK study. Cognitive assessment included a standardized, paired-associates learning task (from the CANTAB battery); the task requires hippocampal-dependent relational memory. Brain structure and function were assessed with MRI protocols adapted from the Human Connectome Project. Resting-state fMRI data were used to measure resting state functional connectivity which supported our investigation of brain network properties. Analysis focused primarily on the measurement of whole-brain network properties. We observed that periadolescent network organization exhibited segregation of functional networks that was qualitatively

similar to that previously reported in young adults. Analysis of the association between modularity and performance on the CANTAB task yielded a non-significant but numerically positive association. Our ongoing study measures the association of brain variables, cognitive performance, and AD polygenic risk score in periadolescent children. This preliminary analysis of brain and cognitive measures illustrates functional network properties of the periadolescent brain with a focus on associations with cognitive performance. Future directions include longitudinal analysis assessing the association between changes in modularity and changes in cognitive performance as well as examining the association between AD polygenic risk score and the same network properties.

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Poster

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Topic: H.08. Learning and Memory

Support: NIA Grant R01 AG064247-03
UNMC Grant Nancy and Ronald Reagan Alzheimer's Scholarship Fund Award

Title: Measuring covariance between spatial working memory performance and resting state functional connectivity in periadolescent children: preliminary findings from the PRANK study.

Authors: *A. HELLER[1], C. PHIPPS[1], J. SEXTON[1], M. RAMIREZ[1], L. BEHM[1], T. DECESARE[1], J. BLAIR[2], A. MAERLENDER[3], V. PHATAK[1], J. CRAMER[1], D. MURMAN[1], D. WARREN[1]; [1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Boys Town Natl. Res. Hosp., Omaha, NE; [3]Unversity of Nebraska Lincoln, Lincoln, NE

Abstract: Periadolescence is a neurodevelopmental period that can be characterized by expansive cognitive development and substantial changes to the brain's functional networks. These functional networks support cognition, and during periadolescence, the frontoparietal (FPN), default mode (DMN), and dorsal attention (DAN) networks exhibit within and between network changes associated with maturation of cognitive abilities, including various aspects of memory. Spatial working memory (SWM) is a cognitive ability involving the rapid, flexible storage and retrieval of (visuo)spatial information, and it is one type of memory that exhibits significant improvement during periadolescence. SWM ability in adults has previously been associated with differences in resting state functional connectivity (rs-FC) within the FPN and DMN. However, the relationship between SWM and FPN/DMN/DAN connectivity has not been characterized in the periadolescent epoch. The current study tested the association between rs-FC and SWM performance in a group of healthy periadolescent children aged 8 - 13 years (N=60). Participants completed the Cambridge Neuropsychological Test Automated Battery (CANTAB) implementation of a spatial working memory task, and they also underwent an MRI study to assess rs-FC. Analysis of covariance between rs-FC of the DMN and task performance (SWM) suggested greater

within-network connectivity was associated with greater SWM task performance; a similar pattern was observed in the (left) FPN. Further, there was some evidence that reduced between-network connectivity in regions resembling the DMN and FPN was also associated with greater SWM scores. Exploratory analysis of age and sex as covariates revealed patterns of varying rs-FC as well. Greater within-network connectivity in the DMN, DAN, and FPN was associated with greater age. Sex-associated differences were also observed, as males appeared to have greater connectivity to parietal regions in the DAN. Characterizing changes in these networks during periadolescence in relation to cognition is an important prerequisite to understanding whether the development of functional brain networks may reveal or drive late-life vulnerability to neurological diseases including Alzheimer's disease.

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Poster

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Program #/Poster #: P821.04

Topic: H.08. Learning and Memory

Support: NIA Grant AG064247

Title: Investigating Relational Memory in Typically Developing Periadolescent Children Using fMRI and a Subsequent Memory Task: Preliminary Data from the PRANK Study

Authors: *M. K. RAMIREZ[1], J. N. SEXTON[1], C. J. PHIPPS[1], L. BEHM[1], T. A. DECESARE[1], A. M. HELLER[1], A. C. MAERLENDER[2], V. PHATAK[3], J. CRAMER[4], J. R. BLAIR[5], D. L. MURMAN[1], D. E. WARREN[1];
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Abstract: Throughout development the brain undergoes significant structural and functional changes that are associated with substantial cognitive changes, and this maturational trajectory continues during the periadolescent epoch. One such change is the enhancement of relational memory abilities. The hippocampus is necessary for normal declarative/relational memory as demonstrated by the hallmark memory deficits of Alzheimer's disease and its accompanying hippocampal pathology. Vulnerability to AD and other memory deficits later in life may be modulated by childhood brain development, and this motivates investigation of the brain's developmental trajectory and associations with AD-vulnerable cognitive abilities including memory. Our ongoing NIA-funded study, the Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study, measures brain structure, function, and cognitive abilities in periadolescent children (age 8-13 years) and will tests whether these variables are associated with AD polygenic risk score. Here, we report preliminary data measuring hippocampal-dependent relational

memory in a task-based fMRI study using a subsequent memory paradigm. A periadolescent sample from the PRANK study provided data for the current project (N=60). MRI data were collected using protocols adapted from the Human Connectome Project. We tested hippocampal dependent relational memory using a subsequent memory task where participants were asked to study pairs of common objects while fMRI-BOLD data were collected. Participants then completed a memory test for the studied materials including two types of stimuli (studied match pairs or non-studied mismatch pairs). For subsequent memory (SM) of pairs there was preliminary evidence that successful SM was associated with increased activity in lateral prefrontal and lateral parietal regions consistent with the frontoparietal networks, in addition to other regions. Additionally, there was some evidence of regionally specific hippocampal activation (anterior hippocampus) associated with successful SM. Findings from this preliminary analysis are novel in this population but congruent with previous studies of older and younger individuals.

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Poster

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Topic: H.08. Learning and Memory

Support: NIH Grant RO1 AG064247

Title: Investigating the relationship between relational memory abilities and hippocampal volume in typically developing periadolescent children: preliminary findings from the PRANK study

Authors: *J. SEXTON[1], C. PHIPPS[1], M. RAMIREZ[1], L. BEHM[1], T. DECESARE[1], A. HELLER[1], A. MAERLENDER[2], V. PHATAK[1], J. CRAMER[1], J. BLAIR[3], D. MURMAN[1], D. WARREN[1]; [1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Univ. of Nebraska at Lincoln, Lincoln, NE; [3]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: There are considerable changes in brain structure, brain function, and cognition during childhood. For example, the maturation of cognitive processes supporting memory for arbitrary relations continues during the periadolescent epoch. The hippocampus is necessary for normal declarative/relational memory, as seen by the dramatic memory deficits seen in patients with Alzheimer's disease (AD) and the underlying hippocampal pathology. It is hypothesized that vulnerability to AD could be modulated by early brain development, so understanding the developmental relationship between hippocampal volume and declarative/relational memory performance would provide an important baseline for comparison of different trajectories. The Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study is an ongoing NIH-funded study that assesses brain structure, brain function, cognition, and polygenic risk score for Alzheimer's disease in periadolescent children (age 8-13). Here, we provide early findings from a sample of subjects from the PRANK study (N=60) investigating hippocampal volume and relational memory. Cognitive variables included relational memory

operationalized as performance on the Picture Sequence Memory Task (PSMT) from the NIH Toolbox (a standard neuropsychological battery). Structural MRI data were collected using protocols adapted from the Human Connectome Project, and hippocampal volume was measured through manual tracing. We then tested the correlation between hippocampal volume (left, right, and bilateral) and performance on the relational memory task in periadolescent children and found preliminary evidence consistent with associations between hippocampal volume and memory performance on the PSMT. Findings from this preliminary analysis illustrate the relationship between brain structure and cognitive abilities during the periadolescent period, in particular, the association between declarative/relational memory and hippocampal volume. Our ongoing PRANK study measures cognitive abilities, brain structure and function, and Alzheimer's polygenic risk score in periadolescent children. Future work from this study will investigate whether polygenic risk for AD is associated with individual differences in brain structure and neuropsychological profile in early life.

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Poster

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Topic: H.08. Learning and Memory

Support: R24-AG054355

Title: Latent states learning in changing environments

Authors: *L. Q. YU[1], A. R. VAIDYA[2], M. R. NASSAR[1];
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Abstract: People can learn flexibly and adaptively in response to changing environments, but there is great variability in the extent to which they do so. An important aspect of adaptive learning is the ability to infer the underlying causes of the outcomes in one's environment, which are known as latent states. Representation of latent states could allow the brain to effectively segregate perceptually similar outcomes according to the causes that gave rise to them, to reduce interference and thereby improve learning. Latent state representations have been identified in humans using fMRI in prefrontal regions that include the orbitofrontal cortex and dorsolateral prefrontal cortex. However, evidence for the functional significance of these representations has been limited due to a lack of behavioral variability in the tasks used to isolate them. We developed a novel predictive inference paradigm that requires participants to learn about outcomes from a generative structure that alternates between two stimulus-dependent outcome contingencies, either with a cue alerting the participant to the contingency change, or without a cue. A key advantage of our task over standard reversal learning paradigms is that it disentangles latent states from both stimuli and actions, thereby allowing us to test whether representations of latent state can explain differences in learning patterns across individuals and cue conditions. We collected behavior on this task

while 25 participants underwent fMRI scanning, and collected additional measures related to IQ, decision-making and cognitive functioning. We found that, on average, participants in both the cued and uncued conditions improved on a key behavioral readout of latent state learning: the error on the first trial in a state was progressively reduced after every instance of returning to that state, indicating that participants leveraged previous learning in that state in their responses. However, the degree to which people used latent states to learn varied across participants. Here we examine whether dynamic latent state representations in the brain (identified using representational similarity analysis of fMRI data) can explain these behavioral differences. In doing so, we provide a direct test of the functional link between latent state representations in the brain and the computational role they are thought to play in learning.

Disclosures: L.Q. Yu: None. **A.R. Vaidya:** None. **M.R. Nassar:** None.

Poster

P821. Cortical Networks III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P821.07

Topic: H.08. Learning and Memory

Support: NIH Grant F32MH116592
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Title: Neural representations supporting valuation based on schemas and experience

Authors: *A. VAIDYA, D. BADRE;
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Abstract: Judging the utility of complex real-world objects often depends on structured, schema-level knowledge about these objects and their relationship to current goals. This capacity allows us to make quick inferences about the value of options without any feedback or prior experience - enabling highly flexible behavior in response to novel problems. However, the representations the brain uses to achieve this rapid transformation of schemas to value judgments remains unclear. In an fMRI experiment, we asked twenty-three participants to make risk-based decisions about items based on values inferred from task knowledge and learned through direct experience. Using a behavioral model fit to these data, we generated trial-wise predictions for the values of items based on the experienced and schema-based values of options. In previously published work, model-based fMRI revealed that the ventromedial prefrontal cortex (vmPFC) encoded information about values inferred from schema-based knowledge as well as direct experience, and that schema-based valuation engaged communication between vmPFC and middle temporal cortex. In the current study, we have re-analyzed these data using model-based multivariate methods to test how patterns of voxel activity represent value signals that we predict are used for decision-making in this task. Model-based predictors were used to create trial-wise hypothesis representational dissimilarity matrices (RDMs) that we regressed against neural RDMs in an fMRI searchlight analysis. We find representations consistent with experienced and schema-based values are maintained in overlapping brain networks in prefrontal cortex and the precuneus distinct from representations of task-relevant semantic knowledge in middle temporal cortex. These results provide

new insight into the representational schemes used by different brain regions in the service of value judgement based on experience and structured world knowledge.

Disclosures: A. Vaidya: None. **D. Badre:** None.

Poster

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Program #/Poster #: P821.08

Topic: H.08. Learning and Memory

Support: R00AG054732

Title: Adaptive learning through temporal dynamics of state representation

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Abstract: People adjust their sensitivity to incoming information rapidly and in accordance with statistical properties of different environments. This adaptive learning behavior has been emulated in error-driven learning models by adjusting a parameter called the "learning rate ". Despite the success of this approach in explaining behavioral performance of humans, experimental studies have fallen short of finding a neural signature of this dynamic learning rate that persists across different statistical environments. Previously identified learning signals, such as the feedback locked p300, seem to relate to behavior differently in different environments. Here, we propose a new theoretical framework of adaptive learning by designing a neural network model that learns to map an internal context representation, or latent states, onto a behavioral response via supervised learning. We used a two-layer feedforward network in which latent states could be represented in the input layer. The "synaptic learning rate" used in our network was held constant – such that all learning dynamics are afforded by trial-to-trial adjustments of the latent state representation. We show our model can either increase or decrease learning through latent state transitions, depending on the structure of the environment. Such internally driven latent state transitions allow the model to achieve near optimal performance in predictive inference tasks across different environments. In an environment with changepoints, the pattern of activity in the latent state layer qualitatively matches dynamics of patterns of activation previously been observed in orbitofrontal cortex of humans, and yields faster learning in response to unexpected outcomes. In contrast, in an environment with one-off outliers, the network decreases learning from large errors through transient latent state transitions that partition learning from oddball events. The degree of latent state transition in our model is positively correlated with learning in the changepoint environment and negatively correlated with learning in the oddball environment, providing a potential mechanistic explanation for bidirectional signals such as the feedback locked p300, and providing a possible solution to the missing link between the neural signals of learning in the brain and the adaptive behavior they facilitate. In conclusion, we suggest that dynamic latent state representations can provide a coherent framework for linking neural correlates of adaptive learning across to their behavioral consequences across different statistical environments.

Disclosures: N. Razmi: None. **M.R. Nassar:** None.

Poster

P821. Cortical Networks III

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Program #/Poster #: P821.09

Topic: H.08. Learning and Memory

Title: Midfrontal theta relates to learning in a bidirectional and context dependent manner

Authors: *T. LI[1,2], M. SINGH[3], R. BRUCKNER[4,5], M. J. FRANK[2,6], M. NASSAR[1,2];
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Abstract: Theta band power over the mid-frontal cortex has been implicated in the neural basis of cognitive control. Existing theories have posited that theta may enhance learning in order to mediate behavioral updating. However, an alternate account is that theta plays a role in updating latent states, which reflect unobservable context and provide a way for the brain to learn different behavioral policies for different contexts. A role for theta in updating latent states could in principle promote either faster or slower learning, depending on exactly how latent states are updated. Here we re-analyze data from a modified predictive inference task where these two alternative accounts can be dissociated to determine whether theta is more closely related to the updating of behavior, or latent states. The task required participants to iteratively predict the aim of an unobservable cannon based on cannonballs shot from it. Predictions were made in two contexts that differed in the persistent versus transient nature of transitions of the latent state giving rise to cannonballs. In a changepoint context, the cannon occasionally re-aimed completely, producing changes in latent state that persisted in time, necessitating rapid behavioral updating. In the oddball context, surprising cannonball locations reflected one-off events, or transient changes in latent state, that should yield reduced behavioral updating. Recent modeling work from our group has suggested that normative behavioral adjustments in both environments can be achieved through adjustment of internal latent states that serve to partition learning across contexts to prevent interference. To examine whether mid-frontal theta is more closely related to adjustment of behavior or latent states, we first extracted theta power (4-7Hz) from the EEG responses for each channel, trial and time point and analyzed it using a mass univariate approach. Second, we examined how theta related to behavior by including it in a regression model that explained trial-to-trial variability in learning. We observed stronger theta signals during surprising trials in both contexts. However, we found that the relationship between theta power and learning depended on statistical structure. In the changepoint context, learning rate was positively correlated with theta signal strength, whereas in the oddball context, learning rate was negatively correlated with theta signal strength. Taken together, these results suggest that the theta signal does not directly reflect behavioral updating, but instead may reflect updating of latent states, which in turn can be used to adjust learning appropriately depending on the statistical context.

Disclosures: T. Li: None. **M. Singh:** None. **R. Bruckner:** None. **M.J. Frank:** None. **M. Nassar:** None.

Poster

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Program #/Poster #: P821.10

Topic: H.08. Learning and Memory

Support: ERC #679253

Title: Investigating the neuronal patterns underlying short term memory using a novel tactile task

Authors: *S. SOMECK, H. SLOIN, E. STARK;
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Abstract: The ability to store information for short periods of time and act upon that information is one of the most fundamental functions of living organisms. Persistent and sequential activity have been observed during short-term memory (STM) tasks in multiple animal species and brain areas. However, a causal relation between specific types of multi-neuronal patterns and STM maintenance has never been derived. Many STM tasks designed for lab animals can be performed successfully by "bridging" the delay: storing the sample or correct response using bodily configurations. To minimize the possibility of bridging, we developed a spatial tactile STM task for mice based on delayed comparison. The apparatus consists of a figure-8 maze with two pairs of motorized texture wheels situated 1.2 m apart. Each wheel-pair contains five distinct textures. In the full STM task, the animal has to turn right if the textures on the two wheel-pairs are identical, and left if the textures are distinct. The 25-combination delayed comparison design prevents response bridging and minimizes the possibility of sample bridging. Using a single pair of wheels yields a discrimination task on the same apparatus. Four mice learned the discrimination task within a week; after learning, the median number of trials per session was 133, and the median success rate was 83%. Two mice learned the memory task within two weeks (144 trials, 64% success). To establish a link between task performance and local network activity, we recorded multi-neuronal spiking activity from hippocampal region CA1 as the mouse learned the discrimination task (eight sessions). 138 of 170 well-isolated units had place-fields on the apparatus. During the sessions in which the animal already performed the task successfully, 27/63 (42%; five sessions) of the units exhibited task-oriented place fields: near the reward, choice or active wheels. In contrast, during the learning sessions, only 5/75 (7%; three sessions) units were task-oriented. The results suggest that CA1 place cells may be relevant to the spatial tactile task.To manipulate the local network at a high spatiotemporal resolution, we implanted μLED probes in the neocortex of two other freely-moving mice. Recording and manipulation sessions were carried out over three months. Synthetic multi-neuronal pyramidal cell spiking sequences were produced in the hippocampus.The combination of a novel behavioral task, high-density electrophysiological recordings, and neuronal-resolution optogenetic manipulations will allow determining which neuronal patterns underlie STM.

Disclosures: S. Someck: None. **H. Sloin:** None. **E. Stark:** None.

Poster

P821. Cortical Networks III

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Program #/Poster #: P821.11

Topic: H.08. Learning and Memory

Support: ERC #679253

Title: Demonstrating the priming phenomenon in mice

Authors: *S. SIVRONI[1,2,3], H. SLOIN[1], E. STARK[1];
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Abstract: Priming is a form of implicit short-term memory (STM), defined as a change in the ability to process an object as the result of a recent encounter with that object. Priming is a key part of our daily life and has been studied extensively at the cognitive level. The hippocampus (HPC) and the posterior parietal cortex (PPC) are active throughout STM and during processing of sensory inputs and are thus possible loci for supporting priming. Yet currently, there is no information whatsoever about the electrophysiological basis of priming. Furthermore, there is no behavioral model for studying priming in lab animals. Here, we first developed a novel behavioral paradigm for studying priming in freely-moving mice. In the mouse priming task, the animals were exposed to three water ports. The mice had to associate a 5 kHz/300 ms auditory "target" stimulus with reward in the left port, and a 10 kHz/300 ms stimulus with reward in the right port. "Prime" stimuli were shorter (5-15 ms) tones that preceded the "target" stimuli. Two types of prime stimuli were used: congruent (same frequency as the target), and non-congruent. We defined "prime effect" as the difference in success rate between congruent trials and non-congruent trials. Four mice were trained on the auditory task. We found a consistent prime effect. Diagnosing behavioral priming in mice implies that priming is not limited to humans or primates. Next, we assessed neural correlates of auditory inputs in HPC. For that, we combined high-density silicon probe (64-128 sites, Diagnostic Biochips) recordings from freely-moving mice (n=3) with playback of auditory pure tones (2-16 kHz) and band-limited white noise. We discovered novel neural correlates of pure tones in HPC. In CA1 stratum oriens, pure tones induced auditory evoked potentials (AEP) that exhibited a positive peak ~20 ms after stimulus onset. The 20 ms from sound onset to AEP extremum was accompanied by increased spiking of CA1 pyramidal cells. AEPs were also observed in the dentate gyrus (DG), but with reversed polarity: negativity in the top half of the layer, and positivity in the bottom half. The results suggest that the HPC contains multiple distinct AEP generators. Together, the novel mouse model of non-conscious priming and the auditory responses observed in the HPC open the door for electrophysiological investigation of implicit STM in freely-moving mice.

Disclosures: S. Sivroni: None. **H. Sloin:** None. **E. Stark:** None.

Poster

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Topic: H.08. Learning and Memory

Support: ERC grant 679253
ISF grant 1871/17

Title: Cortical Sensing for determining the neural mechanisms underlying learning

Authors: *A. LEVI[1], E. STARK[2];
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Abstract: Despite the importance of learning, defined inter alia as the process by which organisms change their behavior as a result of experience, the underlying neuronal mechanisms are not fully understood. Learning is most commonly studied in animals using a standard paradigm in which an animal is required to learn the correct response to sensory stimuli. Indeed, correlative evidence linking changes in neuronal network activity following acquisition of stimulus-response associations is abundant. Nevertheless, a causal link between multi-neuronal neocortical activity and learning has never been demonstrated. Moreover, the way information available in neuronal patterns is utilized by downstream networks is unclear. Learning is intuitively viewed as the brain adapting to external stimuli, but all stimuli are eventually translated into neuronal activity patterns. Therefore, learning can be defined as the brain adapting to its own activity. To determine the neuronal mechanisms underlying learning, we conceived an approach we term Cortical Sensing. The idea behind Cortical Sensing is to bypass the sensory-to-neuronal transformation and directly generate coding-relevant neuronal activity patterns in the cortex of freely-moving mice. By using a host of different types of injected activity patterns and monitoring learning behavior, we can deduce which neuronal activity patterns can be learned best. For Cortical Sensing to succeed, a behavioral task that will guarantee ideal conditions for learning of a new set of rules is required. Specifically, to allow high-throughput screening of multiple activity patterns in the same animal and ensure recording and stimulation stability, single-session learning is required. We trained mice (n=3) on a binary discrimination task, in which the rules of the task change between days. Over multiple sessions, all mice learned that attention is needed in each session to learn whether a new set of rules controls the task. Eventually, all three mice exhibited single session learning of external visual stimuli. One CaMKII:ChR2 mouse that achieved single session learning was also subjected to Cortical Sensing experiments. Different types of neuronal patterns were induced in hippocampal CA1 pyramidal layer. The animal was able to learn a frequency dependent cortical rule, but unable to learn a rate dependent set of rules. Cortical Sensing is expected to shed light on the way the brain responds to its own pattern of activity and by that extend our knowledge of neural mechanisms underlying learning. Funding: ERC #679253, ISF #1871/17

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Poster

P835. Hippocampal Interactions in Humans

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Fondo Social Europeo (FSE) Programa Operativo Integrado de Canarias 2014-2020, Eje 3 Tema Prioritario 74 (85%).

Title: Functional connectivity of hippocampal subfields in an elderly population.

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Abstract: One of the main risk-factors in many neurological diseases is the age of the person. Therefore, understanding how the brain ages could provide us with more information about many diseases. Previous literature in neuroimaging has highlighted the role of a brain structure called the hippocampus in aging (West, 1993; Jack et al., 1997; Driscoll et al., 2003). The hippocampus is composed of the subfields Cornu Ammonis; CA1, CA2, CA3 and CA4; the dentate gyrus and the subiculum (Cajal, 1911). The size of these subfields is very small (~ 1mm in cross section), and their folding pattern is conserved along the longitudinal axis of the hippocampus (Insausti & Amaral, 2004). However, due to the small size of these subfields, their changes throughout aging remain poorly understood. Other studies have suggested that the most notable changes in hippocampal volume occur in older age groups (Schuff et al., 1999; Resnick et al., 2000; Scahill et al., 2003; Stark et al., 2021). Thus, here we observed how aging affects the volume of hippocampal subfields, and how aging affects functional connectivity between hippocampal subfields and DMN regions. The dataset concerned a group of 77 healthy participants over 60 years old (BEACON dataset, UCI) assigned to two groups based on a mean split ("young" group, mean age 67 yrs; "old" group, mean age 77 yrs). Our structural analyses relied on Freesurfer (v6.0) and LME regression model including the fixed effect variables hemisphere (left vs right), age group (young vs old), hippocampal section (head, body, tail) and subfield (CA1, CA2/3, CA4, DG, ML, SUB, PRESUB). Our functional analyses relied on spatially-restricted ICA and Dual Regression to obtain functional connectivity between hippocampal activity clusters and DMN regions on a by-participant basis. The structural results revealed a significant triple interaction between age group, hippocampal section, and subfield ($F(6,2025)=7.14, p<0.0001$). Post-hoc comparisons revealed a significant reduction in the volume of subiculum in the body of the hippocampus between the old and the young group, and a significant reduction in volume of the CA1 subfield in the head of the hippocampus between the old and the young group. The functional results showed how the DMN relied primarily on activity in CA4, DG and presubiculum subfields, and less on CA1 and CA3. In addition, comparing this connectivity between the two different age groups we found that age mostly affected connectivity in the subiculum ($p<0.05$) and the CA4 ($p<0.02$) subfields. These results clarify how different subfields of the longitudinal axis of the hippocampus such as the CA4 or the Subiculum play a different role in the resting-state networks.

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Poster

P835. Hippocampal Interactions in Humans

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Training Grant T32GM008620 to S.G.

Title: Cracking the fundamental neural code of the hippocampal CA1 apical dendritic system: A non-linear transfer function for a key node in the hippocampal circuitry.

Authors: *S. GATTAS[1], A. A. LE[2], B. PRUESS[1], A. SWINDLEHURST[1], G. LYNCH[1], M. A. YASSA[3]; [1]Univ. of California, Irvine, Irvine, CA; [2]Anat. and Neurobio., Univ. of California Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California Irvine Dept. of Neurobio. and Behavior, Irvine, CA

Abstract: Mathematical formulas that fully capture the governing dynamics of synaptic transmission are required for a biologically realistic physical construction of brain networks as well as gaining insight into their fundamental operations. We investigated the feasibility of establishing such a formula - a transfer function for the CA3 to CA1 connection of the hippocampus. Contrary to the field's general belief, in vitro slice experiments indicated that these synapses behave in a nonlinear fashion. We used randomly spaced activation of CA3 projections and the Volterra expansion technique for nonlinear system identification of the CA3-CA1 system. The resultant transfer function reveals the operations the CA1 performs (i.e. attenuation, amplification, linear and nonlinear filtering based on inputs characteristics) and reproduced the continuous waveform of recorded CA1 fEPSP responses with minimal error. Surprisingly, the nonlinear component of the transfer function, which reflects the influence of the temporally adjacent inputs on the output, played an increasingly dominant role in shaping the waveform of responses with input magnitude. The transfer function reported here accurately reproduced fEPSPs collected from a second set of animals and thus appears to describe a fundamental rule for an essential link in hippocampal circuitry. This work paves the path to uncovering such rules for other components of the hippocampal network as well as other brain networks.

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Poster

P835. Hippocampal Interactions in Humans

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Topic: H.08. Learning and Memory

Support: NIMH T32 MH119049
NIA R01AG053555
American Academy of Sleep Medicine Strategic Award

Title: Blood oxygen desaturation due to obstructive sleep apnea is associated with preferential consolidation of negative memories in older adults

Authors: *M. G. CHAPPEL-FARLEY[1], B. A. MANDER[2], A. B. NEIKRUG[4], A. DAVE[4], K. K. LUI[5], M. A. YASSA[6], R. M. BENCA[3];
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Abstract: Obstructive sleep apnea (OSA) is a sleep disorder characterized by frequent pauses in breathing during sleep causing intermittent hypoxia and sleep fragmentation. If left untreated, OSA is associated with damage to the hippocampus which is thought to underlie OSA-related cognitive impairment. The hippocampus, specifically the DG/CA3 subfields, are implicated in pattern separation—the ability to differentiate highly similar experiences as unique events. Recent research has demonstrated that overnight sleep supports mnemonic discrimination (a behavioral correlate of pattern separation) in young adults. However, less is known about the impact of sleep, or sleep disorders such as OSA, on mnemonic discrimination in older adults. Additionally, while recent work has demonstrated that OSA impacts sleep-dependent memory consolidation in several domains, it is unclear whether OSA impacts the consolidation of emotional memories which typically exhibit a sleep benefit. This study aimed to determine whether OSA severity influences sleep effects on mnemonic discrimination of highly similar emotional experiences in older adults. Eighteen cognitively healthy older adults (μ=73.1±5.3, 10F) were evaluated with overnight polysomnography and measures of OSA severity and blood oxygen desaturation were derived. Participants completed the emotional version of the Mnemonic Discrimination Task prior to and following overnight sleep. The Lure Discrimination Index (LDI) was derived to assess mnemonic discrimination and sleep-dependent memory consolidation was measured by calculating overnight change in LDI. Discrimination of highly similar negative stimuli significantly deteriorated following overnight sleep whereas positive and neutral stimuli were relatively preserved. Metrics of OSA severity were consistently positively associated with overnight change in LDI for negative high similarity stimuli. The frequency, duration, and extent of blood oxygen desaturations appear to drive this relationship. These data may suggest that while sleep is generally associated with a loss of high-fidelity negative memories in older adults, OSA severity may exert the opposite effect to promote overnight retention of highly detailed negative experiences. These findings further suggest that blood oxygen desaturation may be a mechanism by which OSA increases risk for mood disorders, such as depression which is associated with a negative memory bias.

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Poster

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Topic: H.08. Learning and Memory

Support: R01MH115932
T32 MH119049

Title: Latent anxiety in clinical depression is associated with worse recognition of emotional stimuli

Authors: *S. GRANGER[1], J. ADAMS[3], S. M. KARK[3], M. T. SATHISHKUMAR[3], I. Y. CHEN[3], R. M. BENCA[2], L. MCMILLAN[3], J. T. JANECEK[3], M. A. YASSA[4];
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Abstract: Major Depressive Disorder, characterized by cognitive affective biases, is a considerable public health challenge. Past work has shown that higher depressive symptoms are associated with augmented mnemonic discrimination of negative stimuli. In contrast, anxiety symptoms have been associated with overgeneralization of emotional memories. Given the high comorbidity of depression and anxiety, it is critical to understand how cognitive affective biases are differentially associated with clinical symptoms. We used continuous measures of depression (Beck Depression Inventory [BDI-II]) and anxiety (Beck Anxiety Inventory [BAI]) to evaluate an adult sample (N=79; 18-41 years old, 58 female). Emotional lure discrimination performance and target recognition were tested using an emotional discrimination task. We applied exploratory factor analysis to questions from the BAI and BDI-II to uncover latent constructs consisting of negative affect, anhedonia, somatic anxiety, hyperarousal, and cognitive anxiety. We report evidence that anxious symptoms were associated with impaired recognition of negative items after accounting for depressive symptoms. Our exploratory factor analysis revealed that impaired negative item recognition is largely associated with somatic and cognitive anxiety factors. Interpretations in a mixed pathology sample, especially given collinearity among factors, may be difficult. We provide evidence that somatic and cognitive anxiety are related to impaired recognition memory for negative stimuli. Future clinical investigations should uncover the neurobiological basis supporting the link between recognition of negative stimuli and somatic/cognitive symptoms of anxiety.

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Poster

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Topic: H.08. Learning and Memory

Support: NSF

Title: Redesigning Highly Superior Autobiographical Memory (HSAM) Assessment Tools with Confidence: The Event Recognition Task

Authors: *L. STITH[1], V. NYE[1], J. ADAMS[1], M. A. YASSA[2];
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Abstract: Although impaired memory and amnesic syndromes have been highly researched and as a result have widespread literature, not much is known about superior forms of memory. One form of superior memory, known as Highly Superior Autobiographical Memory (HSAM), was first identified in an individual by Dr. James L. McGaugh and colleagues in 2006. Since then, dozens of people have contacted researchers, eager to find out if they too have this condition. The current HSAM assessment's limited pool of questions hinders individual performance on the test due to lack of specific knowledge, instead of measuring actual memory ability. In order to identify HSAM ability to further superior memory research, a reliable and valid test must be formulated. This study devised an assessment tool, the Event Recognition Task (ERT), with the goal of correctly identifying individuals with HSAM abilities. The ERT increases the pool of questions and implements a ranking system, allowing for subjects to choose preferred topics, reducing the effect of the subject's specific domain knowledge on performance. Questions are selected based on custom-weighting that takes into consideration individual expertise and preferred topics. Additionally, the ERT assesses confidence ratings, a novel measurement in HSAM individuals. We describe the ERT and its properties, as well as benchmark it against the original assessment tools. We hope the ERT and its adaptive design will be a more valid way to detect and assess HSAM memory abilities due to the assessment being personalized for each study participant and removing the effect of specific domain knowledge and expertise on memory performance.

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Poster

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Program #/Poster #: P835.06

Topic: H.08. Learning and Memory

Title: Modulating amygdala activation to traumatic memories with a single ketamine infusion

Authors: *O. DUEK[1], Y. LI[2], C. GORDON[3], B. KELMENDI[2], S. L. AMEN[2], J. H. KRYSTAL[2], I. LEVY[4], I. HARPAZ-ROTEM[2];
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Abstract: NMDA receptor antagonists have a vital role in extinction, learning, and reconsolidation processes. During the reconsolidation window, memories are activated into a labile state and can be stored in an altered form. This concept might have significant clinical implications in treating PTSD.

Using amygdala activity as a major biomarker of fear response, we tested the potential of a single subanesthetic intravenous infusion of ketamine (NMDA receptor antagonist) to enhance post-retrieval extinction of PTSD trauma memories. Post-extinction, ketamine recipients (vs midazolam) showed a lower amygdala and hippocampus reactivation to trauma memories. Post-retrieval ketamine administration was also associated with decreased connectivity between the amygdala and hippocampus, with no change in amygdala-vmPFC connectivity, which suggests that ketamine may enhance post-retrieval extinction of PTSD trauma memory in humans. These findings demonstrate the capacity to rewrite human traumatic memories and to modulate the fear response for at least 30 days post-extinction.

Disclosures: O. Duek: None. **Y. Li:** None. **C. Gordon:** None. **B. Kelmendi:** None. **S.L. Amen:** None. **J.H. Krystal:** None. **I. Levy:** None. **I. Harpaz-Rotem:** None.

Poster

P835. Hippocampal Interactions in Humans

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P835.07

Topic: H.08. Learning and Memory

Support: University of Kentucky, Department of Neurology, Pilot Grant

Title: Exogenous administration of βeta-hydroxybutyrate (BHB) improves cognition in healthy participants

Authors: *A. C. GLUECK[1], D. Y. HAN[2];
[1]Neurol., Univ. of Kentucky, Lexington, KY; [2]Neurol., Univ. of Kentucky Dept. of Neurol., Lexington, KY

Abstract: βeta-hydroxybutyrate (BHB) is a ketone body produced by the liver in a process known as ketogenesis. During periods of fasting or carbohydrate caloric restriction, ketones are used as an alternative fuel source throughout the body including the brain. Although glucose is the brain's principal energy source, when limited, ketones derived from fats become the primary energy source. Exogenous BHB is safe to administer orally, and enhances energy and physical performance. While growing evidence indicates significant cognitive improvement in animal models following ketone elevation, and in clinical human samples, such as in Alzheimer's disease and severe traumatic brain injury, there is limited literature demonstrating beneficial neurocognitive effects of exogenous administration of ketones in nonclinical samples. Twenty-six healthy participants were randomly assigned to receive a single dose exogenous administration of 11.7g of BHB or a flavor matched placebo. One-hour after ingestion, participants in the BHB condition demonstrated a significant 11-point Standard Score (SS; M=100, SD=15) improvement in memory ($t(13)= 2.48$, $p < 0.05$; $d = 0.77$) and a 15.86-point SS improvement in processing speed ($t(13)= 4.28$, $p < 0.01$; $d = 1.10$) compared to baseline. Participants in the control condition demonstrated a significant 16-point SS improvement in processing speed from baseline ($t(11)= 3.49$, $p < 0.01$; $d = 0.82$) to post-intervention. Changes in processing speed are to be interpreted with caution however, as there appears to be a measurement practice effect potentially confounding these results. Additionally, participants in the BHB condition demonstrated significantly higher BHB blood

levels (M=1.24 mM, SD=0.58) compared to the placebo condition (M=0.27 mM, SD= 0.12) 1-hour following ingestion ($t(24)= 5.68$, $p <0.001$, $d= 2.33$). Results of this pilot study suggest exogenous administration of BHB may have positive effects on cognitive performances in nonclinical participants. More research is needed to further explore the potential benefits and pitfalls of exogenous BHB administration in nonclinical participants and additional clinical populations.

Disclosures: A.C. Glueck: None. **D.Y. Han:** None.

Poster

P835. Hippocampal Interactions in Humans

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Program #/Poster #: P835.08

Topic: H.08. Learning and Memory

Support: National Institutes of Mental Health (MH11117)
Mark Cohen Neuroscience Endowment
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Children's Hospital of Michigan Foundation
Prechter World Bipolar Foundation
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DMC Foundation

Title: Disordered network stability during associative learning in schizophrenia

Authors: *E. MERAM, S. BAAJOUR, A. CHOWDURY, J. STANLEY, V. DIWADKAR;
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Abstract: Background: Schizophrenia (SCZ) is characterized by impairments in associative learning (Diwadkar et al., 2008) but the stability of brain network topology induced *during* phases of learning has not been investigated. Here, we used the graph theoretic measure of betweenness centrality (BC), a metric that indexes the "integrative value" of a node, to summarize brain network topology in four different conditions of an object-location associative learning paradigm: Memory Formation (MF), Post-Encoding Consolidation (PEC), Retrieval (MR), and Post-Retrieval Consolidation (PRC) (Rubinov and Sporns, 2010; Baajour et al., 2020). We then characterized the stability of network topology by assessing the changes in the rank ordering by BC across task phases.
Methods: fMRI data were collected from 59 subjects (32 SCZ, 18<Age<50, 3T Siemens Verio). During MF, nine unique objects were presented in their associated locations (3x3 spatial grid) for naming. During PEC, participants covertly rehearsed memoranda. During MR, locations were cued, and participants were required to name the associated object. The instruction-free PRC epoch was identical to PEC. fMRI data were processed in SPM12. For each condition, time series data were extracted from 90 cerebral nodes. In each participant and for each condition, BC was estimated for each of these 90 nodes. Then, in each group and condition, we ranked nodes based on their estimated BC. Next, we computed the standard deviation (s.d.) of each node's rank across task conditions. Finally, from the observed s.d.s, we identified "stable" (low s.d.) and unstable (high s.d.) nodes in each group.

Results: Patterns of relative "stability" and "instability" were complex. SCZ were characterized by high stability in occipital nodes, but instability in multiple task-relevant frontal and temporal lobe regions, including the right inferior frontal operculum and left fusiform gyrus. By comparison, HC were characterized by stability in multiple regions in the frontal lobe and basal ganglia, including the left middle frontal gyrus, left caudate, and right pallidum. Regions of high stability for both groups (HC, SCZ) tended to be uniformly high-rank *or* uniformly low-rank across task conditions.
Discussion: Occipital nodes relatively peripheral to the essentials of paired-associate learning were highly ranked in SCZ, and *also* highly stable. This observation suggests that learning redirects functional network structure in SCZ toward an emphasis on brain regions that are relatively peripheral to task requirements. The results emphasize the contextual dynamics of the "dysconnection syndrome" that is SCZ.

Disclosures: E. Meram: None. **S. Baajour:** None. **A. Chowdury:** None. **J. Stanley:** None. **V. Diwadkar:** None.

Poster

P835. Hippocampal Interactions in Humans

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Program #/Poster #: P835.09

Topic: H.08. Learning and Memory

Support: R01 MH094743
R01 MH087610
NUS Development Grant

Title: Tuned to learn: An anticipatory hippocampal convergence state conducive to memory formation revealed during midbrain activation

Authors: *J.-H. POH[1], M.-A. T. VU[5,1,2], J. K. STANEK[1], A. HSIUNG[1], T. EGNER[1,3], R. A. ADCOCK[1,3,4,2];
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Abstract: The influence of neuromodulatory activity on hippocampal processing has been a long-standing question in memory research. While there is robust evidence that functional interaction between the dopaminergic midbrain and the hippocampus supports enhanced learning during a motivated state, the mechanism by which midbrain activity influences hippocampal state remains ambiguous. In the current work, we identify a neural signature within the human hippocampus that may provide a candidate mechanism accounting for neuromodulatory influence on hippocampal processing - an anticipatory convergence state. This convergence state was expressed in the hippocampus while awaiting valuable information, predicted later memory, and also accounted for the relationship between midbrain activation and enhanced learning. To examine this modulatory influence on the hippocampus, we leveraged endogenous neuromodulation associated with intrinsic motivation - During fMRI, participants viewed trivia questions eliciting high or low curiosity, each followed seconds later by its answer. We reasoned

that memory encoding success requires a convergence of factors, and as such, hippocampal states associated with remembered trials would be less variable than forgotten ones. Using a novel multivariate approach, we measured convergence by quantifying the typicality of spatially distributed patterns. We found that hippocampal states showed greater convergence under high than low curiosity during anticipation of trivia answers,. Crucially, convergence in the hippocampus increased with greater midbrain activation and uniquely accounted for the association between midbrain activation and subsequent memory recall. We propose that sustaining a convergence state in the hippocampus reflects a modulatory mechanism that links the cascade from motivation, to midbrain activity, to enhanced memory formation.

Disclosures: J. Poh: None. **M.T. Vu:** None. **J.K. Stanek:** None. **A. Hsiung:** None. **T. Egner:** None. **R.A. Adcock:** None.

Poster

P835. Hippocampal Interactions in Humans

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Program #/Poster #: P835.10

Topic: H.08. Learning and Memory

Support: NIH Grant 1R01NS112366-01A1

Title: Individual differences in anterior and posterior hippocampal connectivity and their relationship to memory specificity and generalization

Authors: *L. FRANK, D. ZEITHAMOVA;
Univ. of Oregon, Eugene, OR

Abstract: The hippocampus aids in remembering individual experiences (memory specificity) as well as linking across those experiences to form generalized knowledge (memory generalization). How can the hippocampus support both memory functions? Prior work indicates functional dissociations between the anterior and posterior hippocampus such as distinct connectivity profiles and distinct levels of granularity in memory representations. In this study, we tested the hypothesis that anterior and posterior hippocampal connections will differentially predict behavior, such that anterior hippocampal connections will track with memory generalization while posterior hippocampal connections will track with memory specificity. Participants completed a battery of memory assessments across two sessions that included measures of both memory specificity and generalization. Factor analysis was used to derive individual scores of memory specificity and generalization abilities. A subset of participants returned for a third session to undergo MRI, including a resting-state scan. We then correlated individual differences in whole-brain connectivity with the anterior and posterior hippocampus during rest with individual differences in memory scores. Partially consistent with our hypothesis, we found posterior hippocampal connections (but not anterior hippocampal connections) predicted memory specificity. However, both anterior and posterior hippocampal connections predicted memory generalization, albeit through interactions with distinct regions. These findings provide new probes into the hypothesized functional dissociations of

anterior and posterior hippocampus and indicate that hippocampal interactions with distinct regions may support the complementary functions of memory.

Disclosures: L. Frank: None. **D. Zeithamova:** None.

Poster

P835. Hippocampal Interactions in Humans

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P835.11

Topic: H.08. Learning and Memory

Title: Differential effects of content and location overlap on learning and memory

Authors: *B. CHALOUPKA, D. ZEITHAMOVA;
Univ. of Oregon, Eugene, OR

Abstract: Similarity and overlap of information play a role in learning and memory in two well-established yet conflicting ways: they can facilitate new learning, but also lead to interference. In two studies, we aimed to reconcile this conflict by examining multiple dimensions of overlap. In the first study, we tested the effect of content overlap (same visual stimuli) and spatial overlap (same locations) on new learning. We utilized a novel grid learning task in which participants learned a grid of object-location associations, and then learned a second grid to measure facilitation or interference. The second grid overlapped with the first in stimuli, locations, both or neither. We found that a common set of stimuli between the two grids hindered learning of the second grid while a common spatial pattern between the two grids facilitated learning of the second grid. We found no interaction, indicating that these effects are independent and additive. In the second study (in progress), we added a third dimension of overlap: the shape of the grid. We again found that content overlap had a detrimental effect while spatial overlap had a facilitatory effect on learning of the second grid, replicating our results from the first study. However, the facilitatory effect of location overlap was numerically smaller when the second grid was shaped differently than the first. This suggests that the facilitatory effect of spatial overlap may be dependent on an overlapping context, potentially reflecting changes of location coding when the shape of the environment is altered. Collectively, our results demonstrate the nuance of overlap as a factor in learning and memory: some forms of information overlap, such as content overlap, can cause interference, while other forms, such as spatial overlap, can provide a framework into which new information can be easily integrated. The facilitatory effect of spatial overlap may be due to the early stages of a spatial schema, which has been shown to provide a framework into which new information can be easily integrated.

Disclosures: B. Chaloupka: None. **D. Zeithamova:** None.

Poster

P835. Hippocampal Interactions in Humans

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Topic: H.08. Learning and Memory

Support: Wellcome/Royal Society Sir Henry Dale Fellowship (218535/Z/19/Z)
Wellcome Trust (203147/Z/16/Z)

Title: Hippocampal representations switch from errors to predictions during acquisition of predictive associations

Authors: F. AITKEN, ***P. KOK**;
UCL, London, United Kingdom

Abstract: We constantly exploit the statistical regularities in our environment to help guide our perception. For instance, hearing a particular jingle will prime our sensory systems for the sight (and taste!) of ice cream. But how does the brain acquire and exploit knowledge about these regularities in a changing environment? The hippocampus has been suggested to play a pivotal role in this process. That is, it has been shown to be involved in learning novel associations between arbitrary stimuli, as is required for acquiring many predictive contextual cues. On the other hand, the hippocampus has also been suggested to play a role in exploiting such predictive associations after learning is done, through pattern completion driven retrieval. This raises the question of how the hippocampus balances encoding of new predictive associations with the retrieval of existing ones, a question that has been much discussed in the context of episodic memory but has not been sufficiently considered in the context of perceptual predictions. Here, we present the results of two high resolution human fMRI studies (N=24 for both experiments) directly investigating this. Participants were exposed to auditory cues that predicted the identity of an upcoming visual shape (with 75% validity). On each block of trials (32 trials per block in Experiment 1 and 128 in Experiment 2) new auditory cues were presented, such that novel associations would have to be learnt. Using multivoxel decoding analysis, we found that the hippocampus initially preferentially represented unexpected shapes (i.e. those that violated the cue regularities), but later switched to representing the cue-predicted shape regardless of which was actually presented. These findings are in line with the hippocampus switching between encoding and retrieval modes depending on contextual novelty. That is, when stimuli or associations are novel, hippocampus is in an encoding mode, and is mainly driven by sensory signals that provide the opportunity to update our model of the world, i.e., prediction errors. However, once learning is complete and stimuli are no longer novel, the hippocampus is mainly in retrieval mode, retrieving predicted stimuli based on contextual cues to optimally guide perception. Furthermore, in this latter phase, we found increased informative connectivity between the posterior subiculum and the early visual cortex (V1), potentially reflecting hippocampal predictions being relayed to visual cortex. These findings demonstrate a role for the hippocampus in both acquiring and exploiting predictive associations, and a switch between these modes depending on whether learning is ongoing or complete.

Disclosures: F. Aitken: None. **P. Kok:** None.

Poster

P835. Hippocampal Interactions in Humans

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Topic: H.08. Learning and Memory

Support: 240-846401 NWA Startimpuls 2017

Title: Cells in the human medial temporal lobe are reactivated by pronouns that refer to concepts to which they are tuned.

Authors: *D. E. DIJKSTERHUIS[1], M. W. SELF[1], J. K. POSSEL[1], J. C. PETERS[2], I. E. STRAATEN[3], S. IDEMA[3], J. C. BAAYEN[3], S. M. A. VAN DER SALM[4], N. C. E. KLINK[4], P. VAN EIJSDEN[4], S. HANSLMAYR[5], R. CHELVARAJAH[6], F. ROUX[7], L. KOLIBIUS[5], V. SAWLANI[6], D. T. ROLLINGS[6], S. DEHAENE[8], P. R. ROELFSEMA[1];
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Abstract: Given the lack of experimental methods, we know remarkably little about the neuronal encoding of language at the level of single neurons. In the present study, we exploited the ability to record from single neurons in the human medial temporal lobe, which respond selectively to certain people, animals or places. Some of these 'concept cells' respond to both pictures of individuals (e.g. Jennifer Aniston) as well as textual information (e.g. the text 'Jennifer Aniston'). We here asked whether these cells can also be activated by pronouns that refer to the preferred concept of a cell. Are concept cells activated during reading of nouns and pronouns in sentences?
We tested whether concept cells that are activated by a preferred noun, are re-activated by pronouns (e.g. 'he', 'she') that refer to that noun. We first identified concept cells in the medial temporal lobe of 12 epileptic patients implanted with electrodes as part of their treatment. We obtained ethical approval to use a version of the electrode (Behncke-Fried) that includes a number of microwires so that we could record from single units. We then visually presented two sentences, word-by-word (0.5s per word) on a computer screen. The first sentence contained two nouns and the second sentence contained one pronoun, referring to one or both of the previously presented nouns (for example '*Jennifer Anniston* and *Barack Obama* walked into a bar. *She* sat at the table.'). The subject had to indicate to whom the pronoun referred. Our results show that concept cells (n = 29) gave robust responses to the nouns, and that there was a significant difference between the responses to the pronouns ($p < 0.05$, paired t-test). Concept cells were only re-activated by pronouns that referred to the preferred noun of the cell. A decoder analysis confirmed this result by showing that the same neural activity pattern as response to the noun presentation was also present during the pronoun presentation, but only when it referred to the preferred noun. This implies that these cells are involved in a rapid and dynamic form of memory processing, which is necessary for processing text. The results of this study help us understand the role of the medial temporal lobe in the fast memory processes necessary for language comprehension.

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Poster

P844. Hippocampal-Neocortical Oscillations

Location: Virtual Only

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NIH U01-NS113198

Title: The direction and timing of cortical traveling waves modulates human memory processes

Authors: *U. MOHAN[1], H. ZHANG[2], J. JACOBS[1];
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Abstract: Human behavior requires a complex set of interactions across brain regions. To support the diverse demands of everyday life, the brain must dynamically coordinate neural activity across various regions with diverse functional roles. One potential mechanism for this coordination are traveling waves of brain oscillations, which propagate across the cortical surface. We identified two functional roles for traveling waves in humans by comparing how the direction and timing of traveling-wave propagation related to distinct memory processes, using direct human brain recordings. When the brain exhibits traveling theta- and alpha-band waves that propagated in a posterior-to-anterior direction both before and during stimulus presentation, subjects were 1.4-1.8 times more likely to remember a viewed word compared to waves moving in other directions. Our results suggest that the propagation direction of low frequency oscillations is a new indicator of how oscillations sequentially engage distinct brain networks to support memory encoding. We found that the propagation direction of low frequency traveling waves could be modulated by applying direct cortical stimulation at specific frequencies and locations relative to the regions where traveling waves propagated. Additionally, during the retrieval of working memories, the phase of traveling waves predicted the timing of a subject's memory recall. These findings demonstrate that traveling waves coordinate neuronal activity across widespread regions to support memory processes by directing when distinct brain regions activate and the sequence of interactions.

Disclosures: U. Mohan: None. **H. Zhang:** None. **J. Jacobs:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

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Title: Human hippocampal ripples are associated with the formation and retrieval of spatial memories

Authors: *L. KUNZ[1], B. P. STARESINA[2], P. C. REINACHER[3], A. SCHULZE-BONHAGE[3], J. JACOBS[1];
[1]Dept. of Biomed. Engin., Columbia Univ., New York, NY; [2]Univ. of Birmingham, Birmingham, United Kingdom; [3]Univ. of Freiburg, Freiburg, Germany

Abstract: Sharp-wave ripples are a neural network phenomenon that has been studied most extensively in the rodent hippocampus (Buzsaki, Hippocampus, 2015). They occur preferentially during immobility or sleep, when the activity sequences of single neurons replay the content of previous experiences (Colgin, Nat Rev Neurosci, 2016). Recent studies in both rodents and humans indicate that ripples also play a role in wake behaviors such as the planning of future navigation trajectories (Diba & Buzsaki, Nat Neurosci, 2007) as well as the encoding and retrieval of episodic memories (Norman et al., Science, 2019; Vaz et al., Science, 2020). The relevance of hippocampal ripples for human spatial memory remains poorly understood, however. In this study, we therefore examined the prevalence of ripples in the human hippocampus during a spatial memory task. We acquired intracranial EEG in 20 epilepsy patients, implanted with intracranial depth electrodes for diagnostic purposes, while the patients performed a spatial memory task in a virtual environment (Kunz et al., Neuron, 2021). In this task, the patients first learned the locations of several different everyday objects in the virtual environment. During each of multiple test trials, the patients were then asked to remember the location of a given object, navigated to the remembered object location, received feedback about their response accuracy, and collected the object from its correct location to further improve their spatial memory performance. Following previously established techniques (Norman et al., Science, 2019; Chen et al., Cell Reports, 2021), we identified human ripples in the local field potentials of bipolar recordings from the left and right hippocampus. Our results show that ripple rates were specifically increased during the retrieval periods of the task. Across trials, higher ripple rates during retrieval were associated with better spatial memory performance, suggesting that human hippocampal ripples support the recall of spatial memories. Furthermore, the rate of ripples during resting periods of the task increased over time, which may indicate that human hippocampal ripples are involved in the offline consolidation of spatial memories. Overall, our results thus help translate the functional role of ripples in the rodent hippocampus to the human brain. They also contribute to a growing body of evidence that ripples in the human hippocampus play a role in human memory.

Disclosures: L. Kunz: None. **B.P. Staresina:** None. **P.C. Reinacher:** None. **A. Schulze-Bonhage:** None. **J. Jacobs:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P844.03

Topic: H.08. Learning and Memory

Support: Columbia RISE program

Title: Traveling waves in the monkey frontoparietal network predict recent reward memory

Authors: *E. ZABEH, N. FOLEY, J. JACOBS, J. GOTTLIEB;
Columbia Univ., NewYork, NY

Abstract: Neural communication is critical for cognitive function but its mechanisms are not well understood. Recent studies suggest that a common form of neural communication is through traveling waves (TWs) -- patterns of neural oscillations that propagate continuously within local brain areas as well as between distant brain areas. Here we show that TWs are robust in microarray recordings of monkey frontal and parietal areas, where they predict sensitivity to recent reward history. On each trial, monkeys viewed a visual cue signaling a probabilistic reward and, after a brief delay period, made a visually guided saccade to obtain the reward. Analysis of anticipatory licking behavior showed that the monkeys anticipated the cue-predicted rewards and were also influenced by the (irrelevant) prior reward, consistent with previously documented biases produced by reward history. Analysis of oscillatory activity revealed pronounced TWs in local field potentials (LFP) recorded with Utah arrays in the dorsolateral prefrontal cortex (dlPFC) and in the parietal area 7A. TWs were present in most trials, were most prominent at 10-35 Hz (the dominant LFP frequency), had typical speeds of 0.1-0.3 cm per second and they generally propagated in one of two directions, which followed the anatomy of the principal and intraparietal sulci. Moreover, TWs were pronounced before the appearance of the reward cue and their features related to the monkeys' prior trial reward memory, being more frequent on trials in which the monkeys' anticipatory licking correctly reported the prior trial reward versus trials in which licking was not consistently related to the rewards. Pre-cue TWs arose de novo on each trial rather than being passive continuations of responses to the prior reward, and TWs at other timepoints did not encode cue or saccade target location, reward magnitude, probability or expected value. These findings indicate that TWs are prominent features of local neural activity and that their features correlate with specific cognitive processes such as the representation of recent rewards.

Disclosures: E. Zabeh: None. **N. Foley:** None. **J. Jacobs:** None. **J. Gottlieb:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P844.04

Topic: H.08. Learning and Memory

Title: Hippocampal-neocortical oscillatory dialogue for memory consolidation

Authors: *P. DAHAL[1], O. RAUHALA[1], D. KHODAGHOLY[1], J. GELINAS[2];
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Abstract: Understanding the mechanism behind the formation, consolidation and retrieval of memory is of critical importance. The two-stage hypothesis of memory consolidation proposes that labile, episodic memories are gradually converted into stable, long-term representations through a coordinated dialogue between the hippocampus and the neocortex during sleep. However, the exact mechanisms that underlie consolidation and retrieval (reconsolidation) is not yet fully understood. Using large-scale, high-resolution intracranial electrophysiological recordings in freely-behaving rats, we investigated the functional and behavioral relevance of dynamic oscillatory coupling among hippocampal ripples, spindles and cortical ripples during NREM sleep. We demonstrate that hippocampal-cortical coupling exists through ripple-ripple, ripple-spindle and ripple-spindle-ripple coupling. Individual patterns of NREM sessions transitioning to REM revealed that the rate and coupling of these oscillatory events are dynamically regulated across the sleep structure. To determine the relevance of hippocampal-cortical dialogue to memory, we compared the oscillatory properties in a hippocampal-dependent versus independent navigational maze task. We observed that the rate of hippocampal ripples increases during sleep following learning, regardless of the task. Ripple-spindle and ripple-ripple coupling increased following learning (consolidation), both showing a higher modulation in the hippocampal-dependent task. During sleep following retrieval (reconsolidation), we observed a decrease in ripple-spindle coupling whereas ripple-ripple coupling peaks with highest modulation. Our results suggest that ripple-spindle coupling may play an important role as priming of the functional network connectivity for consolidation. Ripple-ripple coupling gradually increased and is further enhanced by reconsolidation implicating a mechanism that cements the transfer of memory traces to the neocortex.

Disclosures: P. Dahal: None. **O. Rauhala:** None. **D. Khodagholy:** None. **J. Gelinas:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

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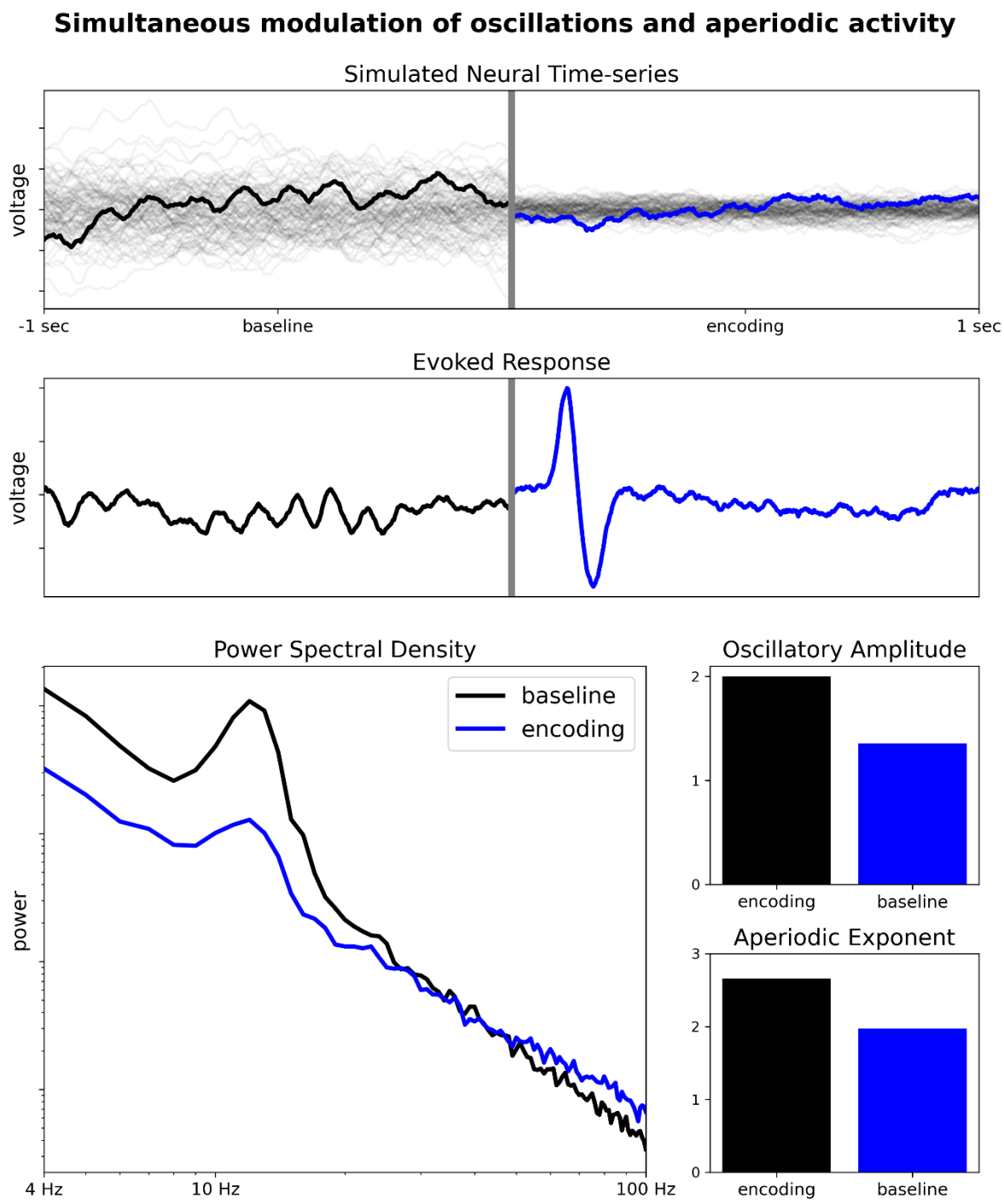
Topic: H.08. Learning and Memory

Title: Simultaneous stimulus modulation of both oscillations and aperiodic electrophysiological activity in human visual cortex

Authors: *M. W. PRESTON[1], N. SCHAWORONKOW[2], B. VOYTEK[3];
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Abstract: Decades of research have linked neural oscillations to memory encoding and retrieval However, recent work has highlighted the importance of non-oscillatory, aperiodic activity in working memory. Here, we hypothesize that both oscillations and aperiodic activity are modulated during memory

encoding paradigms. We further hypothesize that commonly-applied spectral analysis techniques conflate these two signals leading to misrepresentations of their respective roles in encoding. This study aims to disentangle the role of oscillations and aperiodic activity by leveraging the SpecParam toolbox (Donoghue et al., 2020) in conjunction with human intracranial EEG (Fellner et al., 2019) and simulated neural data. Intracranial EEG was available from patients with pharmaco-resistant epilepsy during a subsequent memory paradigm (n=13). Low-frequency oscillations (peak 8–20 Hz) were evident at baseline and exhibited desynchronization during stimulus presentation. Concurrently, the aperiodic exponent was significantly reduced, resulting in a 'flattening' of the power spectrum. Exponent changes were associated with a rotation of the spectrum about a given frequency axis, generally ~40 Hz. We simulated neural time-series with 1/fX scaling and oscillations to investigate how these empirically-observed phenomena interact to influence measures of band-power. Oscillatory de-/synchronization affected spectral power within a limited frequency range, while exponent changes affected broadband power across all frequencies (4–100 Hz). These spectral signatures were distinct from that of evoked responses, which manifest as power increases at low frequencies only (<30 Hz). Commonly-applied spectral analysis techniques were unable to disambiguate oscillatory de-/synchronization, exponent changes, and evoked responses when these processes affected spectral power within overlapping frequency ranges. Our results suggest that consideration of aperiodic activity is critical when measuring oscillations and electrophysiological signatures of memory encoding.



Disclosures: M.W. Preston: None. **N. Schaworonkow:** None. **B. Voytek:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P844.06

Topic: H.08. Learning and Memory

Support: NIH Grant 5R01MH117149-03
NIH Grant 1F99NS120543-01

Title: The memory gene KIBRA regulates experience-induced changes in hippocampal neural activity during sharp-wave ripples

Authors: *L. QUIGLEY, R. PENDRY, M. MENDOZA, L. VOLK, B. PFEIFFER;
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Abstract: Revealing how molecular interactions within single cells contribute to experience-dependent changes in circuit-level neural activity across large-scale brain networks is a major challenge in neuroscience. Disorders of complex cognition have substantial genetic contributions and ultimately manifest via emergent properties of dysfunctional neural networks. Here we investigate *in vivo* network dysfunction following removal of the synaptic scaffolding protein KIBRA. Variants in the KIBRA gene are linked to normal variation in human memory performance, and mice lacking Kibra show substantial impairment in learning and memory in addition to impaired synaptic plasticity. KIBRA is a synaptically localized scaffolding protein that regulates AMPA receptor trafficking. In addition, KIBRA and the protein complexes it organizes are associated with multiple neuropsychiatric disorders known to have synaptic/circuit etiologies. However, the role of KIBRA in regulating circuit dynamics is unknown. Thus, elucidating KIBRA's role in experience-dependent changes in network function is likely to reveal fundamental links between plasticity, memory, and neurological disorders. Particularly relevant for the study of network-level memory processes are hippocampal sharp-wave/ripple (SWR) events, brief high-frequency oscillations that occur during offline states. Considerable evidence implicates SWRs as a mechanism for memory consolidation and retrieval in both rodents and humans, and synaptic plasticity is implicated in encoding recent experience in SWRs. To determine whether KIBRA-dependent plasticity mechanisms regulate behaviorally relevant circuit dynamics, we monitored simultaneous neural activity in both the hippocampus (HC) and frontal cortex (ACC) of mice with forebrain-specific deletion of KIBRA (KIBRA cKO) using *in vivo* electrophysiology in freely behaving mice before and after a novel experience. We found minimal gross differences in baseline hippocampal network function between WT and KIBRA cKO mice. When we examined SWR properties before experience, we found that most fundamental properties of SWR events and associated hippocampal network dynamics are intact in KIBRA cKO mice. However, when we quantified SWR properties during and after experience, KIBRA cKO mice failed to show experience-dependent modifications of SWR properties observed in WT mice that are consistent with information updating. These findings indicate a failure of hippocampal circuits to properly synchronize in response to experience in the absence of KIBRA and reveal network-level mechanisms by which KIBRA function may regulate memory consolidation.

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Poster

P844. Hippocampal-Neocortical Oscillations

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Topic: H.08. Learning and Memory

Support: Sir Henry Wellcome Postdoctoral Fellowship (210924/Z/18/Z)
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Title: The role of theta synchrony in the formation of new audiovisual speech memories

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Abstract: Recent studies showed that the brain takes advantage of the synchrony between rhythmic visual and auditory stimulations peaking at 4Hz theta rate to form new multisensory episodic memories. In our study, we extended this principle to the audiovisual speech domain where syllable boundaries naturally chunk and temporally align visual and auditory inputs on a common theta phase (respectively lip apertures and acoustic envelope modulations). We hypothesised that theta phase alignment across speech modalities increases the synchronisation of neural theta oscillations between the visual and auditory sensory areas in the neocortex. The synchronisation across sensory regions should facilitate binding of information taking place downstream in the hippocampus to form a new episodic memory. We designed a memory task presenting participants with short audiovisual clips of faces of speakers engaged in conversations, for which lip movements and auditory speech signals were either synchronous or asynchronous. In a subsequent retrieval test, participants were visually cued with a speaker's face picture and had to recall which auditory signal was associated with the cue during previous encoding. We recorded the participant's magneto-encephalogram signal (MEG) to address whether the oscillatory dynamics during encoding and retrieval predicted memory performances, depending on audiovisual speech synchrony. Preliminary behavioural results (n = 13) suggest that the theta asynchrony during audiovisual speech encoding decreased subsequent memory performance (i.e., lower correct response rates and longer reaction times) as compared to natural synchronous condition. Concerning the MEG results, we anticipate to find that the higher performance for synchronous speech stimuli is accompanied by increased theta power, and increased theta-to-gamma cross-frequency coupling in the medial temporal lobe.

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Poster

P844. Hippocampal-Neocortical Oscillations

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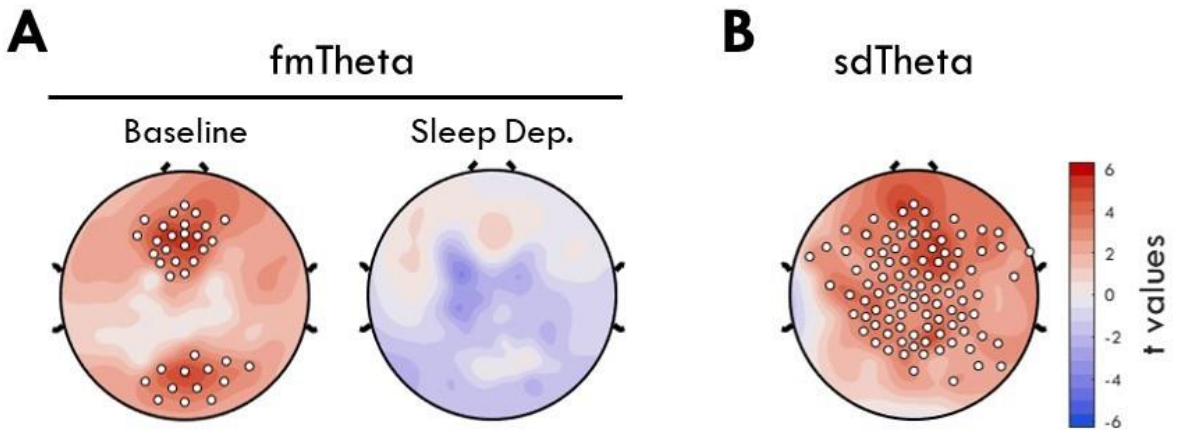
Program #/Poster #: P844.08

Topic: H.08. Learning and Memory

Title: Local sleep or cognitive control? The role of frontal theta oscillations in the wake EEG during sleep deprivation

Authors: *S. SNIPES[1,2], R. HUBER[1,3];
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Abstract: While most research into human theta oscillations (4-8 Hz) from surface EEG has been in the field of cognition, an isolated branch of research has instead identified a relationship between theta and sleep deprivation. As such, theta has been both related to increased cognitive load and increased sleep pressure, leading to conflicting interpretations of theta as a form of prefrontal control or as a form of local sleep. To disambiguate these interpretations, we first wished to determine if they correspond to the same type of oscillation or not, and what happens to theta under both high sleep pressure and high memory load. In an exploratory within-subject design, we compared frontal-midline theta (fmTheta) recorded during a short-term memory task with changes in theta following sleep deprivation (sdTheta). We recorded high-density EEG from 18 adults (18-25 y/o, 9 f) performing a Sternberg/match-to-sample task during 3 sessions at 3 levels of sleep pressure: baseline (BL, morning after 8h sleep), sleep restriction (morning after 4h sleep), and sleep deprivation (SD, 20h of wake). FmTheta was calculated contrasting within-session high-memory load to low-memory load retention periods. SdTheta was calculated comparing across-session SD retention periods to BL retention periods. We found that while fmTheta was localized to clusters of frontal and occipital channels, sdTheta increased in almost all frontal-central channels (see figure). Furthermore, the memory-load dependant difference in fmTheta disappeared during SD (Fig. A, right). The peak frequency of theta in high-load trials was 5.9 ± 0.9 Hz, and of SD trials was 6.3 ± 0.4 Hz (t=2.03, p=.058). From these results we can conclude that sdTheta is not simply an increase in fmTheta in the same frontal locations, but instead involves a greater cortical area. Whether or not they consist of fundamentally different kinds of oscillations remains undetermined, however the disappearance of memory-load dependant theta changes during sleep deprivation suggests that sdTheta either masks fmTheta, or that they may be to some extent mutually exclusive.



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Poster

P844. Hippocampal-Neocortical Oscillations

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Program #/Poster #: P844.09

Topic: H.08. Learning and Memory

Support: ERC CoG 819814

Title: Human hippocampal and cortical oscillations differentially signal surprise and uncertainty

Authors: *D. FRANK[1], J. SARNTHEIN[2], A. GIL-NAGEL[3], R. TOLEDANO[3], B. A. STRANGE[4]; [1]Univ. Politécnica De Madrid, Madrid, Spain; [2]Klinik fur Neurochirurgie, Universitatsspital Zurich, Zurich, Switzerland; [3]Hosp. Ruber Internacional, Madrid, Spain; [4]Lab. for Clin. Neurosci., Univ. Politecnica De Madrid, Pozuelo DE Alarcon, Spain

Abstract: To adaptively encode information into memory, the hippocampus should be able to extract statistical regularities in the environment and generate possible outcomes. Indeed, previous fMRI findings show that the anterior hippocampus tracks the expected uncertainty of an event in a given context (Strange et al., 2005). Such generative hippocampal responses can then inform cortical processing of upcoming sensory inputs. Here, we used intracranial EEG to examine the pre- and post-stimulus temporal dynamics underlying hippocampal and visual ventral regions' sensitivity to contextual uncertainty (Shannon's entropy) and surprise (a given event's improbability). Thirteen medication-resistant epilepsy patients participated in the experiment. All patients had depth electrodes implanted in the anterior hippocampus, seven patients also had contacts in occipital cortex, and six patients had contacts in the fusiform. On each trial, patients were presented with a coloured shape, and performed a match-to-sample task. Two colours and two shapes were combined to form four possible stimuli per block. In each block, there are likely and unlikely stimuli, varying surprise within-block; the entropy of stimuli varied across blocks (different probability distribution of the four stimuli in each block). Time-frequency analysis utilized a trial-wise GLM approach, with two predictors of interest: entropy and surprise. Furthermore, we detected hippocampal ripples and examined their occurrence frequency as a function of entropy and peri-stimulus time. In response to entropy, we found a positive association with gamma oscillatory power in occipital cortex around 700ms pre-stimulus. In the hippocampus, we observed an earlier (800ms pre-stimulus) negative association between entropy and gamma. Furthermore, hippocampal ripples were most frequently detected in high entropy trials, in the same pre-stimulus time-bin. Consistent with previous findings, we also found a positive association between surprise and hippocampal theta and gamma oscillations, from stimulus onset until 300ms post-stimulus. In the fusiform, there was a negative association between surprise and low frequency power (5-25 Hz) around 600ms post-stimulus. Overall, these results suggest an occipital and hippocampal anticipatory signaling of an upcoming stimulus, tracking uncertainty. Once the stimulus has been presented, there is a prediction error/validation response in the fusiform and hippocampus, tracking surprise.

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Poster

P844. Hippocampal-Neocortical Oscillations

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Topic: H.08. Learning and Memory

Support: Graduate Scholar Stipend CRBLM
Bourse Fondation CERVO Desjardins

Title: Theta-gamma phase amplitude coupling in human hippocampus supports auditory short-term memory retention.

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Abstract: Phase Amplitude Coupling between theta and gamma oscillations has been hypothesized to implement the retention of information during short-term memory [1]. However, the role of theta-gamma coupling in short-term memory functions, still needs to be confirmed. In this study, we investigated if auditory and hippocampal theta-gamma PAC supports WM information and its relation to participants' performance. **Objective:** We aimed to identify PAC markers that predict participants' auditory WM performance. We aim to improve our understanding about the functional role of PAC during three well characterized stages of WM: 1) Encoding; 2) Maintenance, and 3) Retrieval [2] in primary auditory regions, hippocampus, and in the ventral auditory pathway. **Participants:** We analyzed a large sample (16 drug-resistant epileptic subjects) of iEEG data recorded while patients volunteered to perform auditory WM tasks. The recordings were collected from left, right lateralized or bilateral implantations in the auditory cortex, hippocampus, and inferior frontal regions, as identified from pre- and post-implantation structural MRI. **Task:** The tasks consisted of comparing sequences of piano tones presented in pairs. The memory load was manipulated (3, 6 items) as well as the duration of the silent retention period between the to-be-compared sequences (2, 4, 8 s). **Hypotheses:** We hypothesize that theta-gamma coupling should increase with increasing memory load and increasing duration of the retention period. Moreover, we expect to observe PAC in auditory cortices during encoding of the sounds, and in hippocampal and inferior frontal regions during memory retention. **Results:** Time frequency analyses during the encoding period of the task show that each tone was encoded by a transient gamma burst in the auditory cortex, while the entire sequence elicited sustained theta oscillations in the ventral auditory stream. During the retention period, theta-gamma PAC strength in auditory and hippocampal regions was correlated with the participants' performance. Moreover, when looking at the statistical dependency between the occurrence of gamma burst as a function of the phase of the theta oscillation, we found that items were encoded in a sequential manner in the hippocampus for correct trials and in a random manner for incorrect trials. **Outcome:** This study expands our knowledge about the functional role of brain oscillation as a biological mechanism for brain information processing and integration. Moreover, it clarifies the role of cross-frequency dynamics in working memory functions in humans [1]. 1.Lisman and Jensen (2013). Neuron 2.Baddeley, A. (2010). Curr Biol

Disclosures: A. Borderie: None. **P. Albouy:** None. **B. Tillmann:** None. **A. Caclin:** None.

Poster

P844. Hippocampal-Neocortical Oscillations

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Program #/Poster #: P844.11

Topic: H.05. Working Memory

Support: SNSF 320030_176222

Title: Information flows from hippocampus to cortex during replay of verbal working memory items

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[1]Universitatsspital Zurich, Zurich, Switzerland; [2]Neurol. Dept., Geneva Univ. Hosp., Geneva, Switzerland; [3]Schweizerisches Epilepsie Zentrum, Zurich, Switzerland

Abstract: Introduction: The maintenance of items in working memory (WM) relies on a widespread network of cortical areas and hippocampus where synchronization between electrophysiological recordings reflects functional coupling. We investigated the direction of information flow between sensory areas and hippocampus during encoding and maintenance of WM items. Methods: Participants (N=15) performed a WM task where a string of letters was presented all at once, rather than sequentially, during the encoding period. Participants mentally replayed the letters during the maintenance period. We recorded sEEG from the hippocampus, scalp EEG and, additionally in 3 participants, cortical electrodes (ECoG). Results: When analyzing the information flow to and from auditory cortex by Granger causality, the flow was from ECoG over auditory cortex to hippocampus with a peak in the 8-18 Hz range while letters were presented. This flow was subsequently reversed during maintenance while letters were maintained in memory. The same pattern appeared to and from hippocampus with ECoG over occipital-parietal cortex. For scalp EEG, the pattern appeared on temporal sites, albeit in the 4-12 Hz theta-alpha range. Whereas the pattern was significantly structured for correct trials, it was unstructured for incorrect trials. Conclusions: The functional interaction between hippocampus and cortex and the reversal of information flow provide a physiological basis for the encoding of memory items and their active replay during maintenance.

Disclosures: V. Dimakopoulos: None. **P. Megevand:** None. **L. Stieglitz:** None. **L. Imbach:** None. **J. Sarnthein:** None.

Poster

P879. Feedback, Reinforcement, and Reward

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Program #/Poster #: P879.01

Topic: H.10. Human Learning and Cognition

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 895213
Sir Henry Dale Fellowship (211155/Z/18/Z) from Wellcome & Royal Society, a grant from the Jacobs Foundation (2017-1261-04)
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the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 946055)

Title: Noise ain't noise: dissociating the contributions of learning imprecision and choice inconsistency in impulsivity

Authors: *V. SKVORTSOVA, T. HAUSER;
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Abstract: Objective. Impulsivity is a well-established personality trait that plays an important role in many psychiatric disorders. However, its underlying neurocomputational mechanisms are poorly understood. Previous works linked impulsivity to exploration via increased *choice stochasticity*[1]. Recently, we showed that imprecision in the learning process (random variability in the update of action values following feedback) account for a large portion of exploratory decisions previously attributed to choice stochasticity[2]. Furthermore, learning noise explained fluctuations within the dorsomedial prefrontal cortex and pupil responses associated with the noradrenergic system linked to impulsivity.[2] Here, we studied whether impulsivity is associated with increased learning imprecision rather than choice stochasticity. **Methods.** Subjects (N=392) completed an online restless two-armed bandit task with continuous drifting payoffs and a self-report Barratt Impulsiveness Scale[3] (BIS).To dissociate overt exploration from learning imprecision, we fitted subjects' choice behaviour with a 'noisy' reinforcement learning (RL) framework which allows for a stochastic update of the values at each trial[2]. **Results.** In line with previous findings[2], the 'noisy' RL model better explained choices relative to an exact model (Pexc=0.99). Learning imprecision accounted for >70% of the decisions classified as exploratory by the exact model. Total BIS score was positively associated with the learning noise parameter (p=0.032) when controlling for age, gender, IQ, choice stochasticity (softmax parameter), and learning rate. Learning noise was strongly associated with a BIS subscale related to *motor impulsiveness* (p =0.0003). When accounting for learning noise, softmax parameter showed no correlation with any BIS scales (all $p>0.06$). Individuals with high BISmotor showed an increase in fraction of exploratory decisions explained by learning noise (78.9±2.1% vs. 71.0±2.0%, p=0.009). We replicated these results in an independent sample of subjects (N=2202) with a short version of the task (www.brainexplorer.net) (association of learning noise with BISmotor p=0.0001; BIStotal p=0.004; choice stochasticity with BISmotor p=0.27, BIStotal p=0.05). Together, these findings provide evidence that learning noise, rather than choice inconsistencies account for inter-individual differences in impulsivity and could be a marker of noradrenergic dysfunction. **References.** 1. Luman et al., 2010. Neurosci. Biobehav. Rev.34,744-754. 2. Findling C., Skvortsova V., et al., (2019). *Nature Neuro,22,2066-2077.* 3. Patton et al. (1995). J Clin Psychol.,51(6),768-74.

Disclosures: V. Skvortsova: None. **T. Hauser:** None.

Poster

P879. Feedback, Reinforcement, and Reward

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P879.02

Topic: H.10. Human Learning and Cognition

Support: NIMH K08MH080239

Title: Identifying coordinated systems during gambling feedback: Integrating EEG/ERP amplitude and phase synchrony measures of reward and loss processing

Authors: *A. A. VIVINO, D. BUTLER, A. PAVULURI, E. M. BERNAT;
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Abstract: While EEG/ERP studies have identified several electrophysiological correlates of reward and loss processing, how these correlates interact to facilitate learning from rewards and losses remains unclear. Here, we examine an array of both previously reported low-frequency and newly assessed high-frequency differences between loss and reward processing in a simple gambling feedback task and use exploratory factor analysis (EFA) to investigate interrelationships among effects across frequencies, scalp regions, and measurement domains. We considered loss-gain differences in total power oscillatory activity and interchannel and intertrial phase synchrony (ICPS and ITPS) within five frequencies (delta, theta, alpha, beta1, and beta2). To isolate the loss-gain differences within each frequency, we band-pass filtered the total power signal in feedback-locked epochs and then applied a series of one-factor principal components analyses in each filtered spectrum, resulting in one measure of loss-gain amplitude differences in each frequency band. Then, we applied these solutions to ICPS and ITPS transforms, yielding associated measures of functional connectivity between the prefrontal, medial frontal, sensorimotor, and centroparietal cortices and the consistency of activity between trials. In line with previous findings, centroparietal delta and medial frontal beta2 power were significantly increased after rewards (ps < .001, r_bs ≥ .54), while medial frontal theta and sensorimotor alpha and beta1 power were greater after losses (ps < .001, r_bs ≥ -.36). In the theta band, the medial frontal cortex and DLPFC show greater coordination following losses (p < .001, r_b = -.76). In the beta1 band, the medial frontal cortex appears to integrate information from the DLPFC and the sensorimotor cortex (ps < .001, r_bs ≥ -.45), a process that correlates strongly (rs ≥ .52) with increased ITPS in beta2 oscillations over the right lateral DLPFC following gains (p = .014, r_b = .21). In total, 17 significant individual measures were included in an EFA (principal axis factoring; promax rotation). A significant four-factor model explaining 41% of the total variance resulted, with factors corresponding to a high-frequency reward-learning system, a secondary low-frequency reward system, a theta-dependent loss-control system, and a motor maintenance system. These results mark a significant step forward by assessing together a broader array of both widely studied and emerging measures sensitive to reward/loss processing, and by describing the interrelationships among these measures to characterize differentiable coordinated systems underlying reinforcement learning.

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Poster

P879. Feedback, Reinforcement, and Reward

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Program #/Poster #: P879.03

Topic: H.10. Human Learning and Cognition

Title: Assessment of a digital behavior change program for weight loss: effects on executive function, mood and quality of life

Authors: *E. S. MITCHELL[1], H. BEHR[1], J. LEE[2], S. ANDERSEN[3], A. HO[1], A. MICHAELIDES[1]; [1]Noom Inc, New York, NY; [2]Stanford Univ., Palo Alto, CA; [3]Attain Focus, Comack, NY

Abstract: Introduction:Previous studies suggest that cognitive behavior therapy and weight loss can modify cognition and brain activity. This pilot study compares the effects of a 16 week behavior change weight loss program to digital education on cognition and behavior. Methods: Forty-four subjects (BMI > 25, aged 18-60) were randomized to 16 weeks of Noom Healthy Weight program or a control (branded health newsletters). Each subject attended at least 4 of 5 visits to evaluate cognition and weight (baseline, 4, 8, 12, and 16 weeks). Baseline characteristics and behavior were summarized using descriptive statistics. Correlations of baseline BMI and resting state EEG were analysed via mixed model with age and gender as covariates, using overweight (BMI: 25-29.9) or obese (BMI>30) categories. Repeated measures ANOVA explored post-hoc differences between groups from baseline to 16 weeks. Results: At baseline the control group (n=23) had an average weight of 219±48 lb, and an average age of 41±9 years. The intervention group (n=21) and an average weight of 205±43 lb, and an average age of 46±8 years. Baseline BMI correlated to resting state parietal alpha asymmetry; $F(1, 40) = 4.1248$, $p = 0.049$ and resting state parietal alpha asymmetry standard; $F(1, 40) = 4.1214$, $p = 0.049$.The control group gained, on average, 0.5 lb while the intervention group lost, on average, 7 lb. Mood (PANAS) and Quality of Life (PANAS) did not change over time or between groups. The Flanker task revealed overall Group differences in accuracy: congruent correct responses (p=0.017) but no Group*Time interaction (p=0.834). A similar finding was observed in congruent incorrect responses: Group differences were significant (p=0.011) but not over time (p=0.743). Reaction time in the Flanker task was significant between groups (p=0.01) and also via a Time interaction (Group*Time, p=0.029). Specifically, control reaction time did not change over the five sessions while the intervention decreased reaction time over 16 weeks.Conclusion:Noom’s behavior change weight loss program improves executive function processing, but not mood or quality of life. Future studies will address whether longer term interventions yield other effects related to mood and quality of life.

Disclosures: E.S. Mitchell: A. Employment/Salary (full or part-time):; Noom. **H. Behr:** A. Employment/Salary (full or part-time):; Noom. **J. Lee:** F. Consulting Fees (e.g., advisory boards); Noom. **S. Andersen:** A. Employment/Salary (full or part-time):; Attain Focus. **A. Ho:** A. Employment/Salary (full or part-time):; Noom. **A. Michaelides:** A. Employment/Salary (full or part-time):; Noom.

Poster

P879. Feedback, Reinforcement, and Reward

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Topic: H.10. Human Learning and Cognition

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NSF Graduate Research Fellowship
Greater Good Science Center Fellowship

Title: Human intracranial recordings reveal mixed coding of reward and salience prediction errors in fronto-insular cortices

Authors: *C. HOY[1], D. KING-STEPHENS[3], K. D. LAXER[3], J. J. LIN[4], R. T. KNIGHT[2];
[1]Helen Wills Neurosci. Inst., [2]Helen Wills Neurosci. Inst. and Dept. of Psychology, Univ. of California, Berkeley, Berkeley, CA; [3]California Pacific Med. Ctr., San Francisco, CA; [4]Departments of Neurol. and Biomed. Engin., Univ. of California, Irvine, Irvine, CA

Abstract: Prediction errors are critical computations underlying reinforcement learning (RL) and cognitive control. The valenced scalar value and non-valenced magnitude of reward prediction errors (RPEs) play complimentary roles in learning and behavioral adaptation, but their corresponding neural circuitry is not clear. Medial prefrontal cortex (MPFC) and insular cortex (IC) are key regions for performance monitoring and encode both RPE value and magnitude. These signals are hypothesized to modulate top-down control in lateral prefrontal cortex (LPFC), but it is unknown how these circuits interact. Here, we track RPE value and magnitude representations across MPFC, LPFC, and IC using intracranial EEG (iEEG) recordings in 10 patients with pharmacoresistent epilepsy (mean ± SD [range]: 35.2 ± 13.1 [21-57] years old; 1 woman). Patients performed an interval timing task with a difficulty manipulation designed to dissociate RPE valence and magnitude, and computational modeling of individual patient behavior yielded single-trial estimates of expected value, which was then contrasted with the actual outcomes to obtain scalar RPE values and magnitudes. iEEG data were preprocessed by removing epileptic and artifactual channels and epochs, bipolar re-referencing, bandstop filtering to remove line noise, and excluding behavioral outliers. We then extracted high frequency band (HFB) power known to correlate with local population activity using multi-taper filtering in 10 Hz sub-bands from 70-150 Hz, which was log transformed, segmented relative to feedback, and baseline corrected via z-score against a bootstrapped distribution of baseline values derived from -0.25 to -0.05 s pre-feedback. HFB power was predicted using single-trial RL features in sliding window multiple regression analyses (HFB power averaged in 50 ms windows, stepping by 25 ms from 0 to 0.6 s). All three regions showed large proportions of electrodes (~30-40%) coding for valenced and non-valenced RPEs. These representations were separate in some electrode, but we also observed electrodes showing mixed selectivity to both RPE features. Surprisingly, IC showed the largest proportion of RPE sensitive sites, as well as the greatest proportion of sites coding for a mixture of both RPE features. Finally, onsets of RPE value effects were earlier in IC (mean ± SD: 0.212 ± 0.114 s) than MPFC (0.289 ± 0.127 s; $t(79) = 2.82$, $p = 0.018$, FDR corrected), supporting a leading role for the insula in RPE coding. Collectively, these results clarify the interactions between neural circuits representing reward and surprise.

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Poster

P879. Feedback, Reinforcement, and Reward

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Support: TSET; Grant # r21-02
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Title: The relationships between iron status, cognitive performance, and smoking cessation in females.

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Abstract: Objective: Research suggests that women are more likely than men to respond to financial incentives to quit smoking, despite having lower overall rates of smoking cessation. Animal models suggest that iron deficiency, which is most prevalent in women, may alter dopaminergic pathways involved in both reward processing and addiction. This proposes a potential mechanism driving the sex differences in cessation rates. The present study examines the extent to which iron status impacts ability to quit smoking. **Methods:** Participants were recruited from a local smoking cessation clinic and followed for 6 months post-quit (PQ). Visits were at baseline, 1-month, and 6-months PQ. At each appointment, participants performed cognitive tests, including the paired associates learning (PAL) and probabilistic selection task (PST), with concurrent EEG, then gave a small sample of blood. Expired carbon monoxide (CO) was used as the smoking outcome of interest. Spontaneous and task-related blink rate (BR) was used as an indirect measure of dopamine levels. The iron status variable of interest was percentile rank of the NHANES III age-, race-, and sex-adjusted distributions of serum ferritin (sFtP). Correlations and regressions examined the associations between iron status variables, and spontaneous and task-related BRs at baseline, and follow-up CO. **Results:** BR during PAL was positively related to sFtP (r = 0.42, p = .012), BR during PST was positively related to sFtP (r = 0.50, p = .003), and spontaneous BR was positively related to sFtP (r = 0.63, p < .0001). This suggests significant relationships between blood iron and dopamine levels. BR had a moderate negative relationship with baseline CO (r = -.40, p = .01), suggesting that lower dopamine levels are related to heavier smoking. Baseline CO and change to CO at 4-weeks PQ had a significant negative relationship (r = -.80, p < .0001), such that smoking more at baseline corresponded to greater change in CO at 4 weeks. After adjusting for baseline CO and sFtP, BR during PST predicted change to CO at 4-weeks PQ (β = -0.32, p = .03). After adjusting for baseline CO, sFtP was significantly predictive of BR during PST (β = 0.53, p = .0009). These results suggest that, even after adjusting for baseline CO, lower iron levels are associated with lower dopamine levels, and after adjusting for baseline CO and sFtP, lower dopamine levels are associated with a smaller reduction in smoking. **Conclusion:** The results from these analyses suggest that iron level predicts dopamine level, and that dopamine level predicts changes to smoking at 4-weeks PQ. Thus, being low in iron may represent an additional burden to females attempting to quit smoking.

Disclosures: L.K. Boozary: None. **R. Caldwell:** None. **L.A. De Stefano:** None. **E. Auger:** None. **J.J.C. Waring:** None. **A. Barnett:** None. **M.J. Wenger:** None. **D.E. Kendzor:** None.

Poster

P879. Feedback, Reinforcement, and Reward

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P879.06

Topic: H.10. Human Learning and Cognition

Support: NIH Grant U54GM104941

Title: Reward feedback leads to exploratory random-walk behaviour

Authors: *A. ROTH[1,2], J. CALALO[1,2], R. LOKESH[2], S. SULLIVAN[2], M. CARTER[4], J. G. A. CASHABACK[2,1,3];
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Abstract: Exploration is critical for adaptation, from a baby learning to walk to a professional golfer adjusting their golf swing. Past work has shown greater exploration (statistical random walks) along task dimensions that have little bearing on task success (task-irrelevant) compared to dimensions that impact task success (task-relevant). These studies have only looked at exploratory random walk behavior only in the context of error-based feedback. Recently we suggested that exploratory random-walk behaviour may be driven by reinforcement-based feedback, but this idea has not yet been tested empirically. Here we test the notion that reward feedback leads to exploratory random walk behaviour. In both of our experiments, we predicted that reward feedback would lead to greater exploration along the task-irrelevant dimension. To investigate, participants grasped the handle of a robotic manipulandum and reached to a target without vision of their hand. Participants received reward feedback (pleasant sound, target briefly expanded, small monetary gain) when their final hand position (endpoint) hit the target. We calculated trial-by-trial endpoint autocorrelations to quantify random walk exploration. A higher autocorrelation indicates greater exploration. In Experiment 1, participants received reward feedback when they reached to a short rectangular target (task-relevant) or long rectangular target (task-irrelevant). Participants displayed greater exploration when reaching to the task-irrelevant target ($p = 0.001$). In Experiment 2 we aimed to replicate the first experiment while also controlling for size differences in the visually displayed targets. Here, participants received reward feedback and were shown the same short rectangular target (task-relevant) during both conditions. In one condition, the reward zone matched the displayed short rectangular (task-relevant) target. Unbeknownst to the participants, in the other condition the reward zone was a long rectangular target (task-irrelevant) even though the participants saw the short rectangular target. Similar to Experiment 1, participants showed greater exploration when reaching to the hidden task-irrelevant reward zone compared to the task-relevant reward zone ($p = 0.001$), despite observing the same short rectangular target. Interestingly, participants reported there were no differences between the two conditions (Fisher's Exact Test, p &lt 0.001), suggesting implicit processes contribute to reward-based exploratory behaviour. Collectively these results suggest reward feedback plays an important role in exploratory random walk behaviour.

Disclosures: A. Roth: None. **J. Calalo:** None. **R. Lokesh:** None. **S. Sullivan:** None. **M. Carter:** None. **J.G.A. Cashaback:** None.

Poster

P879. Feedback, Reinforcement, and Reward

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Program #/Poster #: P879.07

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NIH-NIDA (T32-DA041349)
NIH-NIDA (F31-DA053174)

Title: Hypothesis: valence-partitioned reinforcement learning binds value to the contents and context of conscious experience

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Abstract: Conscious subjective experience is private and dynamic. This poses a significant challenge that has led neuroscientists to shy away from this 'hard problem' and instead focus their attention on the 'easier' problems of information representation and behavior. There is now a major gap in our understanding of the mechanisms underlying conscious subjective experience and its dynamic nature. Computational methods and data from a variety of tools for measuring human brain activity and behavior are beginning to link dynamic changes in subjective affect with reproducible neurobehavioral signals in humans. In particular, research applying computational reinforcement learning theory has shown tremendous utility in investigating human choice behavior and the role the dopaminergic system plays in dynamic behavioral control. A major problem in this line of work, however, pertains to the design and neural implementation of algorithms that explicitly track the statistics of costs or punishments. We propose and describe in detail "Valence-Partitioned Reinforcement Learning" as a candidate approach for optimally learning about rewards and punishments directly from experience. We show that VPRL learns about punishments faster than traditional TDRL and hypothesize neural systems that could execute this algorithm. Further, we propose a *Dynamic Affective Core Hypothesis* that integrates advances in our understanding of the representation of the content and context of conscious experiences with our nascent understanding about how these representations acquire and retain subjective value. We discuss the implications of this model for 1) typical dynamic conscious experiences in humans; 2) the dynamic subjective states experienced by humans afflicted with psychiatric conditions; and 3) its utility for further investigations into the mechanisms of conscious experience in humans.

Disclosures: K.T. Kishida: None. **L.P. Sands:** None.

Poster

P879. Feedback, Reinforcement, and Reward

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NIH-NINDS (R01-NS092701)
NIH-NCATS (KL2TR001421)

Title: Reward is not enough: behavioral and neural evidence for valence-partitioned reinforcement learning in humans and subjective phenomenal experience

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Abstract: Dopamine neurons encode temporal difference reward prediction errors (TD-RPEs), which guide mammalian behavior by teaching the brain what actions lead to the most rewarding outcomes. That dopamine neurons encode TD-RPEs is well documented, but how the mammalian brain learns from punishment is less clear. Temporal difference reinforcement learning (TDRL) theory and its applications in neuroscience and artificial intelligence treat punishments as simply negatively signed rewards. However, dopamine neurons that encode TD-RPEs do not have the capacity to effectively differentiate magnitude variation in losses. We propose Valence-Partitioned Reinforcement Learning (VPRL) to hypothesize a TDRL based framework to account for how an organism might learn optimally about the statistical structure of punishments (and rewards) in parallel and based on experience. Here we test the specific hypothesis that, in humans, rewarding and punishing events are partitioned into two parallel and independent TDRL-based systems (via VPRL), and that these signals are then integrated to estimate the quality of states and actions experienced by the agent. We also test the hypothesis that signals generated during VPRL updating will drive subjective feelings as self-reported by individual participants. Two cohorts of human participants completed a probabilistic reward and punishment task while reporting (33% probability per trial) how they felt about outcomes. Cohort 1 performed the behavioral task only (n=42); cohort 2 replicated the behavioral task with functional MRI brain scanning (n=19). For both cohorts, VPRL better described participant choice behavior on the task compared to standard TDRL. Participants' learning rates and temporal discounting for rewards and punishments were asymmetric. We regressed the learned action values, RPEs, and punishment prediction errors (PPEs) derived from individuals' VPRL models on participants' subjective ratings and found that RPEs have a convex-like, and PPEs a concave-like, functional relationship to affective responses. Model-based fMRI analysis revealed that partially overlapping areas of dorsal and ventral striatum, cingulate cortex, medial prefrontal cortex, and insula track the set of VPRL prediction errors, learned action values, and associated subjective feelings. Taken together, our analyses provide evidence that humans partition rewards from punishments during learning from reinforcement and that a distributed network of subcortical, limbic, and prefrontal regions track prediction errors over rewards and punishments that differentially influence subjective feelings about choice behavior.

Disclosures: L.P. Sands: None. **A. Jiang:** None. **K.T. Kishida:** None.

Poster

P903. Schizophrenia: Molecular Mechanisms II

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Topic: H.13. Schizophrenia

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Title: Chromatin accessibility mapping reveals compound genetic effects at a schizophrenia GWAS risk locus impairing neurodevelopment and synaptic function in human neurons

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Abstract: Genome-wide association studies (GWAS) of schizophrenia (SZ) and other neuropsychiatric disorders have identified hundreds of risk single nucleotide polymorphisms (SNPs). However, functional interpretation of these GWAS risk SNPs has been challenging. Recently, we described an approach to elucidate functional SNPs by their allele-specific open chromatin (ASoC) signatures (Zhang et al., Science 2020). Here, using ASoC mapping and CRISPR/Cas9 genome editing in NEUROG2 (NGN2)-induced excitatory neurons (NGN2-iNs), we aimed at making causal links between GWAS risk SNPs and SZ-relevant disease phenotypes. We initially identified thousands of ASoC SNPs in NGN2-iNs of 20 iPSC lines and found 31 credible functional SNP in 26 SZ risk loci (out of 108) that displayed ASoC. For the four SZ-associated ASoC SNPs (near VPS45, BCL11B, PRBML1/GNL3, and BAG5) that also replicated our previous ASoC results (Zhang et al., Science 2020) in neural progenitor cells (NPCs)-derived glutamatergic neurons, we performed multiplex CRISPRi/single-cell RNA-seq (CROP-seq) in NGN2-iNs and found three SNP sites exhibited cis-regulatory effects on their flanking gene targets. Since the VPS45 locus showed the strongest ASoC in ATAC-seq and transcriptional repression of cis-targets in CROP-seq, we further investigated the function of this ASoC SNP (rs2027349) by CRISPR/Cas9 editing. In NGN2-iNs derived from isogenic iPSC lines carrying the two different alleles of rs2027349, we found that risk allele A was associated with an increased expression of the bi-directionally transcribed genes VPS45 and AC244033.2 (the latter being a lncRNA), as well as a distal gene C1orf54. Notably, NGN2-iNs carrying risk allele A showed transcriptomic changes correlated with gene expression changes in post-mortem brains of SZ, bipolar disorder, and autism spectrum disorder. Phenotypically, NGN2-iNs with A allele exhibited increases in dendritic complexity, synaptic puncta density, neural firing rate, and the frequency of calcium transients. Moreover, RNA knockdown of each cis-regulated gene in risk allele-

carrying neurons partially rescued the risk allele A-associated phenotypic changes, suggesting a phenotypic contribution from all three genes. The influence of rs2027349 was further corroborated by transcriptomic modelling, brain chromatin interaction (Hi-C) data, and the assay of local chromatin accessibility in isogenic NGN2-iNs. Our study thus reveals a complex gene regulation process at a single SZ GWAS locus that impairs neurodevelopment and synaptic function, providing a mechanistic link between a noncoding SZ risk variant and disease-related phenotypes.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Topic: H.13. Schizophrenia

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Title: Intronic haplotypes of ionotropic glutamate receptors are associated with schizophrenia

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Abstract: Schizophrenia (SCH) is a severe mental disorder characterized by a high heritability rate. The heritable component of SCH as a polygenic trait is represented by numerous variants from a heterogeneous group of genes each contributing a relatively small effect. Genome-wide association studies revealed several individual loci contributing to disease susceptibility included ionotropic glutamate receptors (iGluR) genes. In SCH patients, various single nucleotide polymorphisms (SNPs) were found and analyzed already in genes encoding the N-methyl-D-aspartate receptor (NMDAR) subunits but less information is known about genetic variations of genes encoding the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAR) and kainate (KAR) receptor subunits.
We analyzed sixteen iGluR genes in full length including extended promoter regions in 63 first-episode SCH patients and in 32 age and sex-matched healthy control subjects to determine sequence variability of iGluR genes. We aimed to describe the rate of genetic variability, its distribution, and the co-occurrence of variants in patients compared with controls, and to hallmark candidate risk variants or haplotypes. The cumulative effect of genetic risk in SCH was then estimated using a simple scoring model.

The GRIN2A-B and GRIN3A-B from the GRIN gene family as well as GRIK4 had noticeably increased genetic variation in SCH patients compared to the other studied genes. The fixation index statistic (Fst) highlighted eight intronic haplotypes and another four intronic SNPs within the sequences of iGluR genes associated with SCH ($p < 0.05$). The haplotypes were used in the proposed simple scoring model and further as a test of a genetic predisposition to schizophrenia. The positive likelihood ratio (LR) for the scoring model test reached 7.11. In the coding portion of iGluR genes, we observed the 41 protein-altering variants (38 missense variants, four frameshifts and one nonsense variant) that were not significantly associated with SCH. Using MRI scans of the brain, we also determine the BrainAge, a complex value, showing the in brain atrophy from normal brain aging expressed in years, which positively correlated with the increased number of intronic haplotypes in SCH patients. Our data suggest that some intronic regulatory regions of iGluR genes and their common variability are one of the components from which the genetic predisposition to SCH is composed.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Topic: H.13. Schizophrenia

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LQ1604 National Sustainability Program II
project “BIOCEV” CZ.1.05/1.1.00/02.0109

Title: Genetic variations of NMDAR promoter regions in schizophrenia

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Abstract: Schizophrenia (SCH) is a severe psychiatric disease characterized by high heritability and early onset during puberty. It displays a complex phenotype and affects millions of people worldwide. So far, many risk genes and environmental risk factors have been identified. The prevalent hypothesis indicates that etiology involves alterations in excitatory glutamatergic signaling. Previous studies have shown that N-methyl-D-aspartate receptor (NMDAR) plays a role in the emergence and development of SCH because its pharmacologically induced hypofunction mimics clinical symptoms and cognitive deficits observed in SCH. NMDARs are hetero tetramers composed of two GluN1 subunits combine with two GluN2 or GluN3 subunits. During postnatal development, expression changes between GluN2A/B and GluN3A/B subunit that leaves NMDAR vulnerable if genetic changes compromise these processes. Many mutations found in SCH patients occurred in the promoter regions of the genes. However, their effect on the NMDAR expression was not always well characterized. Therefore, we performed targeted sequencing and genetic analysis of the promoter regions of NMDARs of SCH patients and corresponding healthy

controls. The highest number of SNPs was observed in GluN3B subunit, in total 27. We identified 7 SNPs in GluN1 promoter region, 10 in GluN2A, 13 in GluN2B and 8 in GluN3A. Some variants such as rs181870048 (GluN2A) and rs12338602 (GluN2B) had remarkably high in silico predictions of being deleterious. Then, we subcloned specific promoters containing different genetic variations into luc_reporter plasmid and performed a luciferase assay. We found that various genetic changes affected the expression activity of promoters. Since DNA methylation of regulatory regions of the gene also affects gene transcription and is one of the mechanisms by which environmental risk factors may contribute to the emergence of SCH, we also analyzed the methylation status of selected parts of the promoter regions using real-time PCR and bisulfite sequencing. We found the increased level of DNA methylation in GluN1 with the average Tm 74,8°C and GluN3B with the average Tm 76,79°C relative to average control Tm of 74,4°C and 75,93°C respectively. GluN2A with the average Tm 78,2°C1 showed the reduction of methylation level with the average control Tm being 78,61°C. These results suggest that both, genetic changes in the promoter region of the gene as well as the changes in methylation can modulate gene expression of NMDARs and thus may cause the hypofunction of the glutamatergic signaling that contributes to the emergence of SCH.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Topic: H.13. Schizophrenia

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Title: Reversal of schizophrenia-like phenotypes in mice engineered to harbor additional copies of the glycine decarboxylase (Gldc) gene

Authors: *M. WANG[1,2], M. KAMBALI[2], R. NAGARAJAN[2], J. LYU[1,2], J. LIU[3,4], E. ENGIN[3,4], G. E. HOMANICS[5], U. RUDOLPH[2,4,3];
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Abstract: Genetic factors have been shown to increase the risk of developing psychosis. Two patients with bipolar disorder with psychotic features and schizoaffective disorder, respectively, have been found by others to harbor a small supernumerary marker chromosome, which contains multiple genes from the

9p24.1 chromosomal region, including the gene encoding glycine decarboxylase (*GLDC*). GLDC is an astrocytic enzyme that degrades glycine, which is a co-agonist at the NMDA receptor. NMDA receptor hypofunction has been implicated in the pathophysiology of schizophrenia. In these patients, glycine augmentation of antipsychotic therapy with clozapine led to improvements of psychotic and mood symptoms. In order to elucidate the potential mechanism of such reversal of symptoms with glycine, we have generated copy number variant (CNV) mice with increased copy numbers of either the entire 9p24.1 region or of *Gldc* alone. These mice were developed by introducing loxP sites into the genome followed by *trans*-allelic recombination *in vivo*. CNV's were confirmed by comparative genomic hybridization. The goal of the current study was to determine whether glycine alone is sufficient to reverse schizophrenia-like phenotypes in these CNV mice harboring extra copies of the human 9p24.1 region or just of *Gldc*. Our hypothesis was that glycine alone would be sufficient to reverse at least some schizophrenia-like phenotypes in the CNV mice modeling the patients with the 9p24.1 CNV.In our studies, we included both male and female mice with 4 copies of the 9p24.1 region or with 4 or 2 copies (equivalent to wild type) of *Gldc* ($n \geq 8$). Mice were administered glycine in their drinking water for 21 days. Three hours before behavioral experiments they received glycine (or vehicle) by gavage. To assess glycine delivery, blood samples were analyzed with LC-MS/MS. Furthermore, glycine levels were also determined in hippocampus and prefrontal cortex. Behavioral testing included acoustic startle experiments to determine prepulse inhibition and pulse habitation, latent inhibition to conditioned freezing and working memory in the Y maze. The density and morphology of dendritic spines was assessed with Golgi staining. Experiments to date suggest that glycine has differential effects in different behavioral paradigm. Our results indicate that chronic administration of glycine in mice with an increased copy number of *Gldc*, thus presumably with higher rates of glycine degradation in astrocytes, may be sufficient to reverse at least some of the schizophrenia-like phenotypes observed.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Program #/Poster #: P903.05

Topic: H.13. Schizophrenia

Support: NIMH Grant MH043784
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NIMH Grant MH124329

Title: Density of somatostatin neurons in the dorsolateral prefrontal cortex of schizophrenia subjects

Authors: *S. DIENEL[1], K. FISH[2], D. A. LEWIS[2];
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Abstract: Background: Cognitive dysfunction in schizophrenia is associated with altered GABA signaling markers in the prefrontal cortex (PFC). For example, levels of somatostatin (SST) mRNA, expressed in a subset of GABA neurons, are markedly lower in PFC gray matter in schizophrenia. The density of SST mRNA+ neurons is also lower in schizophrenia. However, whether schizophrenia is associated with fewer SST neurons or a failure of certain SST neurons to express detectable levels of SST mRNA remains unknown. **Methods**: To identify all SST neurons, we used multiplex fluorescent *in situ* hybridization to simultaneously label neurons containing SOX6 (expressed in both SST and parvalbumin (PV) neurons) and vesicular GABA transporter (VGAT) mRNAs, neither of which appear altered in schizophrenia, and SST or PV mRNA. SOX6+/VGAT+/SST+ and Sox6+/VGAT+/PV- neurons were considered SST neurons. The density of labeled neurons was quantified in 30 matched pairs of schizophrenia and unaffected comparison subjects. **Results**: In DLPFC gray matter, mean density of SOX6+/VGAT+/SST+ neurons was significantly 31.3% lower in schizophrenia subjects ($p = 0.008$), but the density of SOX6+/VGAT+/PV- neurons (which includes all SST neurons regardless of SST mRNA level) did not significantly differ between subject groups ($p = 0.33$; Bayes' Factor in favor of null hypothesis = 3.01). Studies in the same cohort using high resolution imaging to quantify levels of SST per neuron are in progress. **Conclusions**: These findings indicate that the density of SST neurons is not altered in schizophrenia, but a subset of these neurons fail to express detectable levels of SST mRNA. The presence of a normal complement of SST neurons suggests that these neurons can be targeted by therapeutic interventions to improve cognitive dysfunction in schizophrenia.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Title: Investigation of gaba-ergic interneuron-localized gene expression in the subgenual cingulate cortex of postmortem subjects diagnosed with bipolar disorder and schizophrenia

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Abstract: The human anterior cingulate cortex can be neuroanatomically subdivided, in relation to the corpus callosum, into dorsal (ACg) and ventral subgenual (SCg) components and is collectively well known to be involved in the regulation of emotional behaviors pertinent to mental illness. In a recently completed internal study, our laboratory has observed significant distributional mRNA differences related to GABA-ergic interneuron-localized transcripts, diagnosis, and anatomically distinct subregions within the ACg involving Brodmann's areas (BA) 24 and 32. To further characterize the cingulate cortex, the goal of the current study is to measure mRNA transcripts reflecting the same interneuron subpopulations within the SCg which also employ contrasting synaptic pyramidal cell connectivity. The latter include non-overlapping subpopulations identified by differential expression of parvalbumin (PV), somatostatin (SST), and vasoactive intestinal peptide (VIP). Our experimental methods combined the *in-situ* hybridization (ISH) technique using radiolabeled cRNA probes with 10 ɥm fresh-frozen SCg sections from control (n=20), schizophrenia (n=16), and bipolar disorder (n=22) subjects. Gray-scale optical density values are being used to determine potential diagnosis-related gene expression differences in PV, SST, and VIP mRNA spanning SCg subdivisions that include BA 33, 25, and ventral area 24. The results of this study will further our understanding how information processing may be dysregulated by way of GABA-ergic interneuron function in the SCg of bipolar and schizophrenic patients.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P903.07

Topic: H.13. Schizophrenia

Support: Office of Naval Research

Title: Distinct molecular subtypes in schizophrenia show differences between polyA and riboZ RNAseq from dorsolateral prefrontal cortex

Authors: E. CHILDERS, E. F. BOWEN, H. RHODES, *R. GRANGER;
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Abstract: Distinct molecular subtypes in schizophrenia shows differences between polyA and riboZ RNAseq from dorsolateral prefrontal cortex. *E Childers, E Bowen, H Rhodes, R Granger Dartmouth College*
Well-documented evidence of the physiologic, genetic, and behavioral heterogeneity of schizophrenia suggests that diagnostic subtyping may clarify the underlying pathobiology of the disorder.
We have previously provided evidence (Bowen et al 2019) of two such subtypes based on Illumina array data from the dorsolateral prefrontal cortex (DLPFC) of post-mortem frozen brains of diagnosed schizophrenics and neurological matched controls. "Type 1" and "type 2" schizophrenics had DLPFC transcriptomes that were very similar to, versus radically different from controls, respectively.

In this study we asked whether the two distinct molecular subtype signatures could be identified in RNAseq datasets, using the same subjects but different RNA selection methods: polyA vs. riboZ. The subjects did cluster into two corresponding groups for both datasets, replicating and adding support to the previously published results. Specifics of the commonalities and differences between the two schizophrenic subtypes are further analyzed.

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Poster

P903. Schizophrenia: Molecular Mechanisms II

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Topic: H.13. Schizophrenia

Support: NIH Grant T32MH015330
Maryland Stem Cell Research Fund
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Albstein Research Scholarship

Title: Sex differences in schizophrenia across the dorsolateral prefrontal cortex, hippocampus and caudate nucleus

Authors: K. J. M. BENJAMIN[1,2,3], ***R. ARORA**[1,6], J. STOLZ[1], L. D'IGNAZIO[1,3], L. COLLADO-TORRES[1,7], T. M. HYDE[1,3,4], J. E. KLEINMAN[1,2], D. R. WEINBERGER[1,2,3,4,5], A. C. M. PAQUOLA[1,2,3], J. A. ERWIN[1,2,3,7];
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Abstract: Schizophrenia is a complex neuropsychiatric disorder with sexually dimorphic features, including an increased incidence rate in males, earlier onset of disease in males, differential symptomatology and drug responsiveness. To date, only the prefrontal cortex has been examined by two large-scale transcriptome analyses for sex differences in schizophrenia. To gain novel insight into risk mechanisms underlying sexually dimorphic features of schizophrenia, we examine the BrainSeq Consortium RNA-sequencing and genotypes for the caudate nucleus (n=394), dorsolateral prefrontal cortex (DLPFC; n=360), and hippocampus (n=376) to characterize sex differences in schizophrenia by identifying genomic features (genes, transcripts, exons, and exon-exon junctions) predictive of sex, sex-specific expression in schizophrenia, and sex-interacting expression quantitative trait loci (si-eQTL). We find 442 unique genes with sex differences across brain regions, including ANK3, which showed male biased expression in the caudate nucleus. While our sex-by-diagnosis interaction model revealed only a handful of novel exon-exon junctions with statistical significance, a stringent comparison of schizophrenia dysregulation analyzed by sex identified dozens of sex-specific genomic features which are

enriched in transcriptional response of cellular stress. Our si-eQTL analysis revealed 142 unique genes, including the C4 allele which exhibited vulnerability to increased schizophrenia risk in male individuals. Overall, our results increase the number of annotated sex biased features, identified sex-specific schizophrenia genes, and provided the first annotation of si-eQTL in the human DLPFC and hippocampus. Altogether, these results point to the importance of sex informed analysis of sexually dimorphic traits and have the potential to inform therapeutics strategies in schizophrenia.

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Poster

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Program #/Poster #: P903.09

Topic: H.13. Schizophrenia

Support: ZIA MH002976
MH087473

Title: Psychosis-associated V321L mutation in Neuregulin1 disrupts expression of a schizophrenia susceptibility gene network within the hippocampus and alters adult hippocampal neurogenesis.

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Abstract: The Neuregulin1 (Nrg1) gene produces several structural isoforms of transmembrane (TM) proteins that are most popularly recognized as ligands for ErbB family of receptor tyrosine kinases. However, the type III isoform participates in bi-directional signaling acting as both a ligand (forward signaling) and a receptor (back-signaling) for ErbB4. Upon binding to ErbB4, Nrg1 undergoes regulated intramembrane proteolysis (RIP) by gamma secretase (γ-Sec). This cleavage generates a cytosolic intracellular domain (ICD) which can translocate to the nucleus. The psychosis-associated V321L mutation in Nrg1 disrupts cleavage by γ-Sec and thereby implicates nuclear back-signaling in the underlying pathology. Here we show that nuclear ICD clusters form phase separated condensates that localize to transcriptionally active compartments. Cultured hippocampal neurons stimulated with either soluble ErbB4 (sB4) or potassium chloride (KCl) showed an increase in nuclear ICD clusters, which could be blocked by pre-treatment with a γ-Sec inhibitor. Neurons from mice harboring the V321L mutation failed to show this increase. We investigated the effects of the V321L mutation on the dentate gyrus (DG) transcriptome using RNA sequencing (RNA-Seq). The DG is the gate for incoming input into the hippocampus, a function served by granule cells that are continually produced in the DG neurogenic niche. Pathway analysis of the differentially expressed genes in the V321L DG predicted dysregulation of neurogenesis, cell cycle regulation, dendrite morphogenesis, and differentiation which were confirmed by follow-up experiments. Additionally, we found that several known schizophrenia susceptibility genes were dysregulated. Chromatin immunoprecipitation enrichment analysis (ChEA) revealed many

upregulated genes shared common upstream regulators. Given this, we performed weighted gene correlation network analysis (WGCNA) to identify modules of genes whose expression is co-dysregulated. STRING analysis of statistically significant WGCNA modules showed significant protein-protein interactions within each module indicating common dysregulation of members of macromolecular complexes involved in the ubiquitin proteosome system, RNA splicing, chromatin modifying complexes and the endomembrane system. Taken together, our studies provide a mechanistic link between neurodevelopmental events and schizophrenia susceptibility genes and cellular functions. Ongoing studies are aimed at further investigating this link in an age, sex, and cell-type specific manner.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

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Program #/Poster #: P905.01

Topic: H.13. Schizophrenia

Support: NIMH Grant T32-MH018870
NIMH Grant R01-MH114965

Title: The consequences of base rate neglect on sequential belief updating and real-world beliefs

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Abstract: Base-rate neglect is a pervasive bias consisting of under-incorporation of prior knowledge into newly formed beliefs. Perhaps surprisingly, the underlying neurocomputational mechanisms of base-rate neglect remain poorly understood, and so are its effects on sequential belief updating and real-world beliefs. A Bayesian formalization of base-rate neglect predicts that, under this bias, belief trajectories should depend on the order in which evidence is presented; this should manifest as a recency bias defined by greater weighting of newer evidence and lingering uncertainty over time due to a form of prior-dependent updating, suggesting that base-rate neglecters may be prone to forming unusual long-term beliefs in the real world. We developed a novel 'urn-and-beads' task that systematically manipulated the evidence order of 8-sample sequences and used an incentive-compatible belief-elicitation procedure. Using both model-based and model-agnostic measures, our results in two independent online studies (n=151; n=116) confirm the prediction that base-rate neglect expresses itself as a recency bias and prior-dependent updating. Furthermore, while individuals exhibited base-rate neglect on average, there was substantial interindividual variability that scaled with the magnitude of the recency bias and prior-dependent updating. Given that base-rate neglect induces inaccurate beliefs, it is commonly framed as a suboptimal process. However, bounded-rationality computational models frame it as an optimal response to limited internal resources. Consistent with the latter notion, a noisy-sampling model whereby base-rate neglect results from rational discounting of noisy internal representations of prior probabilities provided an accurate description of our combined dataset (n = 267). Specifically, variability in probability

estimates correlated with base-rate neglect following the predictions of the noisy sampling model. This suggests that base-rate neglect may be driven by imprecision in the internal representation of prior knowledge. Finally, we examined self-reported propensity for unusual beliefs outside the laboratory and found that individuals with more base-rate neglect, and noisier prior representation, tended to report more unusual beliefs in their daily lives. Our results demonstrate a behavioral signature of base-rate neglect in sequential belief updating that conforms to Bayesian predictions and that this bias has a measurable influence on real-world beliefs. Further, our results suggest a candidate mechanism under which base-rate neglect reflects a rational response to an imprecise internal prior representation.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P905.02

Topic: H.04. Executive Functions

Title: Effects of prenatal cannabis vapor exposure on cognitive flexibility and in vivo cortico-striatal-thalamic network activity

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Abstract: Widespread legalization of recreational cannabis has resulted in an increase of past-month cannabis use among pregnant women, yet the long-term effects of prenatal cannabis exposure on cognitive flexibility and its underlying neural substrates remains largely unknown. We have recently used passive cannabis vapor delivery in pregnant rat dams to reveal impairments in cognitive flexibility in cannabis-exposed offspring in adulthood. A network involving the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and medial dorsal thalamus (MDT) is known to critically orchestrate decision making under shifting environmental demands. However, we do not know the extent to which alterations in the cortico-striatal-thalamic network are associated with set-shifting impairments in cannabis-exposed offspring. In ongoing studies, we are measuring local field potentials (LFP) in the mPFC, NAc core and MDT during cue presentation, response selection, and reinforcer delivery in an automated attentional set-shift task that requires rats to shift away from a visual cue-based discrimination strategy to an egocentric spatial discrimination strategy to obtain a sucrose pellet reinforcer. In naïve male rats, we have shown that gamma power in the mPFC and NAc is decreased following acute cannabis vapor exposure, while gamma coherence between the mPFC and NAc is selectively enhanced prior to and during correct response trials in the set-shifting task. Thus, we predict that prenatal cannabis exposure impairs cognitive flexibility in adulthood by altering gamma oscillations within the corticostriatal circuit, which interferes with post-feedback updating of strategy selection. To test this hypothesis, female rat dams were trained to self-administer cannabis vapor (69.9% THC; 150mg/ml, 1-hr sessions, twice daily) or vehicle prior to and during the gestational period. At PND90, male and female offspring were trained in the set-shifting tasks,

and following successful acquisition, were implanted with a stainless steel electrode array targeting the mPFC, NAc core, and MDT. Following recovery, rats were re-acclimated to the task and LFP recordings are currently being conducted during the set shift and reversal learning phases of the task to determine whether the cortico-striatal-thalamic network is differentially recruited in cannabis- and vehicle-exposed offspring. Given the increasing rates of cannabis use among pregnant mothers, these studies will provide translationally relevant data regarding the cognitive effects of prenatal cannabis exposure and offer unique insight into possible neurobiological mechanisms that could underlie these effects.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

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Topic: H.13. Schizophrenia

Support: P50MH086404
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T32MH018870
K01MH107763
F30MH122136
T32GM008444
K01MH107763

Title: Medial Prefrontal Cortex Dysfunction Mediates Working Memory Deficits in Schizophrenia

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Abstract: Schizophrenia (SCZ) is marked by deficits in working memory (WM), which are strongly predictive of poor functional outcomes, and effective treatments remain elusive. Reduced deactivation over the course of WM tasks in regions of the default mode network (DMN), including medial prefrontal cortex (mPFC), has been shown to correlate with reduced task performance in both patients and healthy individuals. However, it is unclear whether deficits in mPFC deactivation could explain impairments present in SCZ.
Medicated (n = 27) and unmedicated (n = 14) patients with SCZ (total n = 41) and matched healthy control subjects (HC; n = 40) performed a visual object *n*-back WM task across 4 fMRI runs, each comprising two 40 s 1-back and 2-back blocks. Deactivation during 1-back and 2-back blocks for each subject was quantified using a GLM framework in SPM12. An mPFC region of interest (ROI) was

employed from the Gordon (2016) parcellation by selecting prefrontal parcels in the DMN, dilating all parcels by 8 mm, and eroding the result by 5 mm. A total of 4,908 voxels (132.516 cm^3) within this mPFC ROI was then found to show significant deactivation during the 2-back task condition either across both groups (SCZ and HC) or within each group separately (assessed via NPC). From among these, a subset of 205 voxels (5.535 cm^3) showed significant associations between task performance and deactivation (FWER corrected with TFCE).
Group differences in mPFC deactivation (a single value for each subject obtained by averaging deactivation across all 205 voxels, above) and 2-back task performance were evaluated using a Welch's t-test and a Mann-Whitney-Wilcoxon test, respectively. MPFC deactivation was evaluated as a mediator of the impact of diagnosis on task performance using the CANlab M3 Mediation Toolbox, with significance evaluated using a BCa bootstrap procedure.
Relative to HC, patients with SCZ exhibited significantly worse performance (median 2-back proportion correct of 0.7813 in SCZ vs. 0.9141 in HC, $p = 0.0018$) and reduced mPFC deactivation during 2-back task blocks ($t_{77.578} = 2.1628$, $p = 0.0336$). Mediation analysis showed a significant indirect relationship between SCZ diagnosis and task performance mediated by mPFC deactivation, in addition to a direct relationship between group membership and task performance, establishing mPFC deactivation as a partial mediator (mediated effect $\beta = -0.0477$, $p = 0.0363$; direct effect $\beta = -0.1291$, $p = 0.0163$).
This work establishes mPFC dysfunction as a potential substrate for working memory impairment in schizophrenia, and a potential neuroimaging target for evaluating the effects of experimental drugs for treating these impairments.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

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Topic: H.13. Schizophrenia

Support: CIHR Grant - FRN114887
CIHR Grant - FRN364273

Title: Response disinhibition as a mediator between sleep disruption and psychotic-like experiences in adolescents

Authors: *J. OUELLET, S. SPINNEY, T. PANCHADSARAM, R. ASSAF, S. POTVIN, P. CONROD; Univ. de Montréal, Montréal, QC, Canada

Abstract: Sleep has long been associated with psychosis with a significant portion of patients reporting comorbid sleep disturbances. Increasing evidence now suggests that sleep may also act as a causal risk factor in the development of psychosis. Sleep is also known to play a role if the development of key cognitive domains, which are known to be disrupted in psychosis. These cognitive domains include

inhibitory control. Psychotic-like experiences (PLEs), sub-clinical hallucinations and delusions, have been found to gradually increase in frequency and intensity over time in adolescents who go on to transition to psychosis. PLEs therefore offer an opportunity to identify and study at risk individuals before the onset of clinically recognisable symptoms. This study aimed to investigate the role of different aspects of response inhibition as mediators in the relationship between sleep and PLEs. A longitudinal cohort of 3779 high-school students (1727 girls [46%]; mean [SD] age, 12.9 [0.5] years) was recruited from 31 Montreal high-schools and assessed on a yearly basis over a five year period. A past-month sleep score was derived from a subjective sleep questionnaire while PLEs were assessed using the Adolescent Psychotic-Like Symptoms Screener. Inhibition was measured using the Passive Avoidance Learning Paradigm. Separate analyses were performed using a multi-level model and four different PALP performance metrics as mediators (i.e. commission and omission errors under reward and punishment conditions). Our model controlled for sex and time squared. Our results support a strong association of sleep and PLEs at the between-subject (B=-1.044; SD=0.145; p<0.001) and within-subject level (B=-0.110, SD=0.053, p=0.015). At the within-subject level, commission errors were associated with sleep disturbances under punishment condition (B=-0.016; SD=0.005; p<0.000) and with PLEs under reward condition (B=0.301; SD=0,126; p< 0.005). Under reward conditions, there was a lagged association of sleep disturbances with both commission (B=-0.02; SD=0.008; P=0.005) and omission errors (B=-0,048; SD=0,018; p=0.015). A significant mediated path revealed that poor sleep was associated with increased commission errors under reward conditions the following year, which is in turn associated with a concurrent increase in PLEs frequency (B=-0.006, SD=0.003, p=0.01). These results suggest that poor sleep may cause a deviation from normal cognitive development trajectories. This weakening of information processing may make individuals more vulnerable to delusions possibly by interfering with the maturation of inhibitory control.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

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Program #/Poster #: P905.05

Topic: H.13. Schizophrenia

Support: NIH Grant MH120174
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NIH Grant MH119219

Title: Utility and diagnostic accuracy of the MMSE and Penn CNB for cognitive screening of youth at-risk for psychosis.

Authors: *J. R. KANTOR[1], R. C. GUR[3], K. RUPAREL[1], M. E. CALKINS[1], S. TROYAN[1], A. M. PORT[1], T. M. MOORE[1], R. E. GUR[1], D. R. ROALF[2];
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Abstract: **Background**: Subtle cognitive impairment is evident in individuals at-risk for developing psychosis. Thus, it is of interest to find useful cognitive screening instruments that are time-efficient and reliably help identify patients who may be at risk. The Mini-Mental State Examination (MMSE) and the Penn Computerized Neurocognitive Battery (CNB) are two validated assessments used to measure cognitive impairment in patient populations. Here, we compare the utility and diagnostic accuracy of the MMSE (Folstein et al., 1975) and Penn CNB (Gur et al. 2014) in the screening of at-risk psychosis in a large mixed longitudinal sample of typically developing (TD) and at-risk psychosis (PS) individuals and provide a crosswalk between MMSE and CNB scores. **Methods**: Participants were assessed using clinical interviews, the MMSE and Penn CNB, and were classified as PS or TD at baseline based on the presence or absence of subthreshold psychosis spectrum symptoms. Participants returned for a follow-up visit and repeated testing and were classified as TD-TD, TD-OP (other psychopathology), TD-PS, PS-TD, PS-OP, or PS-PS based on baseline and follow-up diagnoses. Two-hundred twenty-nine (n=229) participants completed the MMSE at both visits and n=210 of these completed the Penn CNB at both visits. **Results**: PS-PS ($p<0.0001$) and PS-OP ($p=0.011$) had lower MMSE scores than TD-TD participants. On CNB Z-scores, PS-PS were less accurate than TD-TD ($p<0.0001$) and TD-OP ($p=0.0003$), and TD-PS were less accurate than TD-TD ($p=0.044$) and TD-OP ($p=0.030$). ROC analyses comparing TD-TD to PS-PS participants found that the MMSE had higher specificity (71%) than the CNB, while the CNB had higher sensitivity (66%). Calculated cut-off scores resulted in similar classification accuracy for both assessments. When using cut-off scores from both assessments in a stepwise manner, classification accuracy improved to 80%. MMSE scores were highly correlated with CNB Accuracy Z-scores ($r(208)=0.42$, $p=1.528 \times 10^{-10}$) and CNB Efficiency Z-scores ($r(208)=0.41$, $p= 5.456 \times 10^{-10}$). Equipercentile equating was used for score conversion. **Conclusions:** The MMSE and CNB were successful at identifying individuals who are at persistent risk for psychosis based on their cognitive impairment. We found the MMSE to be more accurate at identifying healthy individuals and the CNB to be more accurate at identifying individuals with clinical diagnoses, particularly psychosis-risk. Overall, our results indicate that both tests offer good diagnostic and classification accuracy for screening youth who may be at-risk for psychosis, performance on the two tests is positively correlated, and score conversion is feasible.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P905.06

Topic: H.13. Schizophrenia

Title: The induced Roelofs effect in the psychosis continuum

Authors: *D. ESPOSITO[1,2], M. AMADEO[1], A. ESCELSIOR[3,4], A. INUGGI[3,4], M. AMORE[3,4], M. GORI[1];
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Abstract: Visual estimation of a stimulus' azimuthal orientation is sensitive to task-irrelevant contextual information. For example, in a left-right discrimination task, the presence of a large frame surrounding the target stimulus, shifted some degrees away from the observer's visual midline, has a repulsive effect on the perceived target's side. This effect is called the "induced Roelofs effect", and it is believed it depends on the frame's ability to distort the egocentric reference frame by attracting the apparent visual midline. A previous study showed that schizophrenia, a condition associated with a weakened sense of self, is characterized by a larger induced Roelofs effect than that of the typical population. Here we assessed the induced Roelofs effect size in a group of typical controls, a group of people affected by schizophrenia, and a group of people affected by bipolar disorder. According to the hypothesis of a psychosis continuum, bipolar disorder lies at an intermediate stage between typical and schizophrenic conditions. We predicted that, if the induced Roelofs effect were related to the psychosis severity, the bipolar group's effect size would fall between the typical controls group and the schizophrenic group's effect sizes. Our results confirmed such prediction; we also found that induced Roelofs effect and left-right discrimination ability did not follow the same group-level pattern. These results suggest that the induced Roelofs effect may be used to quantify the degree of psychosis severity. Next, we will use Bayesian optimal observer modeling to evaluate the induced Roelofs effect in terms of balance between egocentric and allocentric reference frames.

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Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

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Program #/Poster #: P905.07

Topic: H.13. Schizophrenia

Title: The brain-heart link: reduced parasympathetic activity mediates the deficit in inhibitory control observed for Schizophrenia and Obsessive Compulsive Disorder

Authors: *M. LAZARIDI[1,2], G. PANAGIOTAROPOULOU[2], P. COVANIS[2], T. KARANTINOS[2], E. KOUMANTAROU MALISIOVA[3], I. MOURIKIS[3], C. KLEIN[4], E. ANGELOPOULOS[5], N. P. SMYRNIS[6];
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Res. Inst. “COSTAS STEFANIS”, Athens, Greece., Athens, Greece; [6]Psychiatry Dept., Natl. and Kapodistrian Univesrity of Athens Med., Athens, Greece

Abstract: The neurovisceral integration model proposes a brain-heart linkage where prefrontal cortical brain areas related to executive functions are connected to midbrain areas that are responsible for the vagal control of the heart. There is evidence documenting autonomic dysregulation among patients with schizophrenia (SCZ) while much less is known in patients with Obsessive Compulsive Disorder (OCD). Both SCZ and OCD patients present deficits in the inhibitory control of saccadic eye movements related to prefrontal cortical areas. The current examined the association between autonomic activity and inhibitory oculomotor control in SCZ and OCD using indexes of heart rate variability (HRV) measured during the performance of saccade and antisaccade tasks. The results from 30 healthy controls (HC), 30 SCZ and 15 OCD patients confirmed the presence of a deficit in antisaccade task performance in schizophrenia and OCD ($F_{(2,72)} = 5.01$, $p < .001$). Electrocardiographic (ECG) recordings were used to determine autonomic activity during saccade and antisaccade task performance. RR intervals were detected in the ECG signal and used to measure the high frequency component of HRV, an indicator of parasympathetic activity. Results showed that schizophrenia and OCD patients had lower hfHRV during antisaccade task, ($F_{(2,72)} = 10.08$, $p < .001$). Mediation analysis was employed to further examine the connection between increased error rate in antisaccade task and decreased hfHRV in patients with schizophrenia and OCD. A specific relationship between inhibitory control and parasympathetic activity was documented, where hfHRV mediated the effect difference between both groups of schizophrenia and OCD patients and controls in antisaccade error rate (6.24 (5.69 - 6.79), t= 22.77 $p < .001$). Our results demonstrate that the higher the parasympathetic activation the higher the inhibitory control and suggest that parasympathetic activity, specifically the hfHRV, is a key feature for explaining the effect difference between patients and controls in inhibitory control.

Disclosures: M. Lazaridi: None. **G. Panagiotaropoulou:** None. **P. Covanis:** None. **T. Karantinos:** None. **E. Koumantarou Malisiova:** None. **I. Mourikis:** None. **C. Klein:** None. **E. Angelopoulos:** None. **N.P. Smyrnis:** None.

Poster

P905. Psychosis and Schizophrenia: Behavior and Symptoms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P905.08

Topic: H.13. Schizophrenia

Support: NIH grant MH103222

Title: Using a B-SNIP biomarker fingerprint to stratify participants for clinical trials:testing the kynurenic acid hypothesis of cognitive impairment

Authors: C. A. TAMMINGA[1], M. E. HUDGENS-HANEY[2], B. A. CLEMENTZ[3], E. S. GERSHON[4], S. KEEDY[5], G. PEARLSON[6], M. KESHAVAN[7], S. K. HILL[8], R. SCHWARCZ[9];
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Abstract: The brain concentration of kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation and antagonist of both N-methyl-D-aspartic acid and α7 nicotinic acetylcholine receptors, is elevated in the prefrontal cortex of individuals with schizophrenia (SZ). This increase is clinically relevant because hypofunction of these receptors is implicated in the pathophysiology and cognitive deficits of the disease. Two enzymes, kynurenine 3-monooxygenase (KMO) and kynurenine aminotransferase II (KAT II) play critical roles in regulating brain KYNA levels. Thus, a reduction in KMO activity, as seen in the brains of people with SZ, increases brain KYNA, and inhibition of KAT II, which produces most KYNA in the brain, could be a fundamentally new approach to treat cognitive impairments (Schwarcz et al., 2012). In examined postmortem SZ cases (BA6 region), the KMO SNP *rs2275163 CC* (but not KMO SNP *rs2275163 CT/TT*) is associated with reduced KMO mRNA expression enzyme activity and elevated KYNA levels. Moreover, and unrelated to a SZ diagnosis, this genotype reduces predictive pursuit function and worsens visuospatial working memory (Wonodi et al., 2011). Based on these results, we now compared a "biomarker fingerprint" of KMO SNP *rs2275163 CC* (the "high KYNA" phenotype) versus *rs2275163 CT/TT* in a large cohort (N=200/genotype) of SZ individuals belonging to Biotypes 1 and 2, as defined by the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium (Clementz, 2015). For this analysis, we conducted four separate canonical discriminant analyses with the biotype cases (each bootstrapped 1000x with 95% sampling), evaluating (i) cognition (BACS and Stop Signal Task), (ii) EEG (evoked and intrinsic activity), (iii) oculomotor function (pro-/anti-saccades and smooth pursuit), (iv) cortical thickness, (v) cortical surface area, and (vi) cortical and subcortical regional volumes. The results revealed a 0.7 SD separation between *rs2275163 CC* and *rs2275163 CT/TT* probands. Notably, probands with z-scores >0.5 had a >95% likelihood of carrying the *rs2275163 CC* genotype. The CC biomarker profile defines "high KYNA" and captures all such cases, secondary to any source. These findings support using biomarkers as co-primary outcome measures to select study populations for clinical trials designed to test KAT II-modifying cognitive enhancers, by recruiting "high KYNA" populations. This approach of prospective enrichment of the patient population through phenotyping is expected to reduce the size of trials as well as increase the likelihood of success by targeting SZ people with a "high KYNA" fingerprint.

Disclosures: C.A. Tamminga: None. **M.E. Hudgens-Haney:** None. **B.A. Clementz:** None. **E.S. Gershon:** None. **S. Keedy:** None. **G. Pearlson:** None. **M. Keshavan:** None. **S.K. Hill:** None. **R. Schwarcz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KyNexis, VistaGen.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.01

Topic: I.04. Physiological Methods

Title: High density, high channel count flexible neural probes realized by integration to CMOS chips

Authors: *E. T. ZHAO[1], J. HULL[1], N. HEMED[1], A. HIERLEMANN[2], J. R. HUGUENARD[3], N. A. MELOSH[1];
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Abstract: Development of ultra-small and flexible electronics have become a key research topic in neural interfaces; these devices have high spatiotemporal resolution and are able to intimately integrate with biological tissue, enabling tracking of individual neurons over weeks. A central challenge limiting the scalability of such devices is the development of high-density and high channel count input/output (I/O) connections between the flexible electrodes and downstream electronics. Here, we introduce a novel nanofabricated microstructure, facilitating connectivity between our neural probe and planar, high-density multielectrode arrays (HD-MEAs) with 34 µm pitch and 3396 individually addressable channels. To our knowledge this is the smallest pitch and highest channel count reported in literature. We realize this technology in two applications, intracortical probes and electrocorticography (ECoG) arrays, and through this are able to study brain-wide transitions that occur during epileptic seizures with unparalleled spatial resolution.

Disclosures: E.T. Zhao: None. **J. Hull:** None. **N. Hemed:** None. **A. Hierlemann:** None. **J.R. Huguenard:** None. **N.A. Melosh:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.02

Topic: I.04. Physiological Methods

Support: German Research Foundation (Deutsche Forschungsgemeinschaft), collaborative research centre CRC 1261 “Magnetoelectric Sensors: From Composite Materials to Biomagnetic Diagnostics”
German Research Foundation (Deutsche Forschungsgemeinschaft), research training group RTG 2154 “Materials for Brain”.

Title: Towards Automated Epileptic Seizure Detection in Electrically Active Implants

Authors: *A. BAHR[1], S. SIMMICH[2], J. SOLIS ARBUSTINI[1], R. RIEGER[2];
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Abstract: In recent years, the design of neural amplifiers has shown tremendous progress. The integration of thousands of recording sites into the electrode enables recordings with high spatial resolution [1, 2]. A key element was the integration of the neural preamplifier into the electrode itself. In future, it is expected that integration will extend to system level towards implantable systems. This will enable new electronically active implants, e.g. medical devices for epileptic seizure detection and treatment or

advanced BCIs.
Implantable systems require a very high energy efficiency to warrant long use time. Therefore, every subsystem has to be power-optimized. In this work, two key subsystems of an automated epileptic seizure detection system are analyzed resp. optimized: neural amplifier and intelligent signal processing unit. A systematic analysis of trends in integrated amplifier designs is performed [3]. Noise-Efficiency-Factor (NEF) is used as figure of merit as it combines the two most important parameters, the noise and the current consumption. The NEF shows a steady improvement over the last decades. In parallel, the area of the preamplifiers has been decreased significantly. Nevertheless, so far, no design has been published that achieves low area consumption and low NEF at the same time [3].
For the detection of epileptic seizures an ultra-low power convolutional neural network is designed [4]. It classifies human brain signals and is implemented on an ultra-low power RISC-V microcontroller. The performance of the classification is comparable with state-of-the art algorithms. Using an energy budget suitable for implantable systems automated epileptic seizure detection in implantable systems will be enabled in future [4].
References:
[1] Jun, J.J.; et. al. Fully integrated silicon probes for high-density recording of neural activity. Nat. Cell Biol. 2017, 551, 232-236
[2] Musk, E.N. An Integrated Brain-Machine Interface Platform with Thousands of Channels. J. Med. Internet Res. 2019, 21, e16194
[3] Simmich, S. et. al. Noise Efficient Integrated Amplifier Designs for Biomedical Applications. Electronics 2021, 10(13), 1522
[4] Bahr, A., et. al. Epileptic Seizure Detection on an Ultra-Low-Power Embedded RISC-V Processor Using a Convolutional Neural Network Biosensors 2021, 11(7), 203

Disclosures: A. Bahr: None. **S. Simmich:** None. **J. Solis Arbustini:** None. **R. Rieger:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

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Program #/Poster #: P941.03

Topic: I.04. Physiological Methods

Support: NIH Grant EB028055

Title: Delivery of Low-Intensity Pulsed Ultrasound in the Cortex to Improve Longevity and Performance of Neural Interfaces

Authors: *N. N. TIRKO[1], A. S. ALSUBHI[1], J. K. GREASER[1], R. S. CLEMENT[2], K. A. SNOOK[1], R. B. BAGWELL[1], M. L. MULVIHILL[1];
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Abstract: Chronic neural implants hold great potential for illuminating features of neural function, treating neurological disorders, and enabling the next generation of neuroprosthetics. Penetrating electrode arrays provide direct access to neural signals across the central and peripheral nervous system

with high temporospatial resolution. However, a consistent point of failure for chronically implanted microelectrode arrays is poor longevity and variability in functionality of these devices. The foreign body response (FBR) can cause glial scarring and neural cell loss near the electrode sites. The FBR begins with electrode insertion, when damage to the blood brain barrier activates astrocytes and microglia, and continues throughout the lifetime of the implant due to the persistent presence of the foreign material in the tissue. Efforts to mitigate the FBR have focused on things like: limiting insertion damage during implantation, reducing the mechanical mismatch between brain and implant, and suppressing the FBR by incorporating exogenous chemicals. Rather than relying on temporary interventions to limit the FBR, we proposed to chronically harness endogenous cortical function to improve the neural interface microenvironment. Here, we investigate the use of sub-threshold low-intensity pulsed ultrasound (LIPUS) to improve tissue health at the neural interface. LIPUS has recently been shown to have protective and healing effects in models of cerebral disease and injury, through promotion of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors. Our studies demonstrate that periodic application of localized LIPUS to tissue at the neural interface can promote improved electrophysiology signal quality, as measured via signal-to-noise ratios, electrode single-unit yields, and histological evaluation of glial scarring.

Disclosures: N.N. Tirko: A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **A.S. Alsubhi:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **J.K. Greaser:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **R.S. Clement:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **K.A. Snook:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **R.B. Bagwell:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **M.L. Mulvihill:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc..

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.04

Topic: I.04. Physiological Methods

Support: NIH

Title: Chronicity of spinal cord injury on the lower urinary system in awake male Wistar rats: Cluster analysis based on the variables related to the technique.

Authors: *D. MEDINA AGUINAGA[1], J. GUMBEL[2], R. F. HOEY[3], C. HUBSCHER[4];
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Abstract: Lower urinary tract (LUT) dysfunction after spinal cord injury (SCI) represents one of most disastrous consecuences over the quality of life of this population. Recently has been describe models for the study of LUTs and SCI in awake animals. However, these models were described on female rats, keeping a lack on the study of males with this important technique. The overall objective is to develop an

animal model of urodynamic study, including needle electromyography of the external urethral sphincter (EUS) in awake male rats with different grades of chronicity, as well as, to include variables related to the cystometric (CMG) and electromyographic (EMG) techniques on the data analysis to reduce the variability and improve the significance. All experiments were approved by the the University of Louisville Institutional Animal Use and Care Committee and carried out in accordance to the National Institutes of Health guidelines. A total of 180 adult male Wistar rats were used for the entirety of these experiments. Six timeline SCI groups included 3, 7, 14, 28, 42 and 84 dpi study endpoints as well as three surgical sham groups matched for endpoints 3, 14 and 42 dpi. The end point day, under isofluorane anesthesia, a PE-60 tubing was placed on the bladder dome and a pair of electrodes were stoked into the EUS and attached to the inguinal ligament and tunneled to the dorsal neck. Passed two hours, a CMG-EMG in awake and restrained rats was performed and 5 void cycles was recorder for further analysis. The CMG records were classified in five categories: non artifact CMG, artifact less than 30%, 30% to 60% of CMG artifact, 60% to 90% of CMG artifact, and 100% artifact. The EMG records were classified in four categories: Clear EMG with minimum movement artifact, EMG including important movement artifact which gone with signal filtering, EMG with important electrical background who includes phasical electric activity during void, and EMG without signal from the EUS. Results. 46 of 49 Sham animals presented voids during the experiment. 120 of 130 injured rats present voids. 14 of 49 present CMG artifacts in sham and 48 of 130 present CMG artifacts in SCI groups. 3 of 49 Sham present EMG artifacts and 12 of 130 SCI have EMG artifacts. The analysis of the CMG and EMG are in process. We present the first report of CMG and needle EMG in awake male rats. The technique implemented in our laboratory make possible to record EUS EMG during void in awake healthy and injured males with a high rate of success. Uninjured animals present higher rate of CMG pressure artifacts, probably caused for movement. Is necessary to refine the CMG technique for improve the quality of the pressure records and obtain more accurate results.

Disclosures: D. Medina Aguinaga: None. **J. Gumbel:** None. **R.F. Hoey:** None. **C. Hubscher:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

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Program #/Poster #: P941.05

Topic: I.04. Physiological Methods

Support: 1R43DA051265-01
2R44NS105500-02

Title: Surgical Implantation of Flexible Penetrating Electrodes in Deep Brain with an Ultrasonic Vibration Insertion System

Authors: *R. S. CLEMENT[1], H.-J. KIM[2], **N. N. TIRKO**[3], S.-H. LEE[2], R. B. BAGWELL[1];
[1]Actuated Med. Inc., Bellefonte, PA; [2]Univ. of North Carolina, Chapel Hill, NC; [3]Actuated Med. Inc, Bellefonte, PA

Abstract: Actuated Medical, Inc. is developing a suite of neural implant insertion systems which utilize ultrasonic micro-vibration to reduce the forces necessary to penetrate and insert devices into neural targets (www.neuralglider.com). With rigid intracortical electrode arrays (IEAs) we have shown the approach reduces insertion force and tissue dimpling, without interfering with electrode integrity or performance. Here we present on the application of the ultrasonic insertion technology to the insertion of flexible neural probes targeting deep brain structures (e.g. Nucleus Accumbens, NAc). The single-shank polyimide probes are 10 mm long, 60 µm thick, with width tapered from 200 µm near the tip to 600 µm at the base, with 16 recording sites linearly arrayed near the tip (Figure 1A). Benchtop insertion tests were first performed in a 2-layer agar model representing meningeal (1.5% density) and underlying brain tissue (0.5% density) at insertion speeds of 50, 250, and 1000 µm/s. Samples were placed on a 10 g capacity load cell which measured the forces during probe insertion (Figure 1B). Ultrasonic actuation of the probes reduced the insertion force peaks by 80-90% at multiple insertion speeds (Figure 1C). In follow-up *in vivo* studies in rats (Sprague-Dawley, 250-300g), ultrasonic vibration enabled probes to be inserted through intact dura for placement in NAc (1.5 mm anterior to bregma, 2 mm right of midline and 7 mm ventral to cortical surface). Functional MRI (fMRI, 9.4T) in response to deep brain stimulation revealed that probes were placed more accurately when ultrasonic micro-vibration was applied during insertion (Figure 1D). Post implant histology revealed comparable or slightly less tissue response for probes inserted with ultrasonic micro-vibration vs. control (Figure 1E). Ultrasonic micro-vibration can simplify neural probe surgery in some cases by eliminating the dura removal step while also improving insertion of flexible probes.

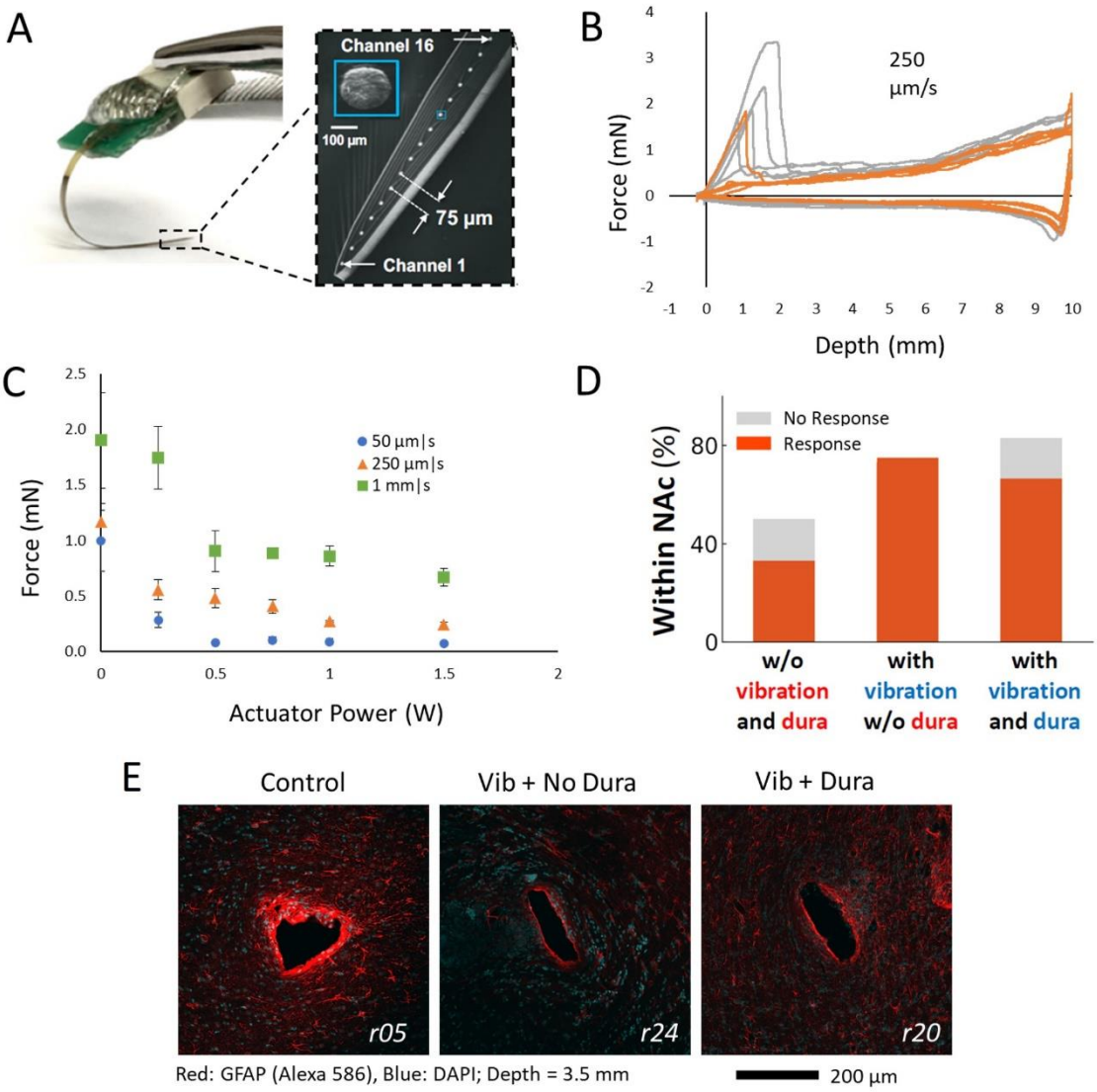


Figure 1. A) Flexible polyimide probes used in study. **B)** Insertion force profile showing insertion (positive force values) and retraction (negative force values) throughout 10 mm insertions into 2-layer agar model (orange with micro-vibration applied, gray: control). **C)** Summary of insertion force peak values for different insertion speeds and actuator powers (agar 2-layer model). **D)** Success rate of targeting NAc and activating in fMRI. Each group consists of 6 (control – no vibration), 8 (vibration without dura), 6 (vibration with dura); Female Sprague Dawley Rat (n=11), body weight 300g ~ 350g. **E)** Post implant histology images from each insertion condition; 3.5 mm below cortical surface.

Disclosures: R.S. Clement: A. Employment/Salary (full or part-time):; Actuated Medical Inc. **H. Kim:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Actuated Medical, Inc. **N.N. Tirko:** A. Employment/Salary (full or part-time):; Actuated Medical Inc. **S. Lee:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug

study, report that research relationship even if those funds come to an institution.; Actuated Medical, Inc. **R.B. Bagwell:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical, Inc..

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.06

Topic: I.04. Physiological Methods

Support: Shirley Ryan Ability Lab
Northwestern University
The Ohio State University

Title: Tattoo Electrode for Long Term High Density Surface EMG Recording

Authors: *S. CHANDRA[1], J. LI[2], A. BARRY[3], N. L. SURESH[4], W. Z. RYMER[5];
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Abstract: High-density surface electromyography (HDsEMG) enables the recording of myoelectrical activity patterns distributed across the skin surface of a muscle during contraction. Due to its ability to provide non-invasive recordings with high spatial fidelity, HDsEMG plays a potentially important role in clinical and neuroscientific research (e.g. identifying neuro-muscular junction location, measuring fiber conduction velocity, Motor Unit discrimination). However, HDsEMG currently has minimal applications in clinical settings. A major reason is the modest signal quality, especially during long-term recording, since these require stable electrode properties and a consistent skin-electrode interface.
We demonstrate here a novel “tattoo” electrode for HDsEMG recording that addresses these limitations. The superior recording performances of the tattoo electrode have been investigated and reported in our earlier work. Here, we explore the performance of the novel tattoo electrode to record HDsEMG signals during long-term wearing in daily life. We fabricated a 4cm×3cm tattoo grid on a deformable electronics membrane incorporating 64 electrodes (2mm diameter). Our dry HDsEMG grid exhibits easy layout programmability, skin breathability, substantial “stretchability” and superior skin conformity, while faithfully recording EMG signals during different levels of isometric contraction of the Medial Gastrocnemius of a healthy individual. The force and sEMG signals were recorded during multiple isometric, non-fatiguing plantarflexion contractions while tracking trapezoidal force-trajectories over various force ranges (20%MVC-100%MVC). 64 channel EMG data were recorded and digitized simultaneously using TMSi Refa-128™ amplifier and saved in a Windows PC. The recordings were performed with a gap of several hours with the tattoo electrode attached to the skin surface while the subject performed normal daily activities.
We have analyzed the sEMG signal during the steady-state part of the contraction force trajectory. Each channel was analyzed individually across the grid. The recordings were found to provide an accurate

representation of of the EMG spectrum, No significant difference in the signal to noise ratio, and spectral power of the recorded signal emerged, even during the next day recording while the tattoo being attached to the skin.
The tattoo grid electrode can potentially be used for recording HDsEMG from skin overlying superficial muscles for long-term recording. This tattoo electrode will potentially facilitate HDsEMG application in clinical scenarios, especially in tracking severe neuromuscular disorders, such ALS and SMA.

Disclosures: S. Chandra: None. **J. Li:** None. **A. Barry:** None. **N.L. Suresh:** None. **W.Z. Rymer:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.07

Topic: I.04. Physiological Methods

Support: U01EB029834
U01EB028662

Title: In Vivo swine model of focal seizures for developing and validating Acoustoelectric Brain Imaging of Neuronal Currents

Authors: *R. WITTE[1], A. ALVAREZ[2], T. TRUJILLO[2], C. PRESTON[2], A. BURTON[2], D. MUSTACICH[3], M. WEINAND[4], K. GOTHARD[5], S. L. COWEN[6];
[1]Med. Imaging, [2]Biomed. Engin., [3]Surgery, [4]Neurosurg., [5]Neurol., [6]Dept. of Psychology, Univ. of Arizona, Tucson, AZ

Abstract: A broad spectrum of brain disorders—from epilepsy to depression—are characterized by abnormal electrical conduction pathways. Although surface EEG is the gold standard for electrical brain mapping, it suffers from poor spatial resolution and inaccuracies, especially when resolving deep current sources. Our goal is to develop 4D transcranial acoustoelectric brain imaging (tABI), a disruptive technology that uses a focused ultrasound beam to map neuronal currents through the human skull at the millimeter and millisecond scales. This study describes an acute *in vivo* swine model of focal onset seizures for developing ABI and validating with high density surface recording. Following a bilateral craniotomy and exposure of the cortical surface, the snout area of the somatosensory cortex of three young farm swine was mapped by electrically stimulating (100 µs pulse at 0.5 Hz, 1-15 mA) the right or left snout using horizontally spaced needle electrodes with ~20 mm separation. Two 16-contact NeuroNexus grid electrode arrays with 4 mm inter-electrode spacing (CS2-2-4) were used to record evoked activity across the contralateral rostrum somatosensory area (0.1 - 0.8 mV peak). Following snout stimulation, an injection of 25 µL of bicuculline was topically applied to the somatosensory cortex to induce transient seizures that typically lasted between 5 and 10 minutes. Local field potentials (Intan) were acquired using before, during and after snout stimulation and seizure induction. Ictal spikes during focal onset seizures corresponded with travelling waves (1 - 2 m/s) that originated outward from the site of the bicuculine injection. For performing ABI, a custom 0.6 MHz 2D US array (126 elements, 18 X 7) with a conical standoff adapter (L=38 mm) was placed over the electrode array for delivering US pulses

(Vantage 64 LE) over the somatosensory cortex. High frequency acoustoelectric signals were recorded on a custom multichannel broadband differential amplifier (0.2 - 6 MHz) and NI DAQ system in 500 ms increments. Initial experiments suggested that the processed signals were near the limits of detection of the weak AE signal (less than 1 μV). In one experiment, a saline-soaked bone flap from an adult human skull was placed between the swine cortex and US array to assess the signal loss of the vibration potential due to the presence of bone (-3 dB/4 mm). Ongoing work is focused on improving the AE instrumentation and acquisition algorithms to dramatically amplify the AE signal and reduce background noise towards feasibility of a noninvasive ABI system designed for functional human brain imaging of neuronal currents.

Disclosures: R. Witte: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ElectroSonix LLC. **A. Alvarez:** None. **T. Trujillo:** None. **C. Preston:** None. **A. Burton:** None. **D. Mustacich:** None. **M. Weinand:** None. **K. Gothard:** None. **S.L. Cowen:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

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Program #/Poster #: P941.08

Topic: I.04. Physiological Methods

Support: Simons Collaboration on the Global Brain 687458
Wellcome Trust 209558
Pew Biomedical Scholars Program
Klingenstein-Simons Fellowship in Neuroscience

Title: A flexible refractory period metric for spike sorting improves accuracy on brainwide electrophysiological datasets

Authors: *N. ROTH[1], .. INTERNATIONAL BRAIN LABORATORY[2], N. A. STEINMETZ[1];
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Abstract: The advent of increasingly large electrophysiological datasets has increased the need for quality metrics that automatically reject poorly isolated neurons. One key method estimates contamination by assuming that each neuron has a refractory period. However, existing methods cannot be applied without prior knowledge of the refractory period duration, limiting their usefulness in datasets that include neurons from multiple brain regions or cell types. Here, we describe a new metric which assesses contamination across a range of hypothetical refractory periods. We compute the maximum allowed number of refractory period violations for many period durations, then generate the likelihood of observing this number of violations via a Poisson process, at a maximum allowed contamination level. A neuron passes the criterion if the count of observed violations is lower than the maximum acceptable, for any choice of refractory period. This metric allows us to assess contamination without assuming a single fixed refractory period duration.To quantify how well this metric classifies neurons, we performed simulations of neurons with a range of true refractory periods, firing rates, and levels of contamination.

As expected, we find that for high firing rates, the metric rejects neurons with more than 10% contamination and passes neurons with less than 10% contamination, for a range of true refractory periods including those less than the traditional 2 ms assumption. When firing rates are low, the metric rejects neurons with brief true refractory periods, as we cannot be statistically confident that the lack of contamination did not arise by chance. As the true refractory period increases, neurons with low contamination begin to pass the metric. Thus, our metric has advantages for assessing neurons with both brief and long true refractory periods. To assess whether this metric improves performance on real datasets, we used data collected by the International Brain Lab across 278 brain regions. We found that true refractory periods were diverse across brain regions (mean ± s.e.m. in cortex: 2.63 ± 0.010 ms; hippocampus: 2.58 ± 0.021 ms; striatum: 2.92 ± 0.018 ms; thalamus: 1.82 ± 0.025 ms). We next compared the performance of the flexible refractory period metric with that of a fixed (2 ms) refractory period metric with equal contamination thresholds, and found that the flexible metric allows us to include 25% more neurons that would have been previously marked as contaminated, and rejects 15% that would have been previously marked as uncontaminated. Thus this new metric improves our ability to apply a single consistent set of quality metrics to brainwide data with high accuracy.

Disclosures: N. Roth: None. **.. International Brain Laboratory:** None. **N.A. Steinmetz:** None.

Poster

P941. Electrophysiology Methods: Electrode Arrays III

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P941.09

Topic: I.04. Physiological Methods

Title: Multifunctional graphene based neuroelectronics

Authors: *C. DELACOUR[1], V. DUPUIT[1], O. TERRAL[1], S. GREENHORN[1], A. BRIANÇON-MARJOLLET[2], G. COURTINE[3], V. COIZET[4], J. WARNKING[4], E. BARBIER[4];
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Abstract: 2D materials such as graphene offer an ideal platform for recording and culturing neural networks, regarding its exceptional neuronal affinity and the presence of readily accessible surface charges which give the unprecedented possibility to realize a direct electrical coupling with cells. In addition, graphene is highly flexible, optically transparent and could be transferred on a wide range of substrate to be combined with multiple electrophysiological tools.Here, we will present the cytocompatibility study of pristine monolayer graphene, and its significant advantage for neuroprostheses and *in-vitro* model networks. We will show that the neuronal affinity of graphene opens avenue of applications such for patterning long-lasting *in-vitro* neural networks [1], and for increasing life time of intracortical brain interfaces [2].
Moreover, the nano-structuration of large (mm²) CVD-grown graphene monolayers allows the fabrication of dense arrays of highly sensitive field effect transistors (G-FETs). Among their successful bio-integrations, the detection of action potentials in numerous electrogenic cells including neurons [3] has

paved the road for the high spatio-temporal and wide-field mapping of neuronal activity. We will show that ultimate sensing could also be achieved such the field effect detection of ion channel activity within neuron networks [4]. We are combining this ultra-sensitive neuroelectronics with microfluidic-designed neural network and numerous imaging methods for fundamental and applied research including brain-on-chip and *in-vivo* monitoring.
[1] Veliev, F., Briançon-Marjollet, A., Bouchiat, V., Delacour, C. Biomaterials, 86 (2016). 33-41.[2] Bourrier, A., Shkorbatova, P., Bonizzato, M., Rey, E., Barraud, Q., Courtine, G., ... & Delacour, C. (2019) Advanced healthcare materials, 8(18), 1801331.[3] Veliev, F. , Han, Z., Briançon-Marjollet, A., Bouchiat, V., Delacour, C. (2017). Front. in Neurosc., 11, 466.[4] Veliev, F., Kalita, D., Bourrier, A., Belloir, T., Bouchiat, V., Delacour, C. (2018) 2D materials, 5(4), 045020

Disclosures: C. Delacour: None. **V. Dupuit:** None. **O. Terral:** None. **S. Greenhorn:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.01

Topic: I.06. Computation, Modeling, and Simulation

Title: Simple models of critical brain dynamics

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Abstract: A large body of work claims that neuronal dynamics are critical. These claims rest on putative signatures of criticality, including power-law scaling of neuronal avalanche size and duration distributions (Beggs *et al*. 2003), avalanche shape collapses (Sethna *et al.* 2001) and long-range temporal correlations (LRTCs) (Palva *et al.* 2013). However, studies typically do not assess the significance of these signatures against strong competing models of the data. Here, we assessed this significance by unbiasedly generating surrogate data from three such competing models: a *canonical* model that preserves the mean and variance at each timepoint and the covariance between adjacent timepoints); a *clustered* model that preserves the mean activity of spatial and temporal clusters, and a *mean signal* model, that preserves the average activity of each region. We compared these models using human stereotactic and intracranial EEG (Johnson *et al.* 2018; Goodale *et al*. 2020), and Monkey ECoG (Yanagawa *et al.* 2013) data. We observed robust signatures of criticality in the *canonical* model, but not in the *clustered* or *mean signal* models. Our results suggest that key signatures of criticality emerge from interactions of basic features of timeseries data. These results emphasize the importance of future rigorous tests of theories of higher-order brain activity and function against strong alternative models.

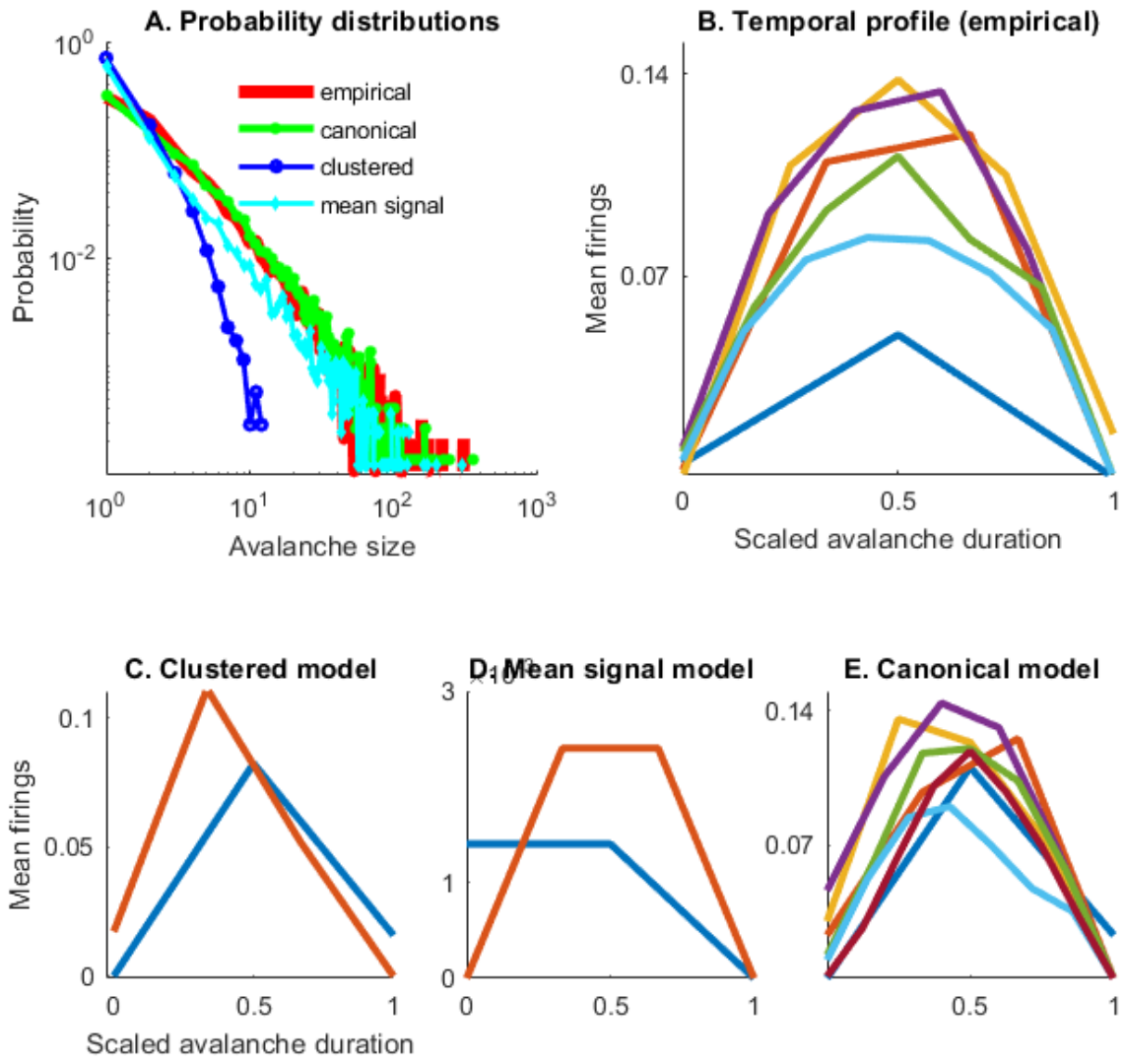


Fig 1. Models of avalanche statistics in monkey ECOG data. **A.** Empirical and model probability distributions of neuronal avalanche sizes. **B.** Empirical scaled mean temporal avalanche profiles profile showing clear shape collapse. **C-E.** Model scaled mean temporal profile showing clear shape collapse for the canonical model.

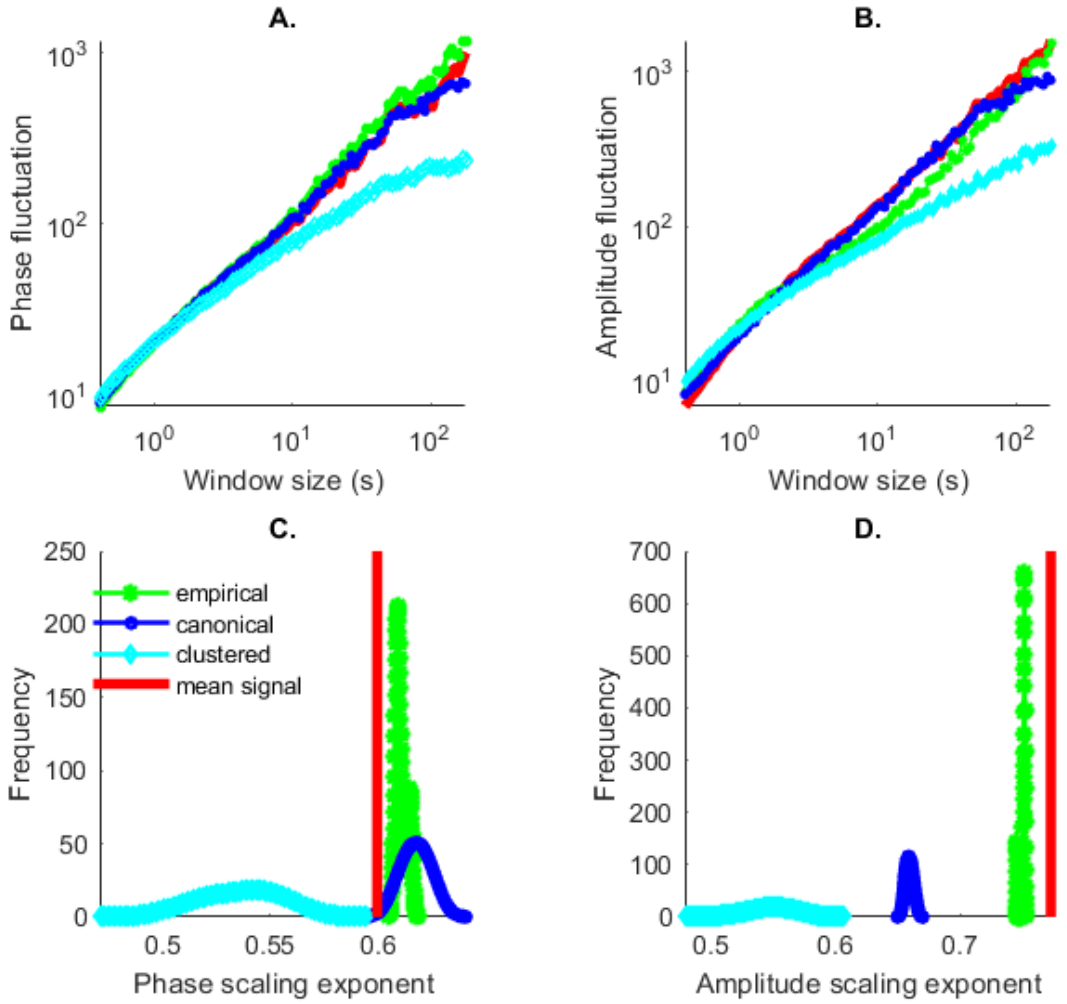


Fig 2: Models of Long range temporal correlations in monkey ECOG data. **A-B.** Empirical and model phase and amplitude fluctuations. **C-D.** Frequency distributions of empirical and model scaling exponents for phase and amplitude fluctuations

Disclosures: A. Nanda: None. **G. Johnson:** None. **D.J. Englot:** None. **M. Rubinov:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.02

Topic: I.06. Computation, Modeling, and Simulation

Support: H2020 Research and Innovation Action programme, VirtualBrainCloud (grant 826421)

Title: Resting state dynamics from the perspective of structured flows on manifolds

Authors: *J. FOUSEK, G. RABUFFO, K. GUDIBANDA, H. SHEHEITLI, S. PETKOSKI, V. K. JIRSA;
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Abstract: Fluctuations of brain activity at rest display correlations between areas involved in task conditions, and their temporal variability possesses functional significance. However, our understanding of the mechanisms underlying these spatio-temporal patterns is still incomplete.
Here we address the main empirical signatures of brain resting state data: bistability of single region activation, low-dimensionality of the global system dynamics, multistability of recurrent coactivation patterns, and their non-trivial temporal dynamics. These constitute the key features of what we describe as structured flows on manifolds (SFMs)[3].
We construct a whole brain network model[2] using 2D neural mass model[4] driven by noise to govern the regional dynamics coupled with a DTI-derived connectome, and equip it with BOLD observer model. The resting-state manifold is defined as the low-dimensional embedding (PCA) of the simulated trajectories. By scaling the coupling strength parameter *G* we find that the dimensionality of the system state space dynamics reduces for the same intermediate values of *G* where the main dynamical signatures of resting state are captured[1].
We then link the manifold subspaces with the clusters of the dynamic functional connectivity, thus separating the high- and low coactivition states. Next we map the complete manifold on which the structured flow (i.e., the dynamics) unfolds by sampling the fixed points of the system, and investigate the gradients of stability. Finally, we relate the characteristic frequency of a node to the stability and show that the model reproduces the gradient of the dominant frequency peak in the empirical data.
These results underscore the central role that the structural connectome plays in the symmetry breaking that shapes the manifold and the resulting structured flow which describes the resting state brain dynamics. All in all, we show in-silico the potential of SFMs formalism as a prime candidate to make current semi-formal descriptions using a variety of mathematical concepts such as attractor landscapes[5] explicit.

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5. J. M. Shine, **The thalamus integrates the macrosystems of the brain to facilitate complex, adaptive brain network dynamics**. *Progress in Neurobiology* (2020)

Disclosures: J. Fousek: None. **G. Rabuffo:** None. **K. Gudibanda:** None. **H. Sheheitli:** None. **S. Petkoski:** None. **V.K. Jirsa:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.03

Topic: I.06. Computation, Modeling, and Simulation

Support: The European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3)
French National Research Agency (ANR) as part of the second "Investissements d'Avenir" program (ANR-17-RHUS-0004, EPINOV)

Title: Virtual epileptic patient workflow: from science to clinical trial

Authors: *B. DOLLOMAJA[1], P. TRIEBKORN[1], J.-D. LEMARECHAL[1,2], M. GUYE[3,4], J. SCHOLLY[3,5], F. BARTOLOMEI[5,1], H. E. WANG[1], V. K. JIRSA[1];
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Abstract: *Introduction*
Identification of the epileptogenic network is crucial for planning surgical interventions in patients with drug-resistant focal epilepsy. The epileptogenic networks are defined by a network of brain regions involved in the production of epileptic activities called epileptogenic zones (EZ). Biomathematical modeling offers methods of causal inference for EZ network estimation by integrating multiple modalities such as magnetic resonance imaging (MRI), diffusion-weighted MRI (dMRI), stereo-electroencephalography (SEEG) and more. The virtual brain (TVB) (Jirsa et al., 2017) technique provides a whole-brain scale modeling approach to make such causal inference possible.
Methods
A VEP pipeline identifies the EZ network in epileptic patients, using patient-specific brain network models. Connections between regions are estimated through streamlined tractography from dMRI, together with the brain parcellation from T1-MRI. Each node contains a neural mass model (2D Epileptor) to represent neural dynamics in a brain region. We compute the source-to-sensor mapping based on a post-SEEG-implant computerized tomography in patients' T1-MRI space. We extract data features from SEEG recordings to fit the brain network model. Model inversion uses algorithms inside a Bayesian framework to obtain a maximum a posteriori estimate of the joint posterior distribution.
Results
We built a solid workflow to estimate the EZ network, for clinical pre-surgical evaluation. The core is the VEP pipeline which uses a patient-specific brain network model within a Bayesian framework to estimate the EZ network given individual SEEG, diffusion and structural MRI data. This workflow has been tested retrospectively in a cohort of 53 patients. The systematical evaluation shows good precision and acceptable recall, comparing VEP results to the routine clinical EZ prediction. The precision shows the VEP results are highly consistent (0.97) with the resected regions for the seizure-free patients. The precision decreased for the patients that are not seizure-free.

Conclusions
The workflow is currently applied prospectively in a clinical trial called Epinov, aiming for 300 patients. The VEP workflow is an important milestone for personalized epileptogenic network estimation and surgery strategy planning, considering patient specific data from multiple modalities. Each element uses current state-of-the-art technology, but can easily be extended and improved in the future. It provides a measure to further our understanding and knowledge for future fundamental improvement in both brain modeling and epilepsy studies.

Disclosures: B. Dollomaja: None. **P. Triebkorn:** None. **J. Lemarechal:** None. **M. Guye:** None. **J. Scholly:** None. **F. Bartolomei:** None. **H.E. Wang:** None. **V.K. Jirsa:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.04

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-NIDA Grant P50 DA044121
NSF-GRF Grant DGE-1324585

Title: A novel approach for analyzing fMRI: deconstructing human brain activity in a 13-dimensional mental domain space with fixed ontological constructs

Authors: *A. APKARIAN[1,2,3,4], R. JABAKHANJI[1,4], A. D. VIGOTSKY[5,4], G. IANNETTI[6,7], M. N. BALIKI[8,3,4];
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Abstract: Science currently lacks a theoretical framework to translate neuronal activity to psychological states. Here we try to overcome this limitation by taking a data driven approach. We assume that the extant fMRI literature (using Neurosynth database) provides a rich representation of brain states that can be used to identify fundamental mental domains and associated ontology. We first derive such a set of dimensions, then project task fMRI activity on them, and test consistency and interpretability of the approach.We used the full Neurosynth dataset (>14,000 studies) and resultant association maps to identify mental domains. Neurosynth association maps are, across-studies averaged, patterns of brain activity related to a particular term (pain, happy, etc.). After excluding uninformative maps, 1848 term-related maps were used to calculate their similarity matrix. The Louvain algorithm was applied, by sweeping Density and Resolution parameters between 0.05-0.3 and 0.5 to 3.0 respectively. The optimal number of clusters was 13. We averaged the maps within each cluster to obtain mental domain spatial patterns, and used Neurosynth to label each dimension with its associated ontology. We label the 13 Mental Domains (MD13) based on top 10 ranked terms: Theory of Mind, Movement/Sensation (MS), DMN, Task/Working Memory (TWM), Language (LNG), Reward, Auditory (AUD), Vision (VS), Attention,

Affect (AF), Episodic Memory (EM), Visuo-Spatial Attention (VSA), and Nociception (Noci).To illustrate decodability of task-fMRI within MD13 space we interrogated two studies: 1) a sound and voice differentiation study (block design, 86 subjects) [1], and 2) a pain, touch, vision, and audition differentiation study (event design, 14 subjects) [2]. We projected the BOLD timeseries on MD13, and examined the signal along each MD dimension.In study 1, vocal auditory stimuli have a high response on the AUD and LNG; for the non-vocal stimuli, the response was on AUD only, in studies 1 & 2. Discrimination using all MD dimensions was 0.96 (0.92 - 0.98). We also observed that during light stimulus response is on VS, and VSA. For the painful heat and the touch stimuli, the responses were on MS, AUD, AF, TWM, and Noci, with higher responses for pain on all of them. Since study 2 could not differentiate between touch and pain using standard GLM, we tested this contrast in MD space, Noci was best discriminant 0.88 (0.67 - 0.97).MD responses are compatible with what we know about the stimuli. The approach consistently maps brain activity onto MD defined ontological space, transforming brain activity to psychological interpretation.
1.Pernet et al. - NeuroImage - 2015 2.Liang et al. - Cerebral Cortex - 2019

Disclosures: A. Apkarian: None. **R. Jabakhanji:** None. **A.D. Vigotsky:** None. **G. Iannetti:** None. **M.N. Baliki:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.05

Topic: I.06. Computation, Modeling, and Simulation

Support: The European Union'sHorizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3)
The French National Research Agency (ANR) as part of the second "Investissements d'Avenir" program (ANR-17-RHUS- 0004, EPINOV)

Title: Systematical evaluation of the Virtual Epileptic Patient (VEP) modelling approach for the identification of epileptogenic zones

Authors: *J.-D. LEMARÉCHAL[1,2], P. TRIEBKORN[1], B. DOLLOMAJA[1], M. GUYE[3,4], J. SCHOLLY[3,5], F. BARTOLOMEI[5,1], H. WANG[1], V. JIRSA[1];
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Abstract: Introduction In the context of focal epilepsy, the *Virtual Epileptic Patient* (VEP) uses a large scale brain modeling approach to predict the spatio-temporal spreading of seizure activity (Jirsa et al., 2017). The localization of the epileptogenic zones (EZ) can be estimated by adjusting the predictions of

the model to the empirical stereo-electroencephalographic (SEEG) recordings of the patient. Precise estimates are crucial as they are indicative of candidate regions for resection. In this study, we used high-resolution neural field model (NFM) simulations to evaluate the robustness of the localization of EZ.
Methods To ensure computational tractability, the localization of EZ is currently implemented for a VEP with a generative neural mass model (NMM), in which brain connectivity is limited to global coupling between brain regions. To assess the quality of this estimation based on NMM, the estimation was performed on a series of data simulated with a neural field model (NFM), which, in addition to global coupling, considers the contribution of local coupling within brain regions to the global brain activity. A set of patients with different epileptic network spatial configurations were selected from the EPINOV trial. For each patient, various scenarios were considered in terms of the geometry of EZ (size, location) in relation with the specificity of the patient (geometry of the brain, implantation scheme).
Results The estimation procedure based on NMM was performed for each dataset simulated with a NFM. The robustness was evaluated based on the correctly identified EZ. For the frequent case of mesial temporal lobe epilepsy, simulated data show very realistic seizure propagation pattern along the cortical surface and VEP estimates of EZ were consistent with simulated ground truth.
Conclusions Overall, the results demonstrate that, given specific epileptic network spatial configurations, NMM may have limitations to capture some complex seizure patterns present in empirical SEEG data. By considering the contribution of both local and global coupling for the propagation of brain activity, NFM can account for a more detailed description of the brain dynamics, as the ones observed during epileptic seizures. The use of NFM for an accurate localization of EZ therefore represents a significative methodological advance to address in the future.
Jirsa, V.K., Proix, T., Perdikis, D., Woodman, M.M., Wang, H., Gonzalez-Martinez, J., Bernard, C., Bénar, C., Guye, M., Chauvel, P., Bartolomei, F., 2017. The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread. NeuroImage 145, 377-388.
https://doi.org/10.1016/j.neuroimage.2016.04.049

Disclosures: J. Lemaréchal: None. **P. Triebkorn:** None. **B. Dollomaja:** None. **M. Guye:** None. **J. Scholly:** None. **F. Bartolomei:** None. **H. Wang:** None. **V. Jirsa:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P952.06

Topic: I.06. Computation, Modeling, and Simulation

Support: W911NF-09-0001

Title: Neuronal population tuning statistics to target and cues for a feedforward Convolutional Neural Network that learns to covertly attend

Authors: *S. SRIVASTAVA, M. P. ECKSTEIN;
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Abstract: Introduction: Attentional effects on perception, once thought to be exclusive to primates, have been more recently measured in simpler organisms such as fruit flies, dragonflies, and honeybees (Nityananda 2016). We investigate whether a simple convolutional neural network (CNN) trained to maximize the detection of a target in a 2-location yes-no task (Posner cueing) results in human-like cueing effects. We analyze individual neurons in the network to understand how they extract and integrate target and cue information.
Methods: We trained a CNN on 6000 images containing oriented lines embedded in noise. A box cue co-occurred with the target on 80 % of the trials. The CNN consisted of 3 convolution layers, with the first layer followed by max-pooling. The third convolution layer is followed by a dense layer and an output layer with 2 neurons. We evaluated human and CNN performance for a Posner cueing task with varying contrast of a peripheral box cue. We extracted responses of each neuron to these images and calculated neuron-specific cueing effects (areas under the ROC (AUROC) for valid vs. invalid cues). Next, for each neuron, we calculated the AUROC for detecting box presence or absence on either side, and the AUROC for detecting target or distractor presence on each side.
Results: The CNN trained to optimally detect the target results in a cueing effect comparable to humans and an optimal Bayesian model. Nineteen percent of the neurons in the dense layer showed positive and negative cueing effects with varying degrees (mean = 0.02; standard deviation = 0.10). Neurons with cueing effects detect both the target and the cue in isolation. The weights between the dense neurons and the two output neurons are correlated ($r=-0.64$, $p<0.0001$; $r=0.58$, $p<0.0001$) with the neuron-specific cueing effects. The convolution layer neurons are retinotopic, while the dense layer neurons are not. The first two convolution layers do not have neurons that integrate either the box or the target information from both the locations, or neurons integrating box and target information. Neurons integrating box and target information from one location first appear in the third convolution layer, and neurons integrating box and target information from both locations appear only in the dense layer. On retraining the network with varying cue validity, the mean ratio of the box cue tuning and the target tuning increases as the validity of the cue increases from 50% to 100%.
Conclusion: Our results show that a simple neural network can learn to utilize cues in a similar manner as humans and establish biologically plausible architectures and neuronal population properties to integrate target and cue information.

Disclosures: S. Srivastava: None. **M.P. Eckstein:** None.

Poster

P952. Theoretical Network Models II

Location: Virtual Only

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Program #/Poster #: P952.07

Topic: H.03. Decision Making

Support: Spanish ministry of science and innovation, and European Regional Development Fund Grant RYC-2015-17236 to K.W.
Spanish ministry of science and innovation, and European Regional Development Fund Grant BFU2017-86026-R to K.W.
Spanish ministry of science and innovation, and European Regional Development Fund Grant RTI2018-097570-B-I00 to A.R.

Generalitat de Catalunya AGAUR 2017 SGR 1565 to A.R. and K.W.
Spanish ministry of science and innovation, and European Regional Development Fund Grant PID2020-112838RB-I00 to K.W.

Title: Bump attractor dynamics underlying stimulus integration in perceptual estimation tasks

Authors: J. M. ESNAOLA-ACEBES[1,2], A. ROXIN[1,2], *K. WIMMER[1,2];
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Abstract: Perceptual decision and continuous stimulus estimation tasks involve making judgments based on accumulated sensory evidence. Network models of evidence integration usually rely on competition between neural populations each encoding a discrete categorical choice. By design, these models do not maintain information of the integrated stimulus (e.g. the average stimulus direction in degrees) that is necessary for a continuous perceptual judgement. Here, we show that the continuous ring attractor network can integrate a stimulus feature such as orientation and track the stimulus average in the phase of its activity bump. We reduced the network dynamics of the ring model to a two-dimensional equation for the amplitude and the phase of the bump. Interestingly, these reduced equations are nearly identical to an optimal integration process for computing the running average of the stimulus orientation. They differ only in the intrinsic dynamics of the amplitude, which affects the temporal weighting of the sensory evidence. Whether the network shows early (primacy), uniform or late (recency) weighting depends on the relative strength of sensory stimuli compared to the amplitude of the bump and on the initial state of the network. The specific relation between the internal network dynamics and the sensory inputs can be modulated by changing a single parameter of the model, the global excitatory drive. We show that this can account for the heterogeneity of temporal weighting profiles observed in humans integrating a stream of oriented stimulus frames. Our findings point to continuous attractor dynamics as a plausible mechanism underlying stimulus integration in perceptual estimation tasks.

Disclosures: J.M. Esnaola-Acebes: None. **A. Roxin:** None. **K. Wimmer:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant OT2OD030537

Title: An ultra-high-resolution imaging and segmentation pipeline of the cat lumbosacral spinal cord for accurate 3D finite element method models

Authors: *L. LIANG[1], A. FASSE[6], M. JANTZ[1], C. GOPINATH[2], F. LIU[2], T. NEWTON[6], C. ROWLAND[3], U. AGBOR[3], L. FISHER[2], M. CAPOGROSSO[4], E. NEUFELD[6], R. GAUNT[2], T. K. HITCHENS[5], E. PIRONDINI[2];
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Abstract: Lower urinary tract (LUT) dysfunction affects 20-40% of the global population, and it significantly decreases the psychological and social well-being of individuals. Recent experimental works in cat showed that epidural spinal cord stimulation (SCS) can be effective in controlling LUT functions. However, experiments alone cannot feasibly address certain physiological questions or guide design decisions about contact size, location, and stimulation parameters. Thus, anatomically accurate computational models of the lumbosacral spinal cord are critical in accelerating the research and development of SCS. Common methods for building spinal cord models involve simplified geometric CAD models lacking anatomical details, or labor-intensive manual segmentation of magnetic resonance (MR) images. Here, we developed a novel imaging and segmentation pipeline that allows construction of high-precision models of the cat lumbosacral spinal cord. First, we obtained a CT scan (250μm isotropic) of *ex vivo* fixed lumbosacral cat spine tissue. Then, the tissue was soaked in 0.2% Gadavist (gadolinium contrast agent) that reduced the longitudinal relaxation time (T1) of the tissue by 80%, significantly accelerating MR image acquisition. The sample was then placed in Fomblin, which improved magnetic field homogeneity, for imaging. T2-weighted and fat-selective structural MR scans (50μm isotropic) were acquired in a Bruker vertical-bore 11.7T microimaging system. This ensemble of acquisitions enhanced contrast between tissues and facilitated rapid segmentation of vertebrae, gray matter, white matter, ventral/dorsal roots and rootlets, epidural fat, and CSF with a convolutional neural network (HardDNet variant) trained on a small set of manual segmentations. In addition, high-resolution diffusion-tensor imaging (200μm isotropic, 61 directions, multi-shell b=1000/3000) tractography was employed to automatically distinguish roots and rootlets of each spinal level. Finally, the 9 segmented tissue masks were used to create a high-definition 3D model to allow realistic simulation of SCS with finite element method. With this pipeline, we successfully replicated imaging and segmentation results in two cat spine samples. The shape, size, and locations of the tissue masks were validated against literature and dissections. This novel pipeline can be extended to efficiently create anatomically accurate spinal cord models at any spinal level of interest, and for various animal models to enable better understanding of SCS functional mechanisms, optimization of SCS protocols, and guide the design of spinal cord neuroprosthesis.

Disclosures: L. Liang: None. **A. Fasse:** None. **M. Jantz:** None. **C. Gopinath:** None. **F. Liu:** None. **T. Newton:** None. **C. Rowland:** None. **U. Agbor:** None. **L. Fisher:** None. **M. Capogrosso:** None. **E. Neufeld:** None. **R. Gaunt:** None. **T.K. Hitchens:** None. **E. Pirondini:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.02

Topic: I.06. Computation, Modeling, and Simulation

Support: NSERC Grant RGPIN-2020-07143

Title: Maximum Entropy-based connectivity estimators are robust to model mismatch

Authors: *A. HAYDAROGLU[1], T. A. VALIANTE[2];
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Abstract: Estimating the functional connectivity of populations of neurons from their activity is a critical problem when anatomical access to the population is not feasible. However, there is often a problem of "model mismatch" when the processes underlying the neural data are not fully explained by the assumed model of the connectivity estimation method used. This is common when methods make simplifying assumptions about the structure of the network, which introduces statistical bias and reduces accuracy. We show that connectivity estimation methods derived to maximize the entropy of the inferred probability distribution of network activity states are more robust to the model mismatch problem. We compare Maximum Entropy (MaxEnt) methods to commonly used Information Theory (IT) based methods on data with known ground-truth connectivity. Data is generated from two processes which have been shown to model biological neural activity under different contexts: Multivariate Autoregressive Models (MVAR) and Glauber Dynamics (GD). The former satisfies the assumptions of IT estimators, while the latter is a time-dependent sampling of a high-dimensional energy landscape which satisfies the assumptions of MaxEnt methods. On cross-validated experiments across a range of network sizes, random seeds and activity levels, MaxEnt estimators outperform Information Theoretic measures in GD datasets, while both methods perform similarly well on MVAR datasets. Thus, MaxEnt models show more robust performance in the presence of model mismatch, e.g. when the underlying process doesn't satisfy its assumptions. We also demonstrate how tuning of data preprocessing steps can improve the accuracy of MaxEnt methods. Furthermore, we show that when both MaxEnt and IT methods are applied to continuous signals, increasing the resolution of the digitization of signals reduces accuracy. This is unexpected since increased resolution makes more information available to the inference methods and may be expected to improve results. This work demonstrates the impact of the model mismatch problem on common connectivity estimation methods and presents novel, experimentally-relevant insights that highlight the robustness of Maximum Entropy models. The recent development of high-speed computers accelerating MaxEnt estimations (such as commercially-available quantum annealers) makes MaxEnt methods a promising choice for analysis on high-dimensional neural datasets and applications in clinical settings. Our ongoing work is aimed at applying these methods to the diagnosis of neurodegenerative diseases such as epilepsy and the design of neural stimulators for their treatment.

Disclosures: A. Haydaroglu: None. **T.A. Valiante:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.03

Topic: I.06. Computation, Modeling, and Simulation

Support: Brain Initiative Grant R34-EB026951- 01A1
Swartz Foundation Postdoctoral Fellowship for Theory in Neuroscience
Beckman Young Investigator Program
Whitehall Foundation

Title: Online neural modeling for adaptive neuroscience experiments

Authors: *A. DRAELOS[1], P. GUPTA[2], N. JUN[3], C. SRIWORARAT[1], M. D. LORING[3], M. NIKITCHENKO[3], E. PNEVMATIKAKIS[4], A. GIOVANNUCCI[5], E. A. NAUMANN[3], J. M. PEARSON[1];
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Abstract: Systems neuroscience is increasingly able to leverage new recording technologies and statistical analyses to describe the coordinated activity of larger populations of neurons, even entire brains. Combined with new precise stimulation technologies, we can begin to dissect large-scale circuits in vivo, constructing models that causally relate neural activity to behavior. Direct testing of hypothesized brain-behavior links, however, requires statistically efficient methods for both estimating and intervening on population-level neural dynamics in real time. To build neural models online, we describe a new method called Bubblewrap that combines fast, stable dimensionality reduction with a soft tiling of the resulting neural manifold, allowing dynamics to be approximated as a probability flow between tiles. This method can be fit efficiently, scales to large populations, and outperforms existing methods when dynamics are noise-dominated or feature multi-modal transition probabilities. We demonstrate the performance of Bubblewrap on both simulated nonlinear dynamical systems and experimental neural data with up to thousands of recorded units. Our algorithm can learn at kilohertz rates, faster than data acquisition, and generate predictions in less than 1 ms.
To demonstrate how real-time interventions can be tailored to individual or population-level neural activity, we address the optimization problem of finding peak neural responses to multidimensional visual stimuli in larval zebrafish. Here we leverage our adaptive software platform, improv, to construct an experimental pipeline that takes in two-photon calcium images, analyzes the neural responses for each observed neuron, and generates the next visual stimulus to display online. We employ a Bayesian optimization approach for choosing stimuli, which uses Bayesian inference to search for optimal function values, particularly in cases where evaluating the function is costly or time-consuming. Our visual stimuli are presented to the zebrafish as moving sinusoidal gratings from below with varying direction, speed, spatial frequency, and contrast. Even with a modest number of choices for each parameter (5-15 options), this results in nearly 8,000 unique stimuli. By contrast, our adaptive approach with Bayesian optimization allows us to determine optimal stimuli for a neural subpopulation within only a few hours, leaving time for subsequent causal testing. Our efficient and scalable methods for online brain state modeling and closed-loop stimulus optimizations can enable automated, large-scale network dissection infeasible with current methods.

Disclosures: A. Draelos: None. **P. Gupta:** None. **N. Jun:** None. **C. Sriworarat:** None. **M.D. Loring:** None. **M. Nikitchenko:** None. **E. Pnevmatikakis:** None. **A. Giovannucci:** None. **E.A. Naumann:** None. **J.M. Pearson:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.04

Topic: I.06. Computation, Modeling, and Simulation

Support: NeuroNEXT Grant U01NS096767

Title: Development of Realistic Simulated EEG Data for Assessing Preprocessing Methods

Authors: *E. AUGER[1], E. BERRY-KRAVIS[2], L. E. ETHRIDGE[1];
[1]Univ. of Oklahoma, Norman, OK; [2]Rush Univ. Med. Col., Chicago, IL

Abstract: Increased objectivity in EEG research via automated methods for artifact rejection in EEG data have been in consistent development and refinement. One major difficulty in developing methods for successfully cleaning EEG data is the inability to know with 100% certainty if the recorded signal is true brain or true artifact. Methods of assessing signal-to-noise ratio (SNR) in real EEG data are only estimates, making quantifiable testing of processing methods using real data challenging. Many researchers use simulated data to assess processing methods. However, current methods of simulating data may not accurately mimic the complexity of real data, which could bias assessments.We created a set of simulated data that more closely resembles real data, which could be used to test data cleaning methods. Data consisted of 56 simulated datasets with 34 components each: 10 brain components, 8 artifact components, and 16 pink noise components to mimic 1/f distributed noise sources. Brain signal was simulated using SimEEG, using a channel waveform from real EEG to estimate power of frequency bands from two components each from delta, theta, alpha, beta, and low gamma frequency bands and mimic dipole topographies. The eight artifact components were derived from real EEG data using independent components analysis and were selected for being stereotypical but appropriately time-varying examples of ocular, cardiac, and muscle artifact. Each artifact was shifted in both time and amplitude to vary the relative timing and variance accounted for by each artifact. Simulated data was tested using an automated EEG processing pipeline that had previously been validated only on real EEG data. This pipeline uses machine learning trained on a large database of EEG data to identify artifact. However, true SNR retention by any pipeline can only be evaluated using simulated signal and noise which can be fully quantified. Given the real EEG training database, realistically modelled EEG artifact in simulated data is necessary to accurately test such a pipeline. Tests of the pipeline via hierarchical linear modeling using approximated SNR from real EEG data and quantified SNR from simulated data confirmed similar loss of signal in both datasets, with quantified simulated signal allowing us to isolate the most significant signal loss to lower frequency bands. Many newly developed automated EEG processing programs utilize machine learning from large databases of real EEG data to identify and remove artifact. This method of simulating data using realistic artifact components allows for quantifiable performance testing on such pipelines to evaluate and optimize SNR retention capabilities.

Disclosures: E. Auger: None. **E. Berry-Kravis:** None. **L.E. Ethridge:** None.

Poster

P958. Experimental Computational Tools II

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Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.05

Topic: I.06. Computation, Modeling, and Simulation

Support: NSERC-Discovery Grant Program

Title: Aperiodic EEG activity masks the dynamics of neural oscillations during loss of consciousness from propofol

Authors: *N. BRAKE[1], F. DUC[2], A. ROKOS[4], F. ARSENEAU[5], S. SHAHIRI[3], A. KHADRA[1], G. PLOURDE[2];
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Abstract: Many states of consciousness can be inferred directly from an electroencephalogram (EEG). Although differences in the EEG are often ascribed to changes in neural synchrony, it is becoming increasingly evident that the aperiodic component of the EEG signal may change as well. The goal of this study was to determine whether the general anesthetic propofol alters the aperiodic component of the EEG, and if so, what implications this may have for interpreting changes in neural synchrony related to loss of consciousness (LOC). To address this question, we recorded the EEG of 14 human subjects undergoing a fixed-rate infusion of propofol. To interpret these data, we derived a biophysical model of the aperiodic component of the EEG which describes the ensemble electric field generated by asynchronous neural activity. This model demonstrated that propofol's known potentiation of $GABA_A$ receptors, in tandem with a suppression of neuronal firing, suffices in explaining over 80% of the observed EEG changes during induction of anesthesia, without requiring any differences in neural synchrony. When accounting for these aperiodic changes, the inferred time course over which propofol-induced rhythms evolved was significantly altered. Whereas a typical spectral analysis of our data indicated that the moment of LOC was correlated with the appearance of both alpha (8-15 Hz) and delta (1-4 Hz) rhythms, consistent with past studies, correcting for changes in the aperiodic component of the EEG produced a clear temporal separation between these rhythms. We concluded that LOC was only correlated with the appearance of delta rhythms, while alpha rhythms emerged and plateaued well beforehand. This study proposes specific physiological parameters that shape the aperiodic component of the EEG signal and provides insight into the mechanisms of propofol-induced LOC.

Disclosures: N. Brake: None. **F. Duc:** None. **A. Rokos:** None. **F. Arseneau:** None. **S. Shahiri:** None. **A. Khadra:** None. **G. Plourde:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH108053-01

Title: Automated whole brain reconstruction of serial sections mapped to a brain reference atlas

Authors: N. J. O'CONNOR[1], B. S. EASTWOOD[1], A. D. LEDUC[1], D. HOPPES[1], C. S. GERFEN[1], P. J. ANGSTMAN[1], J. R. GLASER[1], *C. R. GERFEN[2];
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Abstract: Molecular neuroanatomical methods expand the ability to characterize the connectivity of specific neuron subtypes under varying behavioral or pathological patterns of neuronal activity. Analyses of connectivity and neuronal activity across whole mouse brains that have been registered to a reference atlas reveal details about the functional organization of these brain circuits with the ability to draw comparisons across animals, experiments, and laboratories. Here we present advances to our previous work for automatically aligning and reconstructing images of mouse brain sections labeled with histochemical techniques into whole-brain 3D image volumes, registering these brain image volumes to the Allen Mouse Brain Common Coordinate Framework (CCF), and subsequently automatically mapping neuron populations to regions in experimental brain volumes.
A reference section containing brain regions with well-defined anatomic landmarks is registered to the CCF with a convolutional neural network (CNN)-enhanced transform model that accounts for artifacts due to histological cutting, mounting, and fixation. This reference section's transform is then propagated to other sections with linear and nonlinear refinements to accurately map all sections of the reconstructed whole brain image volume to the CCF.
Examples of whole-brain analysis of connectivity using trans-synaptic rabies labeling of neurons providing inputs to Cre-expressing neuron subtypes, and of behaviorally relevant brain circuits using fos labeling of activity in neurons correlated with specific behaviors, are presented. For analysis, coronal brain sections are reconstructed into a 3D volume, labeled neurons are automatically marked using CNN cell detection classifiers trained for detecting pyramidal neurons and neurons expressing fos, and brain sections and marked neurons are registered to the CCF. The number of labeled neurons in each of the over 830 delineated structures in the CCF are tallied, allowing for comparative quantitative analysis between mice. Fiducial points throughout the brain are used to determine registration accuracy on the order of three to four neuron widths.

Disclosures: N.J. O'Connor: A. Employment/Salary (full or part-time):; MBF Bioscience. **B.S. Eastwood:** A. Employment/Salary (full or part-time):; MBF Bioscience. **A.D. LeDuc:** A. Employment/Salary (full or part-time):; MBF Bioscience. **D. Hoppes:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C.S. Gerfen:** A. Employment/Salary (full or part-time):; MBF Bioscience. **P.J. Angstman:** A. Employment/Salary (full or part-time):; MBF Bioscience. **J.R. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C.R. Gerfen:** None.

Poster

P958. Experimental Computational Tools II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P958.07

Topic: I.06. Computation, Modeling, and Simulation

Title: A multimodal cortical atlas for clinical decision making and function-structure hypotheses in epilepsy surgery

Authors: *T. JAFAR, H. MCGRATH, A. KSENDZOVSKY, H. ZAVERI, P. FAROOQUE, E. COLLINS, L. LAMSAM, A. SIVARAJU, K. WU, E. DAMISAH, X. PAPADEMETRIS, D. SPENCER; Yale Univ., New Haven, CT

Abstract: Epilepsy surgery evaluation generates significant multimodal data, imaging, and electrophysiology. It is critical to aggregate this data in a common space for research and clinical decision making. Existing brain atlases lack an intuitive naming or parcellation that provides for easy cross referencing. We define an atlas which addresses these issues in epilepsy surgery and test its use as a visual database.

We registered multimodal data from epilepsy patients onto the Yale Atlas; our cortical brain atlas parcellated to reflect standard contact spacing of intracranial electrodes and defined by landmarks on the MNI 152 brain. Structural 3T MRI images underwent linear/nonlinear registration, and 3D electrode coordinates were transformed to the atlas and verified with Yale BioImage Suite. Electrophysiology data of seizure onset and spread and bipolar language stimulation mapping was incorporated.

A total of 3386 intracranial electrode contacts from 20 temporal lobe epilepsy patients were transformed to the atlas. In the mesial temporal group, the most common parcel of onset was H A (pes hippocampus) in 50% and H B (hippocampal body) in 40%. While the neocortical group was TP2.2 A (anterior inferior temporal pole) in 40% and T2.1 C (upper middle temporal gyrus) in 30%. In Figure 1, a patient with H B onset underwent a resection of parcels involved at onset, 1st and 2nd spread, and remained seizure free at 1 year. The 2nd patient had spread outside of the resected neocortical parcels and failed surgery. Figure 2 shows language mapping superimposed on the atlas. Seizure onset was observed in the dominant temporal lobe neocortex. Mapping parcels critical for language function, 2 RNS strips were placed to cover the parcels of onset and spread with an ILAE 2 outcome.

We present an epilepsy surgery atlas for aggregating multimodal data, co-registration of multiple data sources onto one visualization, and exact cross referencing for research and clinical purposes. Mapping patient data onto this atlas allows us to compare PET, fMRI, stimulation mapping and electrophysiology for outcome correlation.

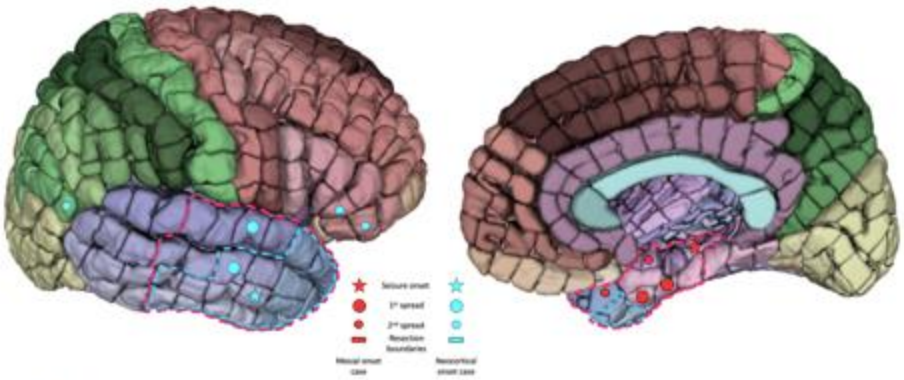


Figure 1.

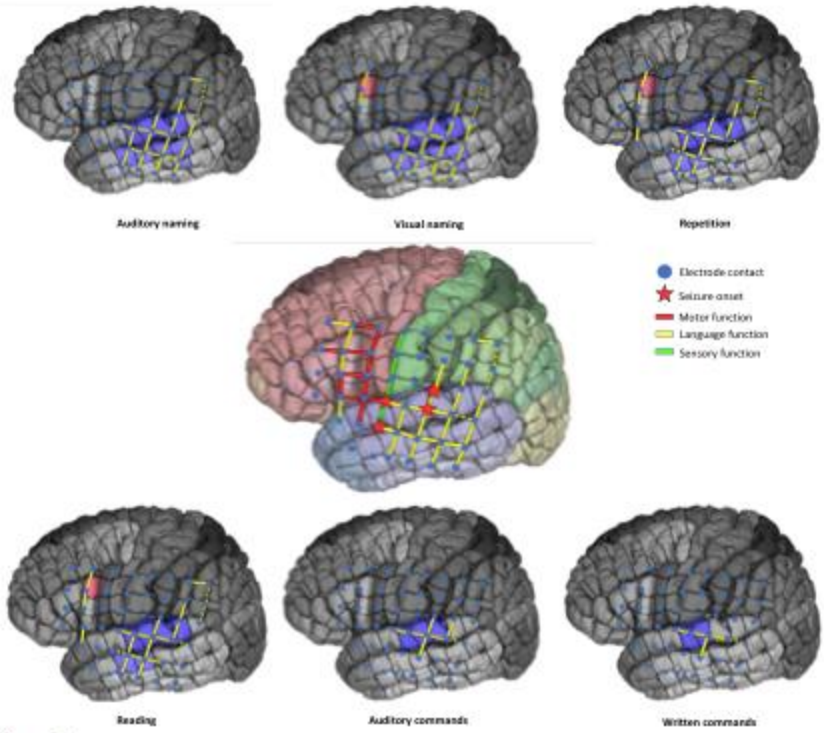


Figure 2.

Disclosures: T. Jafar: None. **H. McGrath:** None. **A. Ksendzovsky:** None. **H. Zaveri:** None. **P. Farooque:** None. **E. Collins:** None. **L. Lamsam:** None. **A. Sivaraju:** None. **K. Wu:** None. **E. Damisah:** None. **X. Papademetris:** None. **D. Spencer:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.01

Topic: I.07. Data Analysis and Statistics

Support: NASA
MIT Lincoln Laboratory
Office of Naval Research
Sandia National Laboratories
Emory University
Georgia Institute of Technology
Department of Defense

Title: Eeg-mediated real-time continuous-scale emotion assessment for applications in robotics using reinforcement learning

Authors: *L. A. THIERGART[1], R. PALEJA[2], E. SERAJ[2], M. C. GOMBOLAY[2];
[2]Sch. of Interactive Computing, [1]Georgia Inst. of Technol., Atlanta, GA

Abstract: Robot technologies trained by human experts hold great promise to improve daily life. Tasks like autonomous driving, surgical robotics or assistive care may benefit from democratised access to robotic systems for human trainers. To achieve this, it is necessary to remove requirements for programming language knowledge, insight into the robot's training process, and the need for ideal task execution by the human. New communication modalities which are intuitive and accessible to non-technical users are needed. While grounding (or tying) natural language to tasks and commands remains difficult, Brain Computer Interfaces (BCI) can create a more natural, direct and effortless communication between the human teacher and the robot student. BCIs circumvent the step of the teacher needing to articulate themselves verbally or through technology and also enables non-able-bodied users to train robots for specialised tasks. The high temporal resolution and non-invasiveness of EEG makes it a suitable BCI technology.
Prior work includes the framework TAMER (Training an Agent Manually via Evaluative Reinforcement learning) in which a human teacher watches a robot student perform a task and provides positive and negative feedback by pressing buttons on a controller. TAMER requires less data and training time than learning from a demonstration (Knox et al, 2008). However, TAMER remains limited to single, scalar value feedback with inherent communication delay.
We propose to leverage a 16-electrode EEG (EMOTIV EPOC+) to augment TAMER for autonomous driving tasks. We record and extract positive and negative emotion on a continuous scale in real-time from an EEG signal. Our human-subjects experiment (n=20) validates the reliable extraction of the desired signal using signal processing and machine learning methods modified from those proposed by Ramirez et al (2012). We show a reduction in latency of the EEG-interface compared to a baseline of button-clicking. We then demonstrate a human can train an autonomous ground vehicle to navigate an urban environment from start to a goal while avoiding obstacles and taking a user-preferred route. Previous work shows users can experience illness from autonomous vehicles not driving in their style (Iskander et al., 2019). We report the results of subjective Likert-scale surveys regarding user's experience for useability and trust in this mode of interaction relative to our baseline method.
This work opens avenues to help non-technical experts more efficiently train robots in specialist domains. The improved access, user experience, latency and training effort enables cheaper and more effective robotic applications.

Disclosures: L.A. Thiergart: A. Employment/Salary (full or part-time):; Georgia Institute of Technology. **R. Paleja:** A. Employment/Salary (full or part-time):; Georgia Institute of Technology. **E. Seraj:** A. Employment/Salary (full or part-time):; Georgia Institute of Technology. **M.C. Gombolay:** A.

Employment/Salary (full or part-time):; Georgia Institute of Technology. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Lockheed Martin, Ford Motor Company. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Konica Minolta.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.02

Topic: I.07. Data Analysis and Statistics

Title: Applying Data Science to Addiction Neuroscience: Importance of Collaborations

Authors: *L. FRIEND[1], A. AVILA[1], S. WRIGHT[1], R. LITTLE[1], W. NILSON[2], W. COMPTON[1]; [1]NIDA, Bethesda, MD; [2]NSF, Bethesda, MD

Abstract: Data science is recognized as an increasingly important cross-cutting research approach in neuroscience as data increases exponentially in volume and velocity. Therefore, increasing the capacity of experts in data science for biomedical research of addiction is crucial. The National Institute on Drug Abuse (NIDA) and National Science Foundation (NSF) are working together to increase collaborations between computer scientists and neuroscientists working in the field of substance use disorders. These cross-disciplinary collaborations have a high potential to mine large and rich data sets that have been previously unstudied. To this end, we are interested in implementing proven strategies and models to improve and expand training in this emerging field. NIDA has published a Notice of Scientific Interest in Data Science research in training and other early career awards (NOT-DA-21-013); however, community input and involvement is critical to this effort. We will also report out on issues and ideas raised at a workshop sponsored by NSF and NIDA this past Fall. We will discuss challenges to such collaborations including expanding the early career pipeline, finding partners in research, and understanding unique career paths and terminology for computer scientists and academic researchers.

Disclosures: L. Friend: None. **A. Avila:** None. **S. Wright:** None. **R. Little:** None. **W. Nilson:** None. **W. Compton:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.03

Topic: I.07. Data Analysis and Statistics

Support: Institute For Data Valorization (IVADO)

Title: Preliminary screening of depressive disorders using electroencephalography signals

Authors: *I. INJAR[1,2], O. GHARBI[1], J.-P. MIRON[1], E. BOU ASSI[1];
[1]Neurosci., Univ. of Montreal Hosp. Res. Ctr. (CRCHUM), Montréal, QC, Canada; [2]Med., Univ. of Sherbrooke, Sherbrooke, QC, Canada

Abstract: Rationale: According to the World Health Organization, depression affects 264 million people worldwide[1]. Unfortunately, the screening of major depressive disorders (MDD) remains descriptive relying on subjective questionnaires (symptoms). The development of quantitative tools to accelerate MDD screening could significantly impact patient management. Recently, a growing interest with auspicious findings on the use of electroencephalography (EEG) to complement the diagnosis of MDD has been witnessed.**Objective:** We explored the use of EEG-based features to distinguish between participants with low and high depressive symptomatology.**Methods:** We performed an exploratory analysis using resting-state EEG signals from the publicly available "James F. Cavanagh & John J.B. Allen depression rest database"[2]. The severity of depressive symptomatology was assessed using the Beck Depression Inventory (BDI)[3]. We studied a group of 73 healthy controls (HC: BDI<10) and 44 individuals with high depressive symptomatology (DEP: BDI>10). Band power features were extracted from 2-sec epochs during vigilance-controlled eyes closed resting conditions. More specifically, 50 measures from different lobes, in 5 frequency bands: delta (0.5 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (13 – 30 Hz) and low gamma (30 – 50 Hz) were assessed. A t-test was used to evaluate the existence of significant differences in EEG features between HC and DEP.**Results:** Fourteen features exhibited significant differences between HC and DEP subjects (Bonferroni corrected). The most informative measures were in the beta band (right-central lobe in beta band: p=.0033; right-parietal lobe in beta band: p=.045).**Significance:** Our preliminary findings highlight the possibility of EEG-based screening of DEP. Further analyses in a larger cohort of patients, with a confirmed diagnosis of MDD, are required. **References:**[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet.[2] Cavanagh, J. F., Bismark, A. W., Frank, M. J., & Allen, J. (2019). "Multiple Dissociations Between Comorbid Depression and Anxiety on Reward and Punishment Processing: Evidence From Computationally Informed EEG". Computational psychiatry (Cambridge, Mass.).[3] Wang Y-P, Gorenstein C, Wang Y-P, Gorenstein C. (2013). "Psychometric properties of the Beck Depression Inventory-II: a comprehensive review". Brazilian Journal of Psychiatry.

Disclosures: I. injar: None. **O. Gharbi:** None. **J. Miron:** None. **E. Bou Assi:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.04

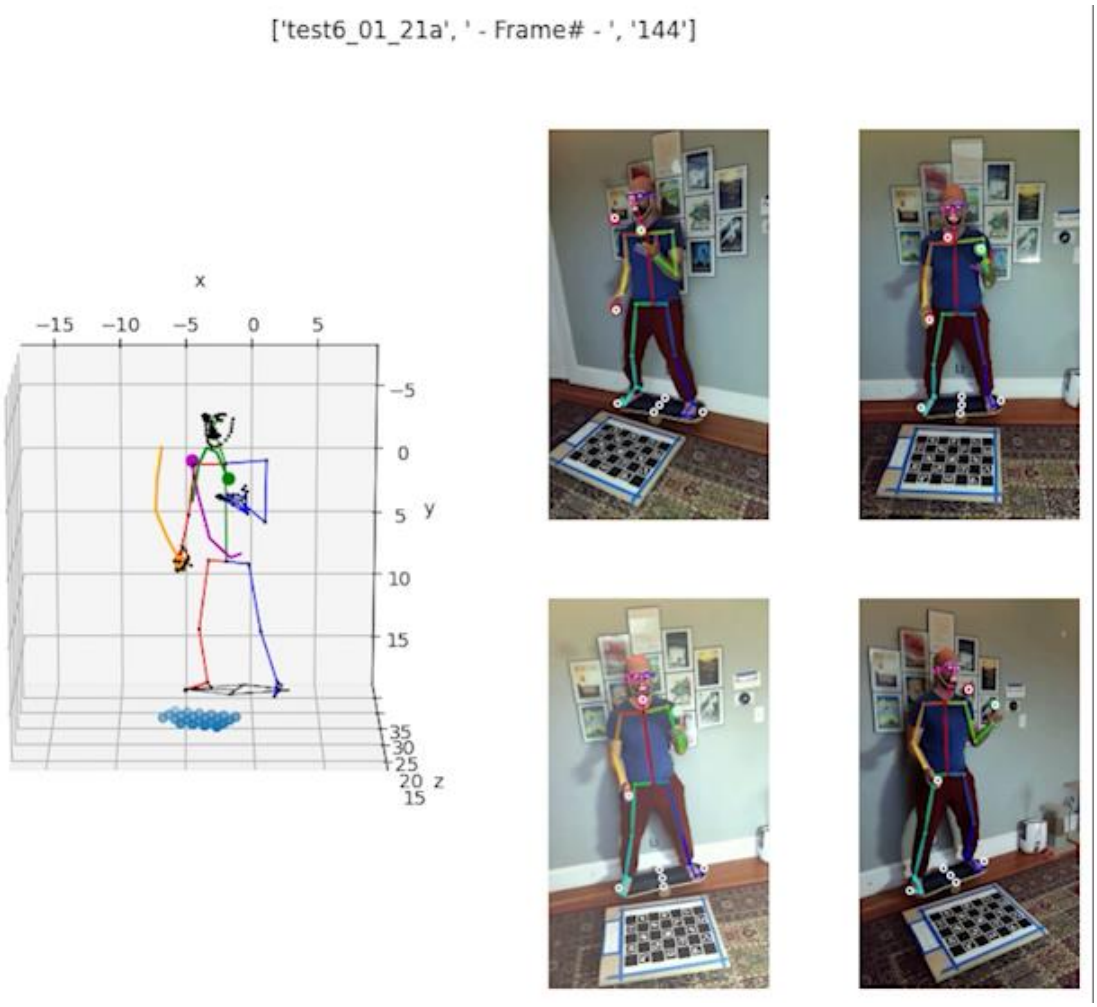
Topic: I.07. Data Analysis and Statistics

Support: NIH R00-EY028229

Title: The FreeMoCap Project: A free-and-open-source, hardware-and-software-agnostic, research-grade, minimal-cost motion capture system and platform for decentralized scientific research, education, and training

Authors: *A. CHERIAN, Y. LU, C. CICALO, J. ALLEX, J. S. MATTHIS;
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Abstract: The computer vision community is making tremendous advances in the field of markerless motion capture software, but because these advances often require a high floor of technical knowledge to be used to their full extent they are of limited utility to the scientific community. We developed the Free Motion Capture (FreeMoCap) system to create a common framework for the recording and analysis of human, animal, and robotic movement in order to advance the scientific frontier while creating a more accessible and equitable approach to research, training, and education. The FreeMoCap system leverages emerging markerless motion capture software (e.g. OpenPose, DeepLabCut, etc) to create a streamlined 'one-click' pipeline for 3D kinematic reconstruction. This system works with arbitrary camera hardware and provides methods for synchronous recording of wired cameras (e.g. USB webcams) as well as the post-hoc synchronization of independent cameras (e.g. GoPros). The FreeMoCap system is developed with the intention of being easily accessible to the scientific community and customizable to research needs. We aim to allow integration of other markerless motion capture methods (e.g. AlphaPose, DAANCE, etc) into the system, as well as reformatting motion capture data from traditional optical (Vicon, Qualisys, etc) and IMU-based (e.g. Rokoko, etc) motion capture systems into a common, human-readable data type to facilitate research collaboration and sharing of analytical methods. Support for eye tracking data (e.g. Pupil Labs) is currently in development. By creating a common framework with shared data types, the FreeMoCap system allows researchers from otherwise disparate fields to combine their findings and methodologies in service of a broad and multi-faceted understanding of human and animal movement in the natural world. The FreeMoCap system allows for the recreation of a research-grade motion capture system for less than 100 US Dollars, which coupled with its ease-of-use, widely expands the accessibility of human and animal movement tracking within the scientific community.



Disclosures: A. Cherian: None. **Y. Lu:** None. **C. Cicalo:** None. **J. Allex:** None. **J.S. Matthis:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.05

Topic: I.07. Data Analysis and Statistics

Support: Samuel F. Hulbert Chair Endowment

Title: Common spatial pattern detection of concept semantic relatedness using combined ERP and frequency spectrum features

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Abstract: One of the chief contributing factors to slowing down BCI spellers for users with profound disabilities is backtracking to delete mistakes or correct certain selections. The ability to design an EEG-based strategy to identify the desire to make corrections in the BCI speller would enhance the user experience and bit rate of the device. Past efforts suggested that Common Spatial Patterns (CSP) may show promise in helping detect and classify semantic violations in reading despite CSP not being widely used in event-related potential (ERP) applications. Semantic violations in EEG often exhibit deflections in the N400 and P600 region coinciding with the violation. The purpose of this research is to create a CSP model that can improve the classification accuracy of semantic violations in reading by incorporating neural oscillation information. Visual stimuli consisting of 150 pairs of nouns from Maguire et. al. (2010) and Calvo et. al. (2018) were presented, where the first word served as the Primer and the second word served as the Target. EEG signals from 14 channels were parsed to obtain the average N400 potential, the average P600 potential, and signal power in the alpha and theta bands, creating a 56-dimension (14 channels by 4 feature types) feature space. The CSP algorithm was implemented to improve orthogonality in the feature space, and the feature space dimension was reduced to 2. Three types of classification strategies Linear Discriminant Analysis (LDA), Naïve Bayes (LB), and K-Nearest Neighbor (KNN) were implemented. Graphical analysis by CSP showed that while individual features did not appear separable, a higher dimension dataset including all four feature types does demonstrate separability. The 10-fold validation results showed that two-class models optimized for individual subjects achieved accuracies ranging from 50% to 66% with LDA, 78% to 98% with KNN, and 76% to 100% with NB. Examining the mixing matrices during the dimension reduction step in CSP suggested that alpha frequency band and EEG locations P7, F4, F3, AF4, and FC6 consistently play a critical role in the success of these classifiers across the different subjects.

Disclosures: M.J. Doyel: None. **A.W.L. Chiu:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Program #/Poster #: P968.06

Topic: I.07. Data Analysis and Statistics

Support: VA Merit BX002876 and NIH/NIMH U01MH122590
NIH/NIMH U01MH122592

Title: Sex-specific DNA (hydroxy) methylation in glutamatergic and GABAergic cortical neurons.

Authors: *J. CHIEN[1,2], J. LI[2], A. KOZLENKOV[3,4], S. DRACHEVA[3,4], E. A. MUKAMEL[2];
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Abstract: Covalent modifications of DNA, including methylation and hydroxymethylation of genomic cytosine, transform the neuronal epigenome during brain development and contribute to the diverse identities of neural cell types. DNA methylation could contribute to alterations in neurodevelopment

underlying psychiatric disease such as schizophrenia, yet the cell type-specific distribution of (hydroxy)methylcytosine in health and disease are largely unknown. We recently reported whole-genome, base-resolution DNA (hydroxy)methylation analysis in three major cell types in human prefrontal cortex (PFC)--glutamatergic excitatory neurons (Glu), gamma-aminobutyric acid (GABA)ergic inhibitory neurons, and oligodendrocytes--that were isolated from the autopsied brains of two neuropsychiatrically intact male donors (Kozlenkov et al. 2018). We detected a unique association between hydroxymethylcytosine (hmC) and gene expression in inhibitory neurons that differed from the pattern in excitatory neurons and oligodendrocytes. We also found that risk loci associated with neuropsychiatric diseases, including schizophrenia, were enriched near regions of reduced hmC in excitatory neurons and reduced mC in inhibitory neurons. To address the potential role DNA (hydroxy)methylation in neural cell types in the context of neuropsychiatric disease, we compared the PFC Glu and GABA neurons in schizophrenia patients and matched control individuals (a total of 29 male and female donors, ranging in age from 14 to 60 years old). We confirmed our previous findings that GABA neurons contain a higher level of tmCG, but lower hmCG compared to Glu. Similar patterns were confirmed for non-CG methylation (mCH). We also detected neuron-subtype-specific sex differences for these two major epigenetic marks, as well as systematic variation with age. In summary, this analysis provides a fine-resolution mapping of cell-type- and sex- specific epigenetic marks in control and schizophrenia brains and highlights the important role of hydroxymethylcytosine.

Disclosures: J. Chien: None. **J. Li:** None. **A. Kozlenkov:** None. **S. Dracheva:** None. **E.A. Mukamel:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:30 AM - 11:30 AM

Program #/Poster #: P968.07

Topic: I.07. Data Analysis and Statistics

Support: Von Behring-Röntgen-Stiftung

Title: A functional map of subthalamic nucleus oscillations in Parkinson disease

Authors: *N. SALEHI[1], E.-L. BAUER[1], M. H. A. BOPP[2], S. MARURI[1], T. DEMBEK[4], D. PEDROSA[3], C. NIMSKY[2], L. TIMMERMANN[3], I. WEBER[3], C. R. OEHRN[3];
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Abstract: Besides beneficial effects on movement, deep brain stimulation (DBS) in the subthalamic nucleus (STN) can have adverse effects on cognition and emotional processing depending on the stimulation site. Parkinson's disease (PD) is associated with functionally distinct changes in subthalamic neural oscillations related to motor, cognitive and limbic functions. However, their spatial distribution within the STN is still unclear. Further, it is unknown, whether the underlying functional signature or lead location is a better predictor for stimulation outcome. Previous studies localizing oscillations used post-

operative instead of intraoperative electrode location, which can be biased e.g., by deviations from the planned trajectory and postoperative lead rotation. Here, we used intraoperative microelectrode local field potentials (MER) and intraoperative computed tomography (iCT) to compute a map of subthalamic oscillations in MNI space. Further, we predict postoperative stimulation outcome including preoperative and intraoperative data. We recorded electrophysiological activity of 43 awake PD patients (32m, age=60±5.5), during bilateral implantation of DBS electrodes in the STN. Location of MER was reconstructed using iCT and preoperative 3T MRI data using DISTAL atlas (Lead-DBS toolbox). Power spectral density was mapped into MNI space with a radius of 1 mm around contact location. We tested spatial power distribution of each frequency against uniform distribution on group level by means of a cluster-based permutation analyses using paired t-tests and localized the of volume of tissue activated based on final lead location and best clinical stimulation settings. We used a linear support vector machine (SVM) incorporating preoperative patient information, structural connectivity and oscillatory activity of the stimulated area, as well as lead location as predictors for the motor, cognitive and limbic outcomes of DBS (UPDRS III, MOCA, BDI-II, Matlab V2016b). Cluster-based permutation analyses indicate largely overlapping local power peaks for alpha and beta oscillations in the dorsolateral STN, which is in accordance with previous studies. Further, theta oscillations were most prominent in the central STN. Gamma activity, on the other hand, was not confined to either portion of STN and appeared as local peaks throughout STN. SVM indicate that stimulating areas with oscillatory signatures has a larger impact on DBS outcome than anatomical location *per se*. Using a combination of iCT and MER, we present a map of subthalamic oscillations and show that the functional subthalamic signature predicts DBS outcome better than structural information.

Disclosures: N. Salehi: None. **E. Bauer:** None. **M.H.A. Bopp:** None. **S. Maruri:** None. **T. Dembek:** None. **D. Pedrosa:** None. **C. Nimsky:** None. **L. Timmermann:** None. **I. Weber:** None. **C.R. Oehrn:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Program #/Poster #: P968.08

Topic: I.07. Data Analysis and Statistics

Support: NIH grant R01 AG067420
NIH grant RO1 DC014296

Title: Toward higher-sensitivity, shorter-interval MRI measures of atrophy in neurodegenerative dementias

Authors: *M. BRICKHOUSE[1], L. HANFORD[2], N. CARVALHO[1], M. ELDAIEF[1], R. MAIR[2], J. NIELSEN[2], A. TOUROUTOGLOU[1], R. BUCKNER[2], B. DICKERSON[1];
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Abstract: Background Conventional single acquisition T1w structural MRI can detect significant change in brain structure given ample latency between scans; most contemporary studies of neurodegenerative dementias collect MRI scans at one-year intervals and calculate annualized rates of atrophy. MRI methods to detect atrophy over shorter (3- or 6-month) intervals would be extremely valuable for basic human neuroscience research about neurodegenerative disease mechanisms as well as for translation into clinical trials. Measurement of change over short intervals would allow neurodegeneration to be monitored in smaller, early-phase therapeutic trials—potentially even as a marker of target engagement in trials of disease-modifying interventions.
Method Our pilot cohort consisted of 5 patients: 4 with primary progressive aphasia (2 semantic variant likely due to FTLD, 2 logopenic variant likely due to AD), 1 with posterior cortical atrophy likely due to AD. We collected 32 accelerated 1mm T1w scans in four 30-minute blocks across two days for each of 3 timepoints (baseline, 3 months, 6 months). We used the FreeSurfer longitudinal processing stream to make robust estimates of the cortex and subcortical structures for each T1w volume. For each timepoint, cortical thickness and volume and subcortical volume estimates were derived from all 32 reconstructed scans. Rates of change were calculated from ROI measures. In addition, a cortical atrophy map was calculated for each subject at each timepoint in comparison with a group of age-matched controls (N=32). Between timepoint surface maps were generated for each subject, showing both cortical spread as well as highlighting regions with greatest change in thickness
Results Each of the patients exhibits a typical pattern of atrophy for their clinical syndrome. Cortical atrophy maps are highly reliable between timepoints, and for each subject show visibly apparent but small changes in the magnitude and spread of atrophy. ROI measures demonstrate a slight but observable decrease in the size of many brain structures, even across a 3-month interval. Cortical thickness changes in regions implicated in the patient's individual clinical syndrome show the greatest magnitude of change over time—detectable in each individual at 3-month intervals.
Conclusion This novel approach to MRI acquisition and analysis can sensitively measure neurodegeneration in individuals over shorter intervals of time, which could lead to substantial changes in methods for measuring disease mechanisms and in clinical trial design.

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Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Program #/Poster #: P968.09

Topic: I.07. Data Analysis and Statistics

Support: NSF IIS-1850102

Title: Cortical thickness correlates with cortical morphology

Authors: N. DEMIRCI, *M. HOLLAND;
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Abstract: The cerebral cortex of the human brain has a highly folded structure with consistently thicker outer gyral tops and thinner inner sulcal bottoms. This intriguing form of the cortex has been noted in numerous studies before, and our work (Holland et al. Phys. Rev. Lett. 2018) has suggested that this is the result of the passive physical forces generated during cortical folding. In this study, we explored the systematic patterns of cortical thickness not only among gyral and sulcal folds but also along the bends and intersections of gyri and sulci. For this purpose, we developed an open-source computational pipeline that extracts the local thickness and shape (i.e. sulcal depth and curvature) from reconstructed cortical surfaces. In an analysis of 564 neurotypical human subjects (aged 7-64 years) from the preprocessed Autism Brain Imaging Data Exchange (ABIDE), we found a strong correlation between the macroscopic morphology and thickness of the cortex. Specifically, the cortex is consistently thicker for convex (outward-bending) points, which tend to be gyral folds or the outside of tangential folds, than saddle-shaped points, which are found primarily along inner tangential folds. Concave (inward-bending) points, which are mostly found in sulcal pits, are consistently thinnest. This suggests that the passive physical forces involved in the curving and bending of gyral and sulcal folds also contribute to the characteristic patterns of thickness in the cortex. This relationship is important to understand before making comparisons between the cortical thickness of differently-folded regions. We are currently exploring these patterns of cortical thickness among different species of non-human primates, which have brains of different shapes and sizes. We expect to observe a similar correlation between shape and thickness, although we hypothesize that the differences should be less extreme in less-folded brains and those with thinner cortices. Our findings might offer a new framework into understanding the rationale for variations of thickness in relationship to both shape and size.

Disclosures: N. Demirci: None. **M. Holland:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

Support: NIH BRAIN Initiative UG3/UH3

Title: Mechanisms of Impaired Consciousness in Medial Temporal Lobe Seizures Investigated with Intracranial EEG

Authors: B. P. LITVINOV, A. KUMAR, **Z. AHMAD**, N. GUNAWARDANE, C. YOTTER, I. QURAISHI, *H. BLUMENFELD;
Yale Univ. Sch. of Med., New Haven, CT

Abstract: Impaired consciousness can have detrimental effects on a patient's quality of life. Our goal was to use intracranial EEG to identify distinct characteristics between medial temporal seizures that either impaired or did not impair consciousness, operationalized by behavioral responses. We hoped to gain mechanistic insights and to also identify signal characteristics that could guide the use of neurostimulation to prevent impaired consciousness. Intracranial EEG of 76 medial temporal lobe onset seizures in 8

patients were analyzed. Behavioral responsiveness was broadly classified into two main categories of either impaired or unimpaired responsiveness to external stimuli based on blinded review of video during seizures. Using the fast Fourier transform (FFT), the EEG signals from each electrode contact were processed to calculate the signal power at different frequencies. Signals were synchronized to the onset time of the seizure and averaged across electrodes in major anatomical regions. The change in power from preictal baseline for seizures with impaired and spared behavioral responsiveness was compared. Group data averages (ictal vs pre-ictal baseline) in various frequency bands (delta, theta, alpha, beta, and gamma) were analyzed for seizures with (n = 18) and without (n = 58) impaired behavioral responsiveness. Seizures with impaired behavioral responsiveness had significantly longer mean duration (99.18 ± 62.07 s) than those without impairment (53.72 ± 33.91 s; $p<0.05$). Additionally, impaired seizures in medial temporal lobe onset contacts had greater EEG signal power across all frequency bands. These findings indicate that broad increases in frequency power in the temporal lobe are associated with impaired consciousness in focal temporal lobe seizures. Our findings suggest that severe local changes in the temporal lobe could trigger impairment in a broad network of cortical and subcortical dysfunction outside the temporal lobe. Additionally, the intracranial signal markers we identified can potentially help develop neurostimulation therapies to restore consciousness in temporal lobe seizures and improve quality of life for people with epilepsy.

Disclosures: B.P. Litvinov: None. **A. Kumar:** None. **Z. Ahmad:** None. **N. Gunawardane:** None. **C. Yotter:** None. **I. Quraishi:** None. **H. Blumenfeld:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Program #/Poster #: P968.11

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 5U19NS104653-04

Title: Methods to discover symmetry in neural data and impose symmetry constraints for clustering neural response patterns.

Authors: *C. CHUN[1,2], D. D. LEE[1];
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Abstract: Neural responses in the brain exhibit many different kinds of symmetries. For example, there exists rotational symmetry of neural responses to directional visual stimuli in the primary visual cortex (V1) and retinal ganglion cells. Also, due to the bilateral symmetry of the brain, there can be a pair of neurons whose response levels to some left-side and right-side stimuli are permuted. However, there lacks a method to incorporate these symmetries when grouping neurons with similar response patterns to identify functional neuronal units. Finding functional units that represent the population of neurons is crucial for simplifying the brain circuit for understanding a neural mechanism of sensory processing. Here we present efficient methods to discover symmetries of different types in noisy data using linear

programming, along with a modified k-means clustering algorithm that finds symmetric clusters by utilizing the symmetry relationship discovered earlier. We applied these methods to neural activities in transgenic Tg(elavl3:GCaMP5G) zebrafish larvae engaged in optomotor response (OMR; fish n=22). The fish were presented with binocular directional visual stimuli to induce OMR, and neuronal activities (neurons n=22782) in the brain parts involved in OMR, i.e. pretectum and anterior hindbrain, were recorded using 2-photon microscopy. In this dataset, we expect to see pairs of neurons whose responses were permutated with a cycle of 2, largely due to the bilateral symmetry of the brain. We found the symmetry between leftward and rightward stimuli, but also between inward (visual fields converging to the body center) and outward (diverging from the body center) which were unexpected and would have been difficult to find without this method. This finding suggests the neural connections to inward selective units and outward selective units are symmetric. This demonstrates that the symmetric clustering method can provide deeper insights into neural circuitry. The method can also find a permutation symmetry of any number of cycles in polynomial time (O(n^2)), and the method can be applied to continuous data by acting on Fourier components of the signals.

Disclosures: C. Chun: None. **D.D. Lee:** None.

Poster

P968. Data Analysis and Statistics: Human Data and Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

Support: National Defense Science and Engineering Fellowship
Lawrence Berkeley National Laboratory-internal LDRD “Deep Learning for Science” led by Prabhat

Title: Optimal noise correlations are biologically implausible

Authors: *P. SACHDEVA[1], J. LIVEZEY[2], S. MADHOW[3], M. DOUGHERTY[4], K. E. BOUCHARD[5]; [1]Univ. of California, Berkeley, Oakland, CA; [2]Biol. Systems and Engin., E O Lawrence Berkeley Natl. Lab., Berkeley, CA; [3]UC Berkeley, Berkeley, CA; [4]Lawrence Berkeley Natl. Lab., Berkeley, CA; [5]UCSF, UCSF, San Francisco, CA

Abstract: *Correlated variability across simultaneously recorded neurons (noise correlations) has been observed across a variety of cortical areas and experimental paradigms. In many contexts, this correlated variability has been shown to improve the coding fidelity of experimental stimulus parameters as measured by the linear Fisher information (LFI), compared to a null model with no correlations. However, most existing results do not shed light on whether neural populations achieve optimal coding properties. Assessing optimality in data is conditional on the choice of null model: the null model specifies both the degrees of freedom that we hypothesize a neural system can control as well as constraints that it cannot change. Here, we propose to assess optimality in diverse datasets by comparing observed LFIs to the distribution expected according to a null model where its degrees of freedom are sampled uniformly. In order to accomplish this, we propose two novel null models: a rotation null model*

and factor analysis null model that have alternative degrees of freedom and therefore distinct biophysical interpretations compared to the shuffle null model. We show that across datasets and dimensionalities, neural populations have suboptimal coding performance according to the rotation and factor analysis null models, relative to the shuffle null model. We explain this finding by demonstrating that the optimal neural response distributions violate two measures of biological plausibility. Furthermore, we find that across datasets, the optimality of the observed responses decreases with dimensionality for all null models. Together, these results shed light on the limitations of neural systems in achieving optimal coding of experimental stimulus parameters, and highlights the importance of carefully considering the biological interpretation of null model degrees of freedom.

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Poster

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Program #/Poster #: P968.13

Topic: I.07. Data Analysis and Statistics

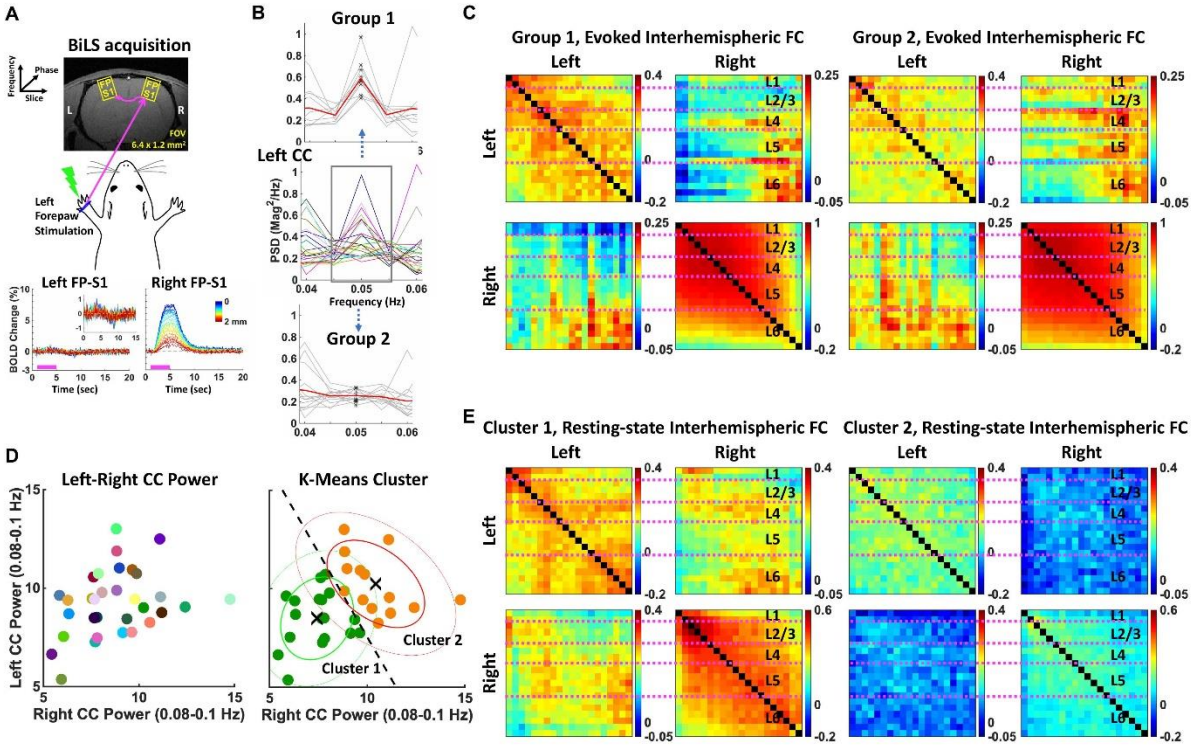
Support: RF1NS113278-01
R01 MH111438-01
S10 MH124733
DFG Yu215/2-1, 3-1
BMBF 01GQ1702

Title: Characterize laminar-specific features of inter hemispheric functional connectivity with bilateral line-scanning fMRI

Authors: *S. CHOI[1,2], X. YU[3];
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Abstract: Despite extensive efforts to identify corpus callosum (CC) mediated interhemispheric (i-) functional connectivity (FC), several reports have demonstrated nearly intact i-FC in post-callosotomy brains. To relate the controversial studies to dynamic functional changes in the brain, it is plausible to investigate how correlations change in i-FC mediated by callosal projection neurons. Here, we developed a bilateral line-scanning functional magnetic resonance imaging (fMRI) method to detect laminar-specific blood-oxygen-level-dependent (BOLD) fMRI signals from symmetric forepaw somatosensory cortex (FP-S1) regions with spatial and temporal resolution (100 μm, 100 ms) in rodent brains. We investigated laminar-specific correlation features under both evoked and resting-state (rs-) conditions in anesthetized rats (55 trials of 4 rats). In evoked fMRI, we sorted all trials into two groups based on BOLD signals detected in left CC ipsilateral to stimulation. Interestingly, Group 1 showed negative correlations between superficial layers of right FP-S1 and all layers of left FP-S1 (Fig. C), possibly highlighting the

transcallosal postsynaptic inhibitory effect in a delayed time scale negatively coupled to the BOLD signal detected in the draining veins of activated right FP-S1. In contrast, Group 2 only showed positive correlations between infragranular layers of right FP-S1 and all layers of left FP-S1, implying direct neuronal activation coupled BOLD signals across bilateral FP-S1. We also sorted all trials into two clusters based on rs-CC fMRI signals detected at a high frequency band (0.08-0.1 Hz) completely distinguishing from an ultra-slow fluctuation (0.01-0.02 Hz). Notably, Cluster 1 showed positive correlations between Layer 2-6 of right and left FP-S1, but weak or zero correlations of Cluster 2 were observed (Fig. E), possibly indicating brain state-dependent i-FC changes. This work provides a unique laminar-specific i-fMRI mapping scheme to investigate evoked and rs-FC, distinguishing transcallosal-mediated neuronal interactions across two hemispheres.



Disclosures: S. Choi: None. **X. Yu:** None.

Poster

P033. Synaptic Structure and Function

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Topic: B.06. Synaptic Transmission

Support: CIHR MOP106556

Brain Canada Foundation
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Title: Neurexins regulate neurotransmission by dopamine neurons

Authors: C. DUCROT[1], G. DE CARVALHO[2], B. DELIGNAT-LAVAUD[1], C. DELMAS[3], N. GIGUÈRE[1], S. MUKHERJEE[1], S. BURKE NANNI[1], M.-J. BOURQUE[1], M. PARENT[3], L. Y. CHEN[2], ***L.-E. TRUDEAU**[1];
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Abstract: Dopamine (DA) neurons of the VTA and SNc project densely to the ventral (vSTR) and dorsal striatum (dSTR, respectively, and are critical regulators of basal ganglia functions, movement and cognition. The connectivity of the DA system is intriguing due to the dual character of its axonal domain, with terminals that are typically non-synaptic in structure, but with a subset that are synaptic and from which glutamate or GABA can be released. The molecular mechanisms underlying the formation of synaptic and non-synaptic terminals is presently undetermined. However, a growing body of work, mainly performed on neurons that are exclusively synaptic, has highlighted the implication of trans-synaptic cell adhesion molecules such as neurexins (Nrxns) in synapse regulation. In this study, we evaluated the role of Nrxns in the formation and function of axon terminals and synapses established by DA neurons. We crossed a triple conditional Nrxn mouse line (Nrxn123 TKO) with a DAT-Ires-Cre mouse to selectively delete Nrxns in DA neurons. We observed that the density of excitatory and inhibitory synapses established by DA neurons *in vitro* was not affected, and that loss of Nrxns does not impair the basic development and connectivity of DA neurons. However, we found that the loss of Nrxns caused an impairment of DA transmission in striatal brain slices prepared from adult mice, revealed by a reduced rate of DA reuptake after electrically-evoked DA release and with impaired amphetamine-induced locomotion. Interestingly, after deletion of all Nrxns, quantitative immunohistochemistry in striatal sections revealed an adaptation of the DA system, with an increased intensity of vesicular monoamine transporter (VMAT2) immunoreactivity and a decrease of DA transporter immunoreactivity, without any change of tyrosine hydroxylase levels in the ventral striatum. Overall, these results suggest that Nrxns play a key role in regulating neurotransmission by DA neurons.

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Poster

P033. Synaptic Structure and Function

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Program #/Poster #: P033.02

Topic: B.06. Synaptic Transmission

Support: UCI School of Medicine Startup Fund

Title: Gaba co-release by dopamine projections in the striatum is regulated by neurexins.

Authors: G. B. DE CARVALHO[1], C. DUCROT[2], N. GIGUERE[2], L.-E. TRUDEAU[2], ***L. Y. CHEN**[1];
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Abstract: Dopamine (DA) afferents projecting from the Ventral Tegmental Area (VTA) and Substantia Nigra (SN) regulate striatal synaptic transmission through releasing neurotransmitters such as DA, glutamate, and GABA. However, little is known about the release mechanisms involved and the synapse specificity in different striatal regions. Neurexins (Nrxns) have been identified as major contributors to presynaptic transmission in a synapse-specific manner. They have been shown to regulate various synaptic functions, including neurotransmitter vesicle docking and release. We examined the role of Nrxns in DA-mediated synaptic transmission by creating DA neuron-specific NrxnKO mice using $Nrxn123^{flox}$ mice crossed with DAT-IRES-Cre mice. Synaptic transmission was measured in medium spiny neurons (MSNs) of the dorsal or ventral striatum in acute brain slices prepared from WT, HET and KO mice via whole-cell patch-clamp electrophysiology. Presynaptic DA afferents projecting to striatal regions were selectively stimulated by expressing channelrhodopsin in VTA/SN neurons via stereotaxic viral injections. Optical stimulation, coupled with pharmacology, was used to measure glutamate or GABA synaptic currents in MSNs. DA/NrxnKO mice showed region-specific changes in inhibitory synaptic responses evoked by optical stimulation (oIPSC) of DA neuron axons. An increase of oIPSC amplitude with an increased decay time constant was observed in the ventral, but not the dorsal striatum. The oIPSCs were blocked by the vesicular monoamine active transporter-2 (VMAT2) inhibitor reserpine. Electrical stimulation was used to measure local synaptic changes where we observed similar region-specific alterations. These findings indicate that Nrxns play an active role in regulating VMAT2-dependent GABA co-release from VTA DA neurons.

Disclosures: G.B. de Carvalho: None. **C. Ducrot:** None. **N. Giguere:** None. **L. Trudeau:** None. **L.Y. Chen:** None.

Poster

P033. Synaptic Structure and Function

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P033.03

Topic: B.06. Synaptic Transmission

Support: MH66198

Title: Probing synaptic $GABA_A$receptor function using Artemisinins

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Abstract: Synapses are the fundamental unit of the nervous system whereby a heterogenous structure and molecular composition facilitate different modes of neurotransmission that ultimately regulate the transfer of information. Extensive work has been conducted at the excitatory synapse delineating the precise arrangement of proteins that drive and facilitate neurotransmitter release and postsynaptic signaling.

However, our knowledge of neurotransmission at the inhibitory synapse is relatively lacking. Recently gephyrin was identified as a primary mammalian target of Artemisinins, a common antimalarial drug. Crystal structures of the gephyrin E domain with Artemisinins demonstrated that Artemisinins target the gephyrin universal binding pocket, which is essential for inhibitory receptor anchoring. However, despite these recent advances in elucidating the interaction of Artemisinins and gephyrin, how Artemisinins modulate synaptic inhibitory neurotransmission at central synapses is not fully known. We used this new family of small molecule compounds to probe the relationship of gamma-aminobutyric acid A receptors ($GABA_A$Rs) and gephyrin. In this study we use Artemisinins as a tool to explore the necessity and utility of gephyrin in mediating inhibitory synaptic transmission. Following the application of Artemisinins to primary hippocampal cultures we investigate neurotransmission using electrophysiology and synaptic proteins using immunocytochemistry. Collectively, our results suggest gephyrin interactions maintain $GABA_A$ receptor organization vital for proper inhibitory neurotransmission.

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Poster

P033. Synaptic Structure and Function

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Program #/Poster #: P033.04

Topic: B.06. Synaptic Transmission

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NIH Grant R01MH116901
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Title: Neurexin-3 defines synapse- and sex-dependent diversity of GABAergic inhibition in ventral subiculum

Authors: *E. E. BOXER[1], C. SENG[2], D. LUKACSOVICH[2], J. KIM[1], S. SCHWARTZ[1], M. J. KENNEDY[1], C. FOLDY[2], J. AOTO[1];
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Abstract: Ventral subiculum (vSUB), the major output structure of ventral hippocampus, regulates stress and reward, and its hyperactivity is implicated in schizophrenia (SCZ), depression, and substance use disorders (SUDs). An understanding of the intrinsic connectivity and synaptic properties of the local vSUB inhibitory circuit, however, is limited. The presynaptic adhesion molecule, Neurexin-3 (Nrxn3), is also associated with SCZ and SUDs and is highly expressed in hippocampal inhibitory neurons, but its function at hippocampal inhibitory synapses has remained elusive. Using slice electrophysiology, imaging and single-cell RNA sequencing in PV-Ai9, PV-Cre, and PV-Nrxn3 KO young adult mice, we investigated the functional role of Nrxn3 at GABAergic parvalbumin (PV) interneuron synapses made onto regular and burst spiking (RS and BS) neurons, the two physiologically distinct classes of vSUB

principle neurons. Surprisingly, we found that intrinsic connectivity of vSUB and synaptic function of Nrxn3 in vSUB are sexually dimorphic. We found that PV inhibitory drive is significantly greater onto RS compared to BS neurons in male vSUB, but greater onto BS compared RS neurons in female vSUB. This synapse-specific circuit organization is facilitated by differences in synapse number in males, but quantal size in females. Furthermore, we found that Nrxn3 KO in PV neurons produced synapse-specific and sex-dependent phenotypes: PV synapse density and inhibitory currents were impaired at male RS synapses, while at female RS synapses, PV release probability and inhibitory currents were enhanced. These effects were specific to PV-RS synapses, as PV inhibitory currents in BS neurons were unaltered. These findings represent the first characterization of vSUB as a sexually-dimorphic region and demonstrate that Nrxn3 can govern distinct aspects of inhibitory synaptic transmission that depend on postsynaptic cell identity and sex. These findings may also provide insight to sex differences observed in neuropsychiatric and mood disorders that involve vSUB dysregulation and Nrxn3 mutations.

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Poster

P033. Synaptic Structure and Function

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Program #/Poster #: P033.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ERC Grant 714291

Title: Deposition chamber technology as building blocks for a standardized brain-on-chip framework

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Abstract: In vitro modeling of human brain connectomes is key to explore the structure-function relationship of the central nervous system (CNS). The comprehension of this intricate relationship will serve to better study the pathological mechanisms of neurodegeneration, and hence to perform improved drug screenings for complex neurological disorders, such as Alzheimer's and Parkinson's diseases. However, currently used *in vitro* modeling technologies lack potential to mimic physiologically relevant neural structures, because they are unable to represent the concurrent interconnectivity between myriad subtypes of neurons across multiple brain regions. Here, we present an innovative microfluidic design that allows the controlled and uniform deposition of various specialized neuronal populations within unique plating chambers of variable size and shape, used as organ-on-a-chip platforms for neuroscience research. By applying our design, we offer novel neuro-engineered Organ-on-Chip (OoC) microfluidics, also known as neurofluidic devices, which demonstrate the capacity to isolate, control, and manipulate cellular environments, allowing to co-culture different neural cell types while these are fluidly isolated. To mimic their *in vivo* environment, *in vitro* neural networks are composed of connected nodes seeded with

specialized neuronal populations. The next step in the creation of OoC for CNS research is to couple a microfluidic architecture that can reconstruct complex interconnected neuronal networks, with a functional recording using multi electrode arrays (MEA). These advances provide essential enhancements to *in vitro* platforms in the quest accurately model the brain for the investigation of human neurodegenerative diseases. Composed of multi-nodes interconnected with physiologically relevant structural connectivity patterns, we were able to create a models of CNS circuits affected in neurodegenerative diseases as the direct way of the basal ganglia loop of the brain, involved in Parkinson disease and Huntington disease. This loop is composed of five anatomic parts represented by five microfluidic compartments aligned on the device with respect to the converted required surface and linked using several arrays of microchannels. The activity of these networks can be record thanks to an electrophysiological recording system that has been specifically design to fit an even distribution throughout the compartments in 256 electrodes MEA.

Disclosures: T. Honegger: A. Employment/Salary (full or part-time):; NETRI. **B.G.C. Maisonneuve:** None. **L. Libralesso:** None. **L. Miny:** A. Employment/Salary (full or part-time):; NETRI. **A. Batut:** A. Employment/Salary (full or part-time):; NETRI. **J. Rontard:** A. Employment/Salary (full or part-time):; NETRI. **M. Gleyzes:** A. Employment/Salary (full or part-time):; NETRI. **B. Boudra:** A. Employment/Salary (full or part-time):; NETRI. **J. Vieira:** A. Employment/Salary (full or part-time):; NETRI. **D. Debis:** A. Employment/Salary (full or part-time):; NETRI. **F. Larramendy:** A. Employment/Salary (full or part-time):; NETRI, CNRS, LTM. **V. jost:** None.

Poster

P033. Synaptic Structure and Function

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P033.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: F32NS100033801
K99NS112604
R01NS032457
U54HD090255
R01NS035129

Title: Early role for a Na+,K+-ATPase (ATP1A3) in brain development

Authors: *R. SMITH[1], M. FLORIO[2], S. AKULA[1], J. NEIL[1], S. MCCARROLL[2], A. BARKOVICH[3], C. A. WALSH[4];
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Abstract: Osmotic equilibrium and membrane potential in animal cells depend on concentration gradients of sodium (Na^+) and potassium (K^+) ions across the plasma membrane, a function catalyzed by the Na^+,K^+-ATPase alpha (α) subunit. Here, we describe *ATP1A3* variants encoding dysfunctional α3

subunits in children affected by a developmental malformation of the cerebral cortex characterized by abnormal folding and laminar organization. To gain cell-biological insights into the early developmental spatiotemporal dynamics of prenatal *ATP1A3* expression, we built an *ATP1A3* transcriptional atlas of fetal cortical development using mRNA *in situ* hybridization and transcriptomic profiling of ~125,000 individual cells with single-cell RNA sequencing (Drop-Seq) from eleven areas of the midgestational human neocortex. We find that fetal expression of *ATP1A3* is most abundant to a subset of excitatory neurons carrying transcriptional signatures of the developing subplate, yet also maintains expression in non-neuronal cell populations. Moving forward a year in human development, we profiled ~52,000 nuclei from four areas of an infant neocortex and show *ATP1A3* expression persists throughout early postnatal development, most predominantly in inhibitory neurons, including parvalbumin interneurons in the frontal cortex. Finally, we discover the heteromeric Na^+,K^+-ATPase pump complex may form non-redundant cell-type specific α-β isoforms combinations, including α3-β1 in excitatory neurons and α3-β2 in inhibitory neurons. Together, the developmental malformation phenotype of affected individuals and single-cell *ATP1A3* expression patterns point to a key role for α3 in human cortex development, suggesting a similar prenatal ion dysregulation pathway as other known genes (i.e. SCN3A).
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Poster

P033. Synaptic Structure and Function

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Program #/Poster #: P033.07

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH R00-NS076661
NIH R01-NS097537

Title: Hyperactive ERK/MAPK in glutamatergic neurons alters connectivity in the mouse cortex

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Abstract: Glutamatergic neurons comprise 80% of the total neuron population in the cerebral cortex, however, the function of the RAS/RAF/MEK/ERK (ERK/MAPK) signaling cascade within this subpopulation of cells is not well understood. Clearly defined mutations within this pathway cause syndromes known as the RASopathies. Clinical symptoms include intellectual disability, developmental delay, cardio-facial deficits, and in some cases hypotonia. A majority of RASopathies are attributed to hyperactivation of ERK/MAPK signaling. Individuals with Neurofibromatosis Type 1 (NF1) and Noonan Syndrome (NS), two common RASopathies, exhibit aberrant structural connectivity in diffusion tensor imaging (DTI) studies, however, the contributions of axonal versus oligodendrocyte deficits to this phenotype are not fully understood. Here, we used a conditional genetic approach to delineate the neuron autonomous effects of hyperactive ERK/MAPK in subpopulations of glutamatergic neurons in the mouse

cortex. We have previously found reduced corticospinal tract (CST) axon extension in these mutants. We now show that this defect is layer V neuron autonomous using a Cre-dependent reporter and anterograde viral tracing. We have also implemented retrograde viral tracings to better understand input into primary motor cortex (M1). Analysis of oligodendrocyte markers revealed limited deficits in these neuron directed mutants. The relationship between structural and functional connectivity has not been explored in these mutants, we therefore investigated the expression of activity dependent genes responsive to glutamatergic signaling. Using both pan-glutamatergic and layer V directed approaches, we found that ERK/MAPK hyperactivation led to both cell autonomous and cell non-autonomous alterations in FOS and ARC expression. ERK/MAPK hyperactivation specifically in GABAergic neurons, did not result in significant changes in activity dependent gene expression. Overall, our data shows that glutamatergic neuron ERK/MAPK hyperactivation during embryogenesis is sufficient to alter both structural and functional connectivity in the mature mouse cortex. Future work will be aimed at elucidating the direct ERK1/2 mediated molecular mechanisms important for circuit formation.

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Poster

P033. Synaptic Structure and Function

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Topic: B.06. Synaptic Transmission

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Title: Control of Activity-regulated cytoskeleton-associated protein (Arc) neurobiology by TNIK

Authors: *A. WALCZYK-MOORADALLY[1], J. HOLBORN[1], K. K. SINGH[1], M. TYLER[2], D. PATNAIK[2], H. WESSELING[3], N. J. BRANDON[4], J. STEEN[3], S. P. GRAETHER[1], S. J. HAGGARTY[2], J. LALONDE[1];
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Abstract: The remarkable capacity of neurons to reorganize their structure, function, and connections in an activity-dependent manner is supported by an extensive network of molecules and effectors. Among those, the 'hub' protein Activity-regulated cytoskeleton-associated protein (Arc, also known as Arg3.1) can be considered one of the central, as well as most versatile, players. Notably, Arc has been shown to maintain direct interactions with key synaptic factors like PSD95, TARPγ2, and CaMKII, as well as participate in many aspects of neuroplasticity such as trafficking of AMPARs and modeling of dendritic

spines. As a protein with homology to the retroviral Gag protein, a particular characteristic of Arc is its capacity to self-assemble into virus-like capsids that can package mRNAs and transfer those transcripts to other cells. How a single protein like Arc can do all this remains difficult to explain, but a complete answer to that question will certainly include a mix of protein post-translational modifications acting to confer molecular and functional specificity. Recently, proteomics and sequence analysis of Arc protein led us to recognize two candidate phosphorylation sites specific to TRAF2 and NCK-interacting protein kinase (TNIK)—a member of the Germinal Center Kinases (GCK) subfamily that is considered a possible risk factor to different psychiatric disorders, including schizophrenia and bipolar disorder. These two sites of interest were found in structurally distinct locations, S67, located within the coil-coiled region of the nuclear retention domain, and T278D which was located within the flexible hinge region between the N- and C-lobe of the capsid-forming domain. Here, we summarize evidence supporting the interaction between Arc and TNIK using co-immunoprecipitation and kinetic assays. These results support Arc as a substrate for TNIK phosphorylation. Next, we present how site-directed mutagenesis to create Arc S67 and T278 mutant variants reveal that TNIK action at those amino acids can strongly influence Arc's subcellular distribution and self-assembly as capsids. Finally, we highlight how modification of Arc's T278 site can change its interaction with other synaptic protein effectors. In summary, we present biochemical, proteomics, and electron microscopy evidence supporting the influence of TNIK on Arc's neurobiology. Together, our efforts offer exciting new scenarios about the interaction of these two factors in the context of synaptic plasticity and the pathophysiology of certain brain disorders.

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Poster

P033. Synaptic Structure and Function

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Program #/Poster #: P033.09

Topic: B.06. Synaptic Transmission

Support: F31MH116583
NSF of China 31872759
R01MH086828
R01DA018928
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R37MH080046

Title: Subsynaptic positioning of AMPARs by LRRTM2 controls synaptic strength

Authors: *A. M. RAMSEY[1], A.-H. TANG[2], T. A. LEGATES[4], X.-Z. GOU[3], B. E. CARBONE[5], S. M. THOMPSON[6], T. BIEDERER[7], T. A. BLANPIED[1];
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Abstract: Recent evidence suggests that nanoorganization of proteins within synapses may control the strength of communication between neurons in the brain. The unique subsynaptic distribution of glutamate receptors, which cluster in nanoalignment with presynaptic sites of glutamate release, supports this idea. However, testing it has been difficult because mechanisms controlling subsynaptic organization remain unknown. Reasoning that transcellular interactions could position AMPA receptors, we targeted a key transsynaptic adhesion molecule implicated in controlling AMPAR number, LRRTM2, using engineered, rapid proteolysis. Severing the LRRTM2 extracellular domain led quickly to nanoscale de-clustering of AMPARs away from release sites, not prompting their escape from synapses until much later. This rapid remodeling of AMPAR position produced significant deficits in evoked, but not spontaneous, postsynaptic receptor activation. These results dissociate receptor numbers from their nanopositioning in determination of synaptic function, and support the novel concept that adhesion molecules acutely position AMPA receptors to dynamically control synaptic strength.

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Poster

P036. Neural Development: Molecular Mechanisms I

Location: Virtual Only

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Program #/Poster #: P036.01

Topic: A.07. Developmental Disorders

Support: ANID Doctoral fellowships Nº21180582 to FR-C
FONDECYT grant 1220393 to MPM
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Title: Lipophorin Receptors participate in mushroom bodies development and function

Authors: *F. ROJO-CORTÉS[1], V. TAPIA-VALLADARES[1], N. FUENZALIDA-URIBE[2], S. HIDALGO[1,3], M.-C. GONZÁLEZ-RAMÍREZ[1], C. B. ROA[1], C. OLIVA[1], J. M. CAMPUSANO[1], M.-P. MARZOLO[1];
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Abstract: The Lipophorin Receptors (LpRs) are members of the Low-density Lipoprotein Receptor family that mediate lipid uptake in insects. In *Drosophila melanogaster* two LpRs have been described,

LpR1 and LpR2, which are orthologs of the Reelin receptors ApoER2 and VLDL-R, present in vertebrates. Reelin is a signaling molecule associated with the correct development of laminated structures like the hippocampus, cerebral cortex and cerebellum. It is currently unknown whether LpRs play similar roles in the fly brain, though Reelin is not present in the Drosophila genome. Herein we show that LpR-deficient flies exhibit impaired olfactory memory and sleep patterns, function that relays on the Mushroom Bodies (MB) in fly brain. These animals also present anatomical defects in this critical association area. Cultured *Drosophila* MB neurons treated with mammalian Reelin increase their neurite complexity, which is similar to what has been observed in hippocampal neurons. This is not observed in neurons from animals bearing mutations in LpRs genes. In vitro experiments showed that the short isoforms of LpRs bind and internalize Reelin. Furthermore, our data suggest that the effect of Reelin on neuron complexity depends on Dab, a protein homologous to vertebrate Dab1, involved in Reelin signaling cascade. These results show for the first time that LpRs have a role beyond lipid metabolism in *Drosophila*, and further support the existence of a Reelin-like molecule in *D. melanogaster*.

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Poster

P036. Neural Development: Molecular Mechanisms I

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Program #/Poster #: P036.02

Topic: A.07. Developmental Disorders

Support: NIH Grant 5R01MH109706-02

Title: Regulation of the excitatory synapse through USP7

Authors: *H. BAKER, R. GU, C. CHANG, V. VO, E. C. OH;
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Abstract: Regulation of the excitatory synapse through *USP7*
Loss of function lesions in Ubiquitin-specific protease (USP) 7 are associated with intellectual disability with significant speech delay, autism spectrum disorder, and seizures. While the deubiquitinating activity of USP7 has been characterized in P53-dependent apoptosis, a role for cell-growth arrest and distinct neurological conditions seen in patients with mutations in *USP7* has not been established. Here, we show that USP7 can regulate the development of the brain by localizing to synaptosomes in the hippocampus and stabilizing neural-specific substrates. Using mass spectrometry, we identify discrete protein complexes that interact with USP7 and are necessary for functions such as signaling, vesicular trafficking, Golgi assembly, and cell polarity at the synapse. Missense mutations in *USP7* abolish these interactions and haploinsufficiency of *USP7* in induced neurons from induced human pluripotent stem cells (iPSCs) results in the perturbation of neural synchrony and network oscillations. We characterized heterozygous loss of function mice and show that mutant phenotypes can be associated with stability of neural proteins

that are required to form the excitatory synapse. Taken together, our iPSC and mouse models suggest that USP7 is necessary to promote synaptic function and cognition during development.

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Poster

P036. Neural Development: Molecular Mechanisms I

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Program #/Poster #: P036.03

Topic: A.07. Developmental Disorders

Support: PCDH19-Alliance
Wellcome Trust

Title: Proteolytic processing and nuclear function of PCDH19

Authors: *S. NEWBOLD, C. LLINARES-BENADERO, I. W. FOX, I. MARTINEZ-GARAY; Cardiff Univ., Cardiff, United Kingdom

Abstract: Mutations in the X-linked gene Protocadherin-19 (*PCDH19*) lead to epilepsy with cognitive impairment in heterozygous females and post-zygotic mosaic males. The disorder phenotype is currently explained by cellular mosaicism of *PCDH19* expressing and non-expressing cells in the brain, which leads to defective cell-cell communication and circuits. Although the gene codes for a cell adhesion protein of the cadherin superfamily expected to localize at the cell membrane, recent reports have implicated PCDH19 in the regulation of gene expression and have identified the protein in the nucleus. The aim of this study was to determine if PCDH19 could undergo proteolytic cleavage resulting in the generation of an intracellular fragment (PCDH19-ICD) that could translocate to the nucleus in order to regulate gene expression. In addition, we wanted to identify pathways which are regulated by PCDH19 processing in neural progenitors and neurons. To test this hypothesis, we have analysed how the absence or inactivation of specific proteases affects the generation of PCDH19-ICD in heterologous cells and neurons. Our results show that PCDH19 can be processed by ADAM10 and gamma secretase, and that PCDH19 undergoes activity-dependent proteolytic processing in neurons. To determine potential transcriptional targets of PCDH19, we have generated a mouse embryonic stem cell line that overexpresses the cytoplasmic domain of PCDH19 from the Rosa26 locus (CYTO), and an isogenic PCDH19-knockout line (KO). Both lines, together with a control, have been used for RNAseq analysis. RNAseq analysis indicates changes in several synaptic pathways in those neurons overexpressing PCDH19 cytoplasmic domain, suggesting a potential role for PCDH19 processing in the modulation of synaptic function. We are currently complementing our *in vitro* analysis with an *in vivo* overexpression of PCDH19-CYTO in order to assess an effect on dendritic morphology *in vivo*. We believe that PCDH19 is capable of transducing information about events happening at the membrane to the nucleus to elicit appropriate cellular responses and expect that our *in vivo* analysis will provide new mechanistic insights into the function of PCDH19 in post-mitotic neurons.

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Poster

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Topic: A.07. Developmental Disorders

Support: NIH, R01HD092593
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Simons Foundation, SFARI Pilot Award
Research Foundation of Cerebral Palsy Alliance, #3720

Title: Placental endocrine function loss may contribute to human preterm cerebellar white matter alterations

Authors: *C.-M. VACHER[1], H. LACAILLE[1], S. SEBAOUI[2], J. SALZBANK[1], J. O'REILLY[1], A. A. PENN[1];
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Abstract: We have recently reported a novel conditional mouse model that was designed to study the specific contribution of placental endocrine function to normal and pathological fetal brain development (*Nature Neuroscience*, in press). In our model (named plKO), the gene encoding 3alpha-hydroxysteroid dehydrogenase (3α-HSD) is deleted in trophoblasts, resulting in the insufficient production of placental allopregnanolone (ALLO), a progesterone derived neurosteroid, during the second half of mouse gestation. Adult mice that lacked placental ALLO exhibit sex-linked neurodevelopmental and behavioral alterations. The anatomical and molecular alterations included cerebellar white matter (WM) abnormalities that correlated with autistic-like behavior only in male offspring. A single injection of ALLO during late gestation abolished these alterations. To evaluate the translational potential of our findings, we have asked whether human preterm birth, a well-described risk factor for human autism, was associated with similar cerebellar myelin alterations comparable to those seen in the plKO mice. We examined 24 post-mortem cerebellar vermises from term (>37 weeks of gestation) and preterm (<34 weeks of gestation) infants who died at a mean corrected age of 6 weeks. Compelling similarities between our mouse model and human pathology were found. Specifically, cerebellar myelin protein contents were augmented in males and reduced in females born preterm as compared with term counterparts, showing a sex-divergent myelination trajectory in the cerebellum after preterm birth. In addition, the higher levels of *pdgfra*- and *cspg4*-mRNA in the cerebellum of preterm males suggest either delayed progression of the oligodendrocyte lineage or increased proliferation of oligodendrocyte precursor cells, as temporarily seen in the plKO males. This striking correlation between mice exposed to ALLO insufficiency and infants born preterm suggests that altered ALLO exposure may contribute to abnormal preterm brain development. Our study also indicates that placental hormone replacement may offer novel therapeutic opportunities to prevent later neurobehavioral disorders.

Disclosures: C. Vacher: None. **H. Lacaille:** None. **S. Sebaoui:** None. **J. Salzbank:** None. **J. O'Reilly:** None. **A.A. Penn:** None.

Poster

P036. Neural Development: Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P036.05

Topic: A.07. Developmental Disorders

Support: Shriners Hospitals for Children Research Grant 85134-PHI-21 to S.K
NINDS Grant R01NS04038 to S.K.

Title: P53-mediated rescue of microcephaly caused by Pals1 loss

Authors: *N. STERLING[1,2], S. KIM[1,2];
[1]Shriners Hosp. Pediatric Res. Ctr., [2]Dept. of Neural Sci., Temple Univ., Philadelphia, PA

Abstract: The protein associated with Lin7 (Pals1) is an integral apical polarity complex protein which is necessary for cortical progenitor self-renewal. Previous studies have demonstrated that loss of Pals1 in cortical progenitors nearly abrogates formation of the cerebral cortex resulting in microcephaly in mice. However, the mechanism by which cell reduction occurs in Pals1 mutant cortices is not fully understood. To determine the effects of Pals1 loss on cortical progenitors, we generated Pals1 conditional knockout mice (cKO) using Emx-1 Cre to target cortical progenitors. Using time-lapse experiments and analyses of mitotic phases, we found that Pals1 mutant cortical progenitors display significantly increased time to undergo mitosis with a larger proportion of these cells found in ana/telophase, and observable cytokinesis defects. These findings show that Pals1 is required for normal mitotic progression in cortical progenitors. Mitotic defects resulting from loss of Pals1 may cause the cell death which leads to microcephaly in Pals1 mutants. Previous studies have shown that microcephaly-associated cell death may be caused by activation of the tumor suppressor protein p53. To determine if p53 activation plays a role in the neural progenitor cell death and microcephaly caused by Pals1 deficiency, we have examined whether p53 is activated in Pals1 mutants. In the developing cortices of Pals1 cKO mice, p21, a prime downstream target of p53, is upregulated, suggesting that p53 is activated. To test whether genetic elimination of p53 will prevent cell death and restore cortical size in Pals1 mutants, we have generated a double conditional knockout of p53 and Pals1. To examine the effects of p53 loss in Pals1 reduction, we have analyzed cortical size, cortical layering, and progenitor cell mitosis. Cortical size and cell numbers are significantly increased in the p53 co-deletion compared to Pals1 mutants. Importantly, when p53 is co-deleted, the time to undergo mitosis and cytokinetic defects observed in Pals1 mutants are also significantly rescued. Collectively, these findings indicate that p53 activation plays a critical role in the development of the microcephaly phenotype caused by Pals1 depletion in the mouse cortex, not simply by preventing cells from undergoing apoptotic cell death, but also by rescuing the mitotic defects resulting from Pals1 reduction.

Disclosures: N. Sterling: None. **S. Kim:** None.

Poster

P036. Neural Development: Molecular Mechanisms I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P036.06

Topic: A.07. Developmental Disorders

Support: NIH Grant 2211079 RO1

Title: Understanding Cell Type Specific Impacts of HCMV Infection and Viral Entry within a 3D Cortical Organoid

Authors: *B. S. O'BRIEN[1], A. D. EBERT[1], S. S. TERHUNE[2], S. RAO[3,4], K. PULAKANTI[3,5], M. L. SCHUMACHER[2], R. L. MOKRY[2];
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Abstract: Title: Understanding Cell Type Specific Impacts of HCMV Infection and Viral Entry within a 3D Cortical Organoid
Authors: Benjamin S. O'Brien[1], Rebekah L. Mokry[2], Megan L. Schumacher[2], Kirthi Pulakanti[3], Sridhar Rao[1,3] Scott S. Terhune[2], and Allison D. Ebert[1]
Affiliations:1 Department of Cell Biology, Neurobiology, and Anatomy2 Department of Microbiology and Immunology, and Biomedical Engineering3 Department of Pediatrics, Hematology, Oncology, and Transplantation Medical College of Wisconsin, Milwaukee, WI, United States
Human cytomegalovirus (HCMV) is a beta herpesvirus that can cause severe congenital birth defects including microcephaly, vision loss, and hearing loss. Currently, no approved treatment options exist for managing in utero infections. Our previous work showed that HCMV infection in undifferentiated human induced pluripotent stem cell (iPSC) derived neural progenitor cells (NPCs) and iPSC derived cortical organoids have reduced baseline calcium levels, were unresponsive when evaluated 5 days post infection, and struggle to generate cortical neurons. To identify underlying mechanisms, we have used RNA sequencing to understand how the infection impacts the transcriptome in infected organoids. We infected cortical organoids using HCMV TB40/E expressing eGFP and cell populations were sorted via FACS and then sequenced. Our studies demonstrate that HCMV infection significantly impairs neural function and several developmental pathways. Further, these transcriptional effects were not limited to cells expressing GFP and instead were found throughout the organoid. We are now using single cell RNA sequencing (scRNAseq) to gain a deeper understanding of specific populations impacted by HCMV infection as we and others have shown that NPCs are more susceptible to HCMV infection than more terminally differentiated cells. One mechanism for this selective preference could be due to the entry receptor profile found on NPCs compared to more terminally differentiated cells. Therefore, we are using flow cytometry and scRNAseq to determine the relative expression of trimeric and pentameric entry receptors to better characterize HCMV infection properties in human NPCs and organoid-derived tissues. Together, these data will further define HCMV infection properties in human neural tissues with the ultimate goal of identifying potential targets of therapeutic intervention.

Disclosures: B.S. O'Brien: None. **A.D. Ebert:** None. **S.S. Terhune:** None. **S. Rao:** None. **K. Pulakanti:** None. **M.L. Schumacher:** None. **R.L. Mokry:** None.

Poster

P036. Neural Development: Molecular Mechanisms I

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Program #/Poster #: P036.07

Topic: A.07. Developmental Disorders

Support: NIH Grant 5R01MH109706-02

Title: Characterization of neuronal protein-protein interactions using baits from the 15q11.2 locus

Authors: *N. BASAZINEW, N. GHANI, C. CHANG, R. GU, H. BAKER, M. GHANI, V. VO, E. C. OH;
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Abstract: The 15q11.2 microdeletion syndrome results in neurodevelopmental deficits that include developmental delay and psychiatric conditions. While comprehensive microarray studies have demonstrated that four genes (*NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*) within the 15q11.2 locus are associated with behavioral and anatomical pathology, a unifying hypothesis to correlate gene function to phenotype has not been established. Copy number variations within chromosome 15 are relatively frequent in approximately 1% of the population. An increasing number of genes are associated with intellectual disability (ID) and autism spectrum disorders (ASDs). Fragile X mental retardation gene 1 (*FMR1*), whose silencing causes the Fragile X syndrome, is the most common form of ID and autism. The precise functional significance of the CYFIP/FMRP interaction is not understood fully; however, among the interactors of FMRP, CYFIP1/2 are good candidates for ID and autism, based on their genetic implication and functional properties. CYFIP1 and CYFIP2 represent a link between Rac1, the WAVE complex, and FMRP, favoring the cross-talk between actin polymerization and translational control. Thus, the role of Cyfip1 in brain connectivity is yet to be explored. Using mass spectrometry, immunoblotting, and immunoprecipitation datasets, we will characterize protein-protein interactions and mechanisms associated with the manifestation of neural disorders linked with the 15q11.2 microdeletion syndrome, and more specifically, with CYFIP1 copy number variation.

Disclosures: N. Basazinew: None. **N. Ghani:** None. **C. Chang:** None. **R. Gu:** None. **H. Baker:** None. **M. Ghani:** None. **V. Vo:** None. **E.C. Oh:** None.

Poster

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Program #/Poster #: P036.08

Topic: A.07. Developmental Disorders

Support: NIH Grant 5R01MH109706-02

Title: Interrogating a centrosomal-specific role for DDX3X during brain development

Authors: *N. GHANI, N. BASAZINEW, C. CHANG, R. GU, H. BAKER, V. VO, E. OH;
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Abstract: DEAD-box proteins are RNA helicases that are characterized by a conserved Asp-Glu-Ala-Asp motif. These proteins are involved in a variety of processes within cells, ranging from cell cycle progression to the innate immune response. DDX3X is a protein-coding gene found on the X chromosome that codes for a DEAD-box RNA helicase and variants in this gene are believed to be involved in 1-3% of unexplained intellectual disabilities in females. The DDX3X protein is vital for cell viability and is found in all tissues within the body. While mutations in the human *DDX3X* gene have been characterized to cause intellectual disabilities, seizures, and autism, the mechanism that associates the genetic lesions to pathology is still under investigation. Here, we use mass spectrometry to characterize a complex interactome of DDX3X in the mouse brain. We also verify the novel interactions using immunoblotting techniques and show that phenotypes associated with loss of function *DDX3X* mutations can be explained through some centrosomal proteins identified in our screen. The data suggest that the loss of DDX3X from the centrosome can perturb neuronal development.

Disclosures: N. Ghani: None. **N. Basazinew:** None. **C. Chang:** None. **R. Gu:** None. **H. Baker:** None. **V. Vo:** None. **E. Oh:** None.

Poster

P036. Neural Development: Molecular Mechanisms I

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Program #/Poster #: P036.09

Topic: A.07. Developmental Disorders

Support: NSERC RGPIN-2020-06403
NSERC USRA
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McMaster University

Title: Age, sex, and race impact the expression of coronavirus receptors in the human brain

Authors: *N. HALABIAN[1], K. NAEEM[1], L. MONTEIRO[2], B. KUMAGAI[1], K. M. MURPHY[1,2];
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Abstract: The symptoms and severity of COVID-19 can vary based on host factors such as age, sex and race. For example, older adults, males and African Americans who become infected with the SARS-CoV-2 virus are more likely to experience severe outcomes. Those include a range of neurological symptoms, such as stroke, delirium and anxiety. Some of the sequelae might be secondary to the viral infection, but the virus can invade the brain, directly causing cell death and localized inflammation. However, few studies have characterized the expression of coronavirus receptors in the human brain, and none have examined if there are age- sex- or race-related differences that might help understand the host factor

vulnerabilities. Here we used two publicly available transcriptomic databases to assess the impact of age, sex and race on the expression of a network of 29 SARS-CoV-2-related genes, including coronavirus receptors (e.g. ACE2, NRP1, DPP4), proteases (e.g. TMPRSS2, furin), and integrins (e.g. ITGA5) in the human brain. First, we used data from 16 brain areas (n=48, F=21, M=27, age:4 mo-80 yrs) to assess the impact of age by determining the lifespan trajectory (LOESS curves) for each gene in each area. We used PHATE, a dimension-reduction analysis and visualization technique, to reveal the high dimensional development of the 16 brain areas. We found 4 distinct developmental trajectories that clustered the 16 areas into 1 subcortical trajectory and 3 cortical trajectories. Second, we used a larger dataset to assess the impact of age, sex and race (African American & Caucasian) on the developmental profile of the prefrontal cortex (n= 269, F/AA=58, F/CAUC=31, M/AA=89, M/CAUC=89, age:4 mo-80 yrs). Developmental trajectories (LOESS curves) were calculated separately for female and male samples and African American and Caucasian samples for each of the 29 genes. Hierarchical clustering of the female and male trajectories identified 7 clusters. Each cluster had trajectories from male and female samples, but most of the genes differed. Clustering of the trajectories separated by race found 4 clusters. Similar to the analysis of sex differences, most of the genes in a cluster were different for Caucasian and African American samples. This series of studies identified robust age, sex, and race differences in the development of SARS-CoV-2 genes. Furthermore, those differences may influence the brain's vulnerability to SARS-CoV-2 infection.

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Poster

P036. Neural Development: Molecular Mechanisms I

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Program #/Poster #: P036.10

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 DC014428
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NIH Grant R01 GM118751

Title: Plexins Promote Hedgehog Signaling Through Their Cytoplasmic GAP Activity

Authors: *T. M. HOARD[1], J. M. PINSKEY[4], X.-F. F. ZHAO[2], N. E. FRANKS[2], Z. C. FRANK[2], A. N. MCMELLEN[5], R. J. GIGER[3], B. L. ALLEN[1];
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Abstract: Hedgehog signaling is essential for patterning tissues and organs during embryonic development, including in the developing brain and spinal cord, and continues to play critical roles postnatally and throughout life. Despite the importance of Hedgehog signaling to embryogenesis, tissue homeostasis, and tissue renewal and regeneration, we still lack a complete understanding of the entire

complement of Hedgehog pathway components, and their contributions to the regulation of Hedgehog pathway activity. Previous work has identified Neuropilins, well-characterized components of Semaphorin signaling, as positive regulators of Hedgehog signaling. In the context of Semaphorin signaling, Neuropilins work closely with Plexin coreceptors, but a role for Plexins in Hedgehog signaling has not yet been explored. Here we provide evidence that multiple Plexins promote Hedgehog signaling in NIH/3T3 fibroblasts. Further, we find that the cytoplasmic GAP activity of Plexins is required for Hedgehog signaling promotion, and that constitutive activation of the Plexin GAP domain further amplifies Hedgehog pathway activity, including the stimulation of neural progenitor migration in the developing chicken neural tube. Notably, Plexins regulate Hedgehog signaling at the level of GLI activation and require intact primary cilia to mediate Hedgehog signal promotion. Finally, we demonstrate that Plexin loss-of-function significantly reduces the response to Hedgehog activation in fibroblasts and in the mouse dentate gyrus. Together, these data identify Plexin receptors as novel components of the Hedgehog signaling pathway.

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Poster

P134. Oscillations and Sleep

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P134.01

Topic: B.09. Network interactions

Support: MR/S01134X/1

Title: Intense unilateral flash stimulation leads to local signatures of sleep pressure in the contralateral primary visual cortex in laboratory mice

Authors: *J. PRIUS MENGUAL[1], L. B. KRONE[1], A. CHAKRABARTY[1], C. BLANCO DUQUE[2], M. C. KAHN[2], C. J. AKERMAN[1], V. V. VYAZOVSKIY[1];
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Abstract: It is established that extended wakefulness leads to a global increase in EEG slow-wave activity (SWA; power density between 0.5-4 Hz) both in the wake EEG and during subsequent sleep. In addition, SWA is regulated at the local level, which led to the hypothesis that sleep is an activity- or use-dependent process. While several molecular, cellular and circuit mechanisms have been proposed to account for the global and local sleep regulation, there is a scarcity of experimental models that afford the opportunity to selectively and physiologically manipulate local sleep need in the neocortex of freely behaving animals. Here we present a new model for investigating the neurobiological mechanisms of local sleep, based on a selective local cortical activation during waking, achieved by sensory stimulation. We adopted a paradigm previously established in rats for investigating mechanisms of enduring neuroplastic changes in the visual cortex as a result of sensory experience. To induce sustained synaptic activity unilaterally in the visual cortex, we built removable devices that enabled us to position light-emitting diodes (LEDs) in front of one of the eyes of a freely behaving mouse. EEG and/or 16-channel

laminar electrodes were used to record cortical activity and animals were kept awake for 4 hours starting at light onset, during which LED stimulation was performed by delivering trains of 8 Hz light pulses (pulse duration 10 ms, train duration 2 s), every 30 s. The LED device was subsequently removed, and animals were allowed to sleep undisturbed for the remainder of the 24 hours. In all animals with laminar probes and EEG recordings, visual stimulation reliably evoked responses in the contralateral visual cortex that were visible in the local field potentials and/or neuronal spiking activity. As expected, EEG spectral analysis revealed an elevated power at 8 Hz, which exceeded the non-stimulated side. No discernible responses were detected in the ipsilateral EEG or frontal cortex.
Having established that visual stimulation induces local neuronal responses, we asked whether the paradigm leads to signatures of high sleep pressure in the wake EEG. We observed that in all animals, the occipital EEG spectral power density in the SWA frequency range was consistently higher in the stimulated hemisphere, compared to the non-stimulated side (mean values, SEM: 132.8±12.8% and 107.2±5.7% respectively). These preliminary results establish a new model for local manipulations of neural activity in freely behaving mice using a physiologically relevant frequency. This paradigm will be useful for investigating the neurobiological mechanisms of homeostatic sleep need.

Disclosures: J. Prius Mengual: None. **L.B. Krone:** None. **A. Chakrabarty:** None. **C. Blanco Duque:** None. **M.C. Kahn:** None. **C.J. Akerman:** None. **V.V. Vyazovskiy:** None.

Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.02

Topic: B.09. Network interactions

Title: The human iEEG exhibits long-range temporal correlations which follow a hierarchical organization, decline under antiepileptic drug action and break down during slow wave sleep

Authors: *C. MEISEL[1], P. MUELLER[2];
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Abstract: Cortical network function in general, and information integration specifically, are believed to benefit from a network's ability to integrate inputs over long timescales. Such long-range temporal correlations (LRTCs) generically arise when networks are poised at or near a critical point. Monitoring LRTCs in cortical networks therefore provides a measure of information integration capabilities and, more generally, about the dynamical state of these networks. Previous research in non-human primates has indicated the existence of a gradient in LRTCs aligned with functional hierarchy, which may explain how inputs are integrated over increasingly longer timescales as a signal progresses higher along the hierarchical axis. However, whether LRTCs follow such a hierarchical gradient in the human brain also is still unclear. Further, whether LRTCs are impacted by different vigilance states, e.g., to provide a functional analog to the breakdown of information integration during slow wave sleep, is currently unknown. Lastly, the effect of antiepileptic drugs (AEDs), many of which impact network information processing, on these timescales remains to be determined. Here, we assessed LRTCs in human invasive EEG (iEEG) across different states of vigilance, as a function of AED load and across the hierarchical

organization in cortical networks. We assessed LRTCs in iEEG data from 17 patients with epilepsy undergoing presurgical monitoring (9 female, mean age = 27 ± 14 years, total duration 756.3 hours). LRTCs were determined at the individual channel level of power band fluctuation in the high gamma band (log power 56-96 Hz, 0.125 sec binning). LRTCs were calculated from the decay of power band autocorrelation functions (2 min segments, half-width at half maximum). Vigilance and slow wave sleep (SWS) states were classified as in Reed et al. 2017. Anatomical channel locations were determined from MNI coordinates. Evaluations included high and low AED drug days (24 h each). First, LRTCs were found to align along a functional hierarchy across different anatomical areas, thus electrophysiologically confirming similar findings from non-human primates in humans for the first time (Fig. 1). Second, LRTCs were found to break down during SWS compared to non-SWS ($p<0.02$, two-sample ttest). Third, LRTCs decreased under AED administration ($p<0.02$, two-sample ttest). Our results provide mechanistic and functional links between specific measurable changes in cortical network dynamics relevant for characterizing the brain's changing information processing capabilities along a hierarchical cortical gradient, across vigilance states and during antiepileptic drug action.

Disclosures: C. Meisel: None. **P. Mueller:** None.

Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.03

Topic: B.09. Network interactions

Title: Characterising sleep spindles in human anterior thalamic nuclei and thalamocortical spindle propagation

Authors: *H. BERNHARD[1], J. REITHLER[1], B. JANSMA[1], R. P. W. ROUHL[2], V. H. J. M. VAN KRANEN-MASTENBROEK[3], E. GOMMER[3], P. DE WEERD[1], M. J. ROBERTS[1];
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Abstract: Sleep spindles are thought to be an important mechanism for memory consolidation during NREM sleep, potentially allowing windows of communication in thalamocortical circuits. However, research into thalamocortical interaction during spindles in human brains has been sparse. Spindles are transient (0.3 - 2 s) oscillatory patterns of 8 to 16 Hz originating in the reticular nucleus of the thalamus (RN). Cortical slow oscillations lead to inhibition of the thalamus through the RN, followed by rebound spikes which form the spindle. Through thalamocortical connections, these thalamic spindles may then propagate to the cortex. Spindles can be categorized into slow spindles (8-12Hz) that tend to occur in frontal cortical areas, and fast spindles (12-16Hz) at centro-parietal sites, as has been shown both in EEG and iEEG. Most spindles tend to occur at one electrode only (local spindles), but there can also be global spindle events spanning larger parts of the cortex. Spindle frequency might be determined by the underlying thalamic nuclei, with more anterior nuclei oscillating at slower frequencies (although this has only been shown in posterior parts of the thalamus). Cortical globality of spindles might be related to the spread of spindles within the thalamus.

In this study, we investigated spindles in human anterior thalamic nuclei. We recorded one night of sleep in 7 individuals with epilepsy (2 female, mean 35 years, range: 17 - 59 years) undergoing implantation of deep brain stimulation electrodes targeting the anterior nucleus of the thalamus. Anterior thalamic nuclei showed both slow and fast spindle activity during NREM sleep. When assessing their spread to the cortex, we found that predominantly frontal EEG spindles tended to co-occur with thalamic slow spindles. For fast spindles, we observed two opposing scenarios: Some thalamic electrodes showed overlap with fronto-central EEG electrodes, whereas others showed de-coupling from the cortex, i.e. fast spindles occurring at this thalamic site lowered the probability of a spindle occurring in the cortex.Characterising the anterior thalamic involvement underlying spindle activity in EEG may elucidate the involvement of the different thalamic nuclei in sleep spindle modulation, and thus serve as a bridge between previous iEEG studies and the vast EEG literature on sleep spindles and their functional role in e.g. memory consolidation.

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Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.04

Topic: B.09. Network interactions

Title: Distinctive response of sleep slow oscillations to acoustic stimulation is determined by different underlying synchronization processes

Authors: M. NAVARRETE[1], D. HENAO[1], M. LE VAN QUYEN[2], ***M. VALDERRAMA**[3]; [1]Dept. of Biomed. Engin., Univ. of los Andes, Bogotá, Colombia; [2]Lab. d´Imagerie Biomédicale (LIB), U1146 INSERM- SU – CNRS 7371, Paris, France; [3]Dept. of Biomed. Engin., Univ. of Los Andes, Bogotá, Colombia

Abstract: Slow oscillations (SO) during sleep are large amplitude waves with frequencies between 0.5-2Hz and thought to be crucial for cognitive and physiological processes. Closed loop acoustic stimulation (CLAS) has shown to boost SO amplitude, spindle power (11-16Hz) and related functional activities1. However, the neural mechanisms causing this boost are not understood. Recently, it was suggested that the SO response to the stimuli may be linked to their underlying cortical synchronization2. Also, it has been proposed that spontaneous SO are determined by two different synchronization processes: generalized thalamocortical Type I and the localized corticocortical Type II waves. These processes are thought to have different functional roles and be differentially affected by external stimuli3. We hypothesized that SO response to CLAS depends on these underlying synchronization dynamics. Hence, we applied CLAS during NREM sleep of healthy subjects (n=10) during one control (CNT, when sounds were muted) and one stimulation night (STM). Then, we identified tree main clusters using a k-means algorithm according to their synchronisation attributes (SO relative scalp involvement and mean slope). These clusters denoted (C1) steep slope SO with global spread (Type I like), (C2) localized flat slope SO

(Type II like) and (C3) flat slope SO with global spread (sharing features of Type I and Type II waves). Two-way ANOVAs examining stimulation and cluster conditions showed a significant interaction between these effects and spindle coupling ($P < 0.001$), while post-hoc analyses indicated that most spindles were coupled with C1 clusters ($P < 0.001$). Then, the proportion of SO events by cluster showed a significant interaction between the effects of stimulation (CNT vs STM) and cluster type (C1, C2, C3) ($P < 0.001$). Post-hoc analyses showed that the proportion of C3 and C2 events decreased (both $P<0.01$) while the proportion of C1 events increased ($P < 0.001$) as response to CLAS. Finally, evaluating the mean SO amplitudes for spontaneous (CNT) and stimulated (STM) SO clusters, we found a significant amplitude enhancement for all of them in STM (all $P<0.05$). The stimuli then promoted C1 waves by enhancing C2 and C3 waves, while spindle coupling mainly increased for C1 waves. Our findings support the hypothesis of distinctive SO response to CLAS depending on different synchronization processes during NREM sleep. Because the response of C1 clusters to CLAS, our results suggest that acoustic stimulation enhances SO by boosting thalamocortical synchronization during NREM sleep. 1. Ngo et al. Neuron 78, 2013. 2. Navarrete et al. Curr. Opin. Beha. Sci. 32, 2020. 3. Siclari et al. Sleep 37, 2014.

Disclosures: M. Navarrete: None. **D. Henao:** None. **M. Le Van Quyen:** None. **M. Valderrama:** None.

Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.05

Topic: B.09. Network interactions

Title: Probing cortical excitability using 40 Hz auditory stimuli during NREM sleep

Authors: *D. HENAO[1], M. NAVARRETE[1], J. NIETO[1], M. VALDERRAMA[1], M. LE VAN QUYEN[2]; [1]Univ. De Los Andes, Bogotá, Colombia; [2]Lab. d'Imagerie Biomédicale INSERM U1146, Sorbonne Univ. UMCR2 UMR7371 CNRS, PARIS, France

Abstract: Neocortical excitability can be studied by assessing the response to a stimulation as a function of ongoing brain activity [1]. Especially during non-rapid eye movement (NREM) sleep, auditory stimuli lead to a series of state-dependent evoked potentials (ERP) [2]. Specifically, an attenuation of the early N100 component has been observed while P200 is enhanced [3]. In addition, sleep specific late ERP components such as the N350, P450, N550 and P900 responses arise (all substantially larger when K-complexes are present in the average). From these observations, it has been suggested that these evoked responses during NREM reflect a decreased cortical excitability and increased inhibitory processes [4].In our work, we investigated how 40 Hz Auditory Steady State Responses (ASSR) can directly test the excitability of neocortical networks during NREM sleep. For this, we performed polysomnographic recordings (10-20 international EEG system, 2 EOG and 1 EMG) and stimulated 12 healthy subjects (mean age 22.16 ± 3.06) during one complete night. Trials consisted of a 400 ms train of white noise clicks of 1.5 ms duration applied at 40 Hz and with a maximum intensity of 15 dB. Stimulation was applied in blocks of 30 trials during NREM sleep (mean 200 events/night) using earbuds. We compared the corresponding ERP and the 40 Hz Inter Trial Coherence (ITC) response, depending on electrode locations and sleep stages N2 and N3. We report strong ITC responses in both sleep stages and resulting

ERPs with major components at P200, N550 and P900. Specifically, the 40 Hz ITC response was significantly stronger in frontal electrodes during N2, while in N3 this was higher in parietal and occipital electrodes. Comparing ERP components, P200 and N550 amplitudes were larger in frontal areas for N2 but higher for central and posterior regions and with shorter latencies for N3. Finally, P900 amplitudes were larger and latencies shorter for most of the channels in N3 compared to N2.
Our results suggest that 40 Hz ASSR is a powerful tool to study state-dependent shifts in neocortical excitability during NREM sleep. In particular, changes in ERP components and ASSR responses between N2 and N3 within NREM sleep might be related to increased inhibitory processes and different hyperpolarization levels of the thalamo-cortical system.

Disclosures: D. Henao: None. **M. Navarrete:** None. **J. Nieto:** None. **M. Valderrama:** None. **M. Le Van Quyen:** None.

Poster

P134. Oscillations and Sleep

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P134.06

Topic: B.09. Network interactions

Title: Correlation structure of cortical activity at slow-wave timescales across sleep states and wakes.

Authors: *T.-Y. LIU, B. WATSON;
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Abstract: Interaction between a pair of neurons is the fundamental building block to construct a complex neural network. These interactions can be inspected by cross-correlations. Much research is focused on short-time scale (<4 msec) correlations to examine the functional connectivity between neurons, while less is known about interactions at longer time scale (hundreds of msec). We examined cross-correlations between cortical neurons in a longer time scale across sleep states and wake. We expected that at ~1 Hz timescales we would see synchronization between neurons during non-rapid eye movement (NREM) sleep, given the UP/DOWN fluctuations of neuronal membrane potentials during this state. Surprisingly, in addition to synchronized pairs, we found anti-synchronized pairs and the effects are augmented during the most NREM or high deltas. In particular, this correlation structure is preserved during the course of sleep and wake. The degree of correlation or anticorrelation is modulated by the local field potential (LFP) in the delta frequency range during NREM and in the gamma frequency range during wake. These anticorrelations persist across 24 hour recordings and are consistent between given pairs of cells. Furthermore, removing the spikes with lower interspike interval (ISI) reduces the degree of the anticorrelation.

Disclosures: T. Liu: None. **B. Watson:** None.

Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.07

Topic: B.09. Network interactions

Support: NINDS Grant 1R21NS116519
AES JIRA
NIAAA Grant AA016852

Title: Modulation of network excitability by sleep oscillation phase

Authors: *D. KLORIG, A. O'DELL, T. SMITH, D. GODWIN;
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Abstract: We have observed a strong association between behavioral state (wake, REM, and NREM) and network excitability using active optogenetic probing of hippocampal circuitry. In order to understand the mechanisms responsible for this association and determine the influence of the sleep rhythms, we examined the effect of state specific pre-stimulus oscillatory phase on population discharge (PD) probability. We measured population discharge probability in chronically implanted transgenic mice using optogenetic dose-response curves (Klorig et. al. eNeuro 2019). Our chronic preparation consists of an optrode above area CA1 of Thy1-ChR2 (line 18) mice and 7 individually placed microwires in hippocampal and peri-hippocampal structures to monitor the network wide propagation of optogenetic stimulation. A range of light intensities was presented in randomized order, occasionally producing all-or-none high amplitude optogenetic PDs (oPD). The conditional probability of oPD given each light intensity was calculated and fit with the Boltzmann equation to determine an I50, or the light intensity at which oPDs occur 50% of the time. This metric, the I50, can be used to precisely track network excitability in freely moving mice. Using long-term oPDT recordings, we segmented the data by behavioral state using a convolutional neural network to automate sleep scoring. Pre-stimulus oscillation phase was determined using generalized phase (Davis et. al. Nature 2020). Phases were binned and the conditional probability of an oPD was calculated for each bin. In addition, an unbiased estimate of the influence of the pre-stimulus period was generated by averaging the pre-stimulus period of stimuli near the I50 (where the P(oPD) ~ 0.5) separated by outcome (oPD and non-oPD) and by behavioral state (wake, NREM, and REM). Separating the pre-stimulus period by sub- or supra-threshold responses reveals a detectable but relatively weak effect of ongoing phase on PD probability that varies by behavioral state (wake, REM, NREM). During wake periods and REM periods, probability was modulated by the phase of hippocampal theta with the highest probability of oPD on the peak and lowest probability during the trough. During NREM, slow-wave activity modulates the oPDT with oPDs more likely during the peak. The greatest differences in the average pre-stimulus period for oPD vs. non-oPD outcomes were observed in PFC, CA1, CA3, and subiculum. Although phase dependent modulation was detected, the magnitude of the effect was not sufficient to explain the large behavioral state dependent shifts in network excitability observed.

Disclosures: D. Klorig: None. **A. O'Dell:** None. **T. Smith:** None. **D. Godwin:** None.

Poster

P134. Oscillations and Sleep

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Program #/Poster #: P134.08

Topic: B.09. Network interactions

Support: VA Merit 1I01RX001640
NIH Grant 5K02NS093014
AHA Grant 831442

Title: Role of hippocampal sharp-wave ripples in motor memory consolidation during sleep

Authors: *J. KIM[1,3], A. JOSHI[2], L. FRANK[2], K. GANGULY[1,3];
[1]Neurol. department, [2]HHMI and Departments of Physiol. and Psychiatry, Univ. of California San Francisco, San Francisco, CA; [3]Neurol. and Rehabil. Service, San Francisco Veterans Affairs Med. Ctr., San Francisco, CA

Abstract: Sleep appears to play an essential role in driving brain plasticity and the consolidation of both declarative and procedural memories. A growing number of studies have now found evidence for the important role of the hippocampal formation, in general, and hippocampal sharp-wave ripples (SWRs), in specific, during the sleep-dependent consolidation of declarative memories. Interestingly, while initially it was thought that procedural/motor memories were consolidated through a separate non-hippocampal process, recent functional neuroimaging studies have suggested a role of the hippocampus in early motor skill learning. However, little is known about the precise neurophysiological mechanisms that might allow for the hippocampus to contribute to motor memory consolidation. In this study, we tested the hypothesis that hippocampal SWRs during sleep may play a role in motor memory consolidation by transiently supporting cross-area communications between prefrontal cortex (PFC) and primary motor cortex (M1) during NREM sleep. Using a reach-to-grasp skill learning task in rats and multi-area recordings from the hippocampus, PFC, and M1, we specifically found that hippocampal SWRs during the post-training sleep were linked, in a temporally precise manner, to globally coordinated slow oscillations (SO) in PFC and M1 in the early phase of skill learning. Strikingly, we observed a sharp drop in SWR activity during the transition to a slow/later phase of skill learning, where there were only slow improvements in performance across days. Across animals, we observed that increases in SWRs in the post-training sleep were most correlated with practice sessions with marked changes in task success within a session; increases were also closely linked to task sessions with elevated neural variability. Thus, our results suggest a salient role for hippocampal SWRs in the early phase of skill learning through large-scale coordination of cortical regions during NREM sleep. Our results further suggest a universal role for hippocampal SWRs in sleep-dependent memory consolidation.

Disclosures: J. Kim: None. **A. Joshi:** None. **L. Frank:** None. **K. Ganguly:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P145.01

Topic: B.10. Epilepsy

Support: fund from the Massachusetts General Hospital Department of Anesthesia, Critical Care and Pain Medicine to HJF
Jialing Guo was a recipients of the graduate fellowship from China Scholarship Council

Title: Genistein, a dietary isoflavone, prevents seizure-induced respiratory arrest in DBA/1 mice

Authors: J. GUO[1,2], D. MIN[1], ***H.-J. FENG**[1];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Neurol., Xiangya Hospital, Central South Univ., Changsha, China

Abstract: Background: Sudden unexpected death in epilepsy (SUDEP) is a fatal event that ranks second in years of potential life lost among neurological disorders. Both clinical and animal studies demonstrate that seizure-induced respiratory arrest (S-IRA) is the primary instigator leading to death in many SUDEP cases. However, there are currently no effective pharmacological interventions to prevent S-IRA. In the present study, we examined the effect of genistein, a naturally occurring isoflavone found in a variety of dietary vegetables such as soybeans, on the incidence of S-IRA in DBA/1 mice. **Methods:** DBA/1 mice, after priming (3-4 daily acoustic stimulation at 96 dB SPL), exhibit generalized tonic-clonic seizures and S-IRA evoked by acoustic stimulation. The susceptibility to S-IRA in primed DBA/1 mice of both sexes was confirmed 24 hr prior to experiments. Genistein, dissolved in 60% DMSO and 40% saline, or vehicle was intraperitoneally (i.p.) administered, and the effect of genistein or vehicle control on the incidence of S-IRA and seizure behaviors was examined 2 hr after injection. Videos were digitally recorded for off-line analysis. The comparison of S-IRA incidence between the treatment and the control was performed using Chi-square test. **Results:** Acoustic stimulation evoked generalized tonic-clonic seizures in primed DBA/1 mice, which were composed of wild running and clonic/tonic seizures followed by S-IRA. The incidence of S-IRA in DBA/1 mice was significantly reduced 2 hr after i.p. administration of genistein at 1 mg/kg (12.5%, $n = 8$; $p < 0.01$), 10 mg/kg (25%, $n = 8$; $p < 0.05$), 30 mg/kg (23.1%, $n = 13$; $p < 0.01$), 60 mg/kg (41.2%, $n = 17$; $p < 0.05$) and 90 mg/kg (22.2%, $n = 9$; $p < 0.01$) as compared with that in the vehicle control (87.5%, $n = 8$). Compared with that in the vehicle control, the incidence of S-IRA was not significantly suppressed by genistein at 0.2 mg/kg (50%, $n = 8$). Among those DBA/1 mice whose S-IRA was blocked by genistein, genistein at 1 mg/kg blocked S-IRA without interfering with any component of seizures in 100% of mice, suggesting that genistein specifically blocks S-IRA in these mice. Genistein specifically blocked S-IRA in 100% of mice at 10 mg/kg, 90% at 30 mg/kg, 80% at 60 mg/kg and 42.9% at 90 mg/kg. **Conclusions:** Our data show that genistein, a natural isoflavone, reduces the incidence of S-IRA in DBA/1 mice. Genistein can specifically block S-IRA, especially at relatively lower doses. These data suggest that genistein can be potentially used to prevent SUDEP in at-risk patients.

Disclosures: J. Guo: None. **D. Min:** None. **H. Feng:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

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Program #/Poster #: P145.02

Topic: B.10. Epilepsy

Support: NIH Grant R01NS040109
NIH Grant R35NS116852

Title: Brain extracellular matrix alters local ion concentrations and responses to injury

Authors: *K. NORMOYLE[1,2], V. DZHALA[1,2], K. LILLIS[1,2], K. EGAWA[3], J. C. GLYKYS[4], N. RAHMATI[1,2], K. STALEY[1,2];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Neurol., Harvard Med. Sch., Boston, MA; [3]Dept. of Pediatrics, Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan; [4]Dept. of Pediatrics, Univ. of Iowa. Carver Col. of Med., Iowa City, IA

Abstract: The reversal potential of $GABA_A$ receptors (E_{GABA}) is dependent upon the chloride concentrations on both sides of the neuronal membrane. The chloride on the extracellular aspect of the membrane ($[Cl^-]_o$) is canonically considered to equal the chloride in the bulk cerebrospinal fluid. However, neurons are surrounded by an extracellular matrix (ECM) comprised of variably sulfated glycosaminoglycans that can alter local $[Cl^-]_o$ and can be hydrolyzed by active matrix metalloproteinases released by tissue injury. Having synthesized a single-wavelength, pH-insensitive chloride-sensitive fluorophore and constrained it to the extracellular space by conjugation with 10 kilodalton dextran, we used 2-photon Fluorescence Lifetime IMaging (FLIM) to measure extracellular chloride in acute and organotypic cultures of hippocampal slices. We first tested whether the extracellular sulfate moieties change the baseline local chloride concentration. We found that $[Cl^-]_o$ between neurons in the depths of acute hippocampal slices and at all depths of organotypic hippocampal slice cultures was only half of the bulk CSF chloride. We next measured $[Cl^-]_o$ after the sulfate moieties in the matrix were freed by endogenous matrix metalloproteinases (MMPs) after brain injury. We found a strong dependence of $[Cl^-]_o$ vs distance from injury, with chloride concentration increasing to the ACSF levels near the injured surface of acute slices or proximity to photolysed neurons in organotypic slices, respectively. These changes in $[Cl^-]_o$ should also alter the neuronal intracellular chloride ($[Cl^-]_i$) via the activity of the high-velocity equilibrative membrane chloride transporters. We have previously reported such changes in slices and confirmed them in both injury models here, in addition to an *in vivo* piglet model for which preliminary data is presented. If the injury-induced increases in $[Cl^-]_o$ and $[Cl^-]_i$ were due to release of extracellular sulfates and replacement by chloride, these sulfates should be released to the perfusate, and we confirmed this using colorimetric assays of chondroitin sulfate. Finally, the release of sulfates should be inhibited by MMP antagonists, which we confirmed with both broad-spectrum and more specific inhibition (ZX-1 or SB3CT, respectively) each of which reduced $[Cl^-]_o$ and $[Cl^-]_i$ and neuronal volume at the surface of cut slices and in proximity to photolysed neurons. We conclude that $[Cl^-]_o$ is partially displaced by sulfates in the ECM and that damage to ECM following brain injury alters the transmembrane chloride distribution. These findings have immediate implications for the treatment of cytotoxic edema and seizures after acute brain injury.

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Poster

P145. Epilepsy: Post-Seizure Modifications

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P145.03

Topic: B.10. Epilepsy

Support: NIH Grant EY027380-04

Title: Developmental exposure to seizures perturbs the functional integration of newly born neurons into the Xenopus optic tectum and promotes seizures in later life

Authors: *A. C. THOMPSON, C. A. VADUVA, D. R. MENDOZA, C. D. AIZENMAN;
Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: Neurogenesis begins in development, continues after birth and persists into old age. Neurogenesis is a tightly regulated process involving proliferation and survival of neural precursor cells, before the specification, migration and functional integration of newly born neurons into the established circuitry. As newborn neurons have a high propensity to undergo synaptic modification, they are uniquely placed to contribute to experience-dependent modification of circuit function. In disease states, including epilepsies, newly born neurons have been found to both protect cognitive function and cause abnormal neural activity following their integration into the circuitry. While it has been well characterized that epilepsies can result from prior seizure activity, a cellular level understanding of the mechanisms and principles by which prior seizures affect the functional integration of later born neurons, and whether this is causative for epileptogenesis, is incomplete.
To characterise how seizure activity impacts the development and functional integration of newly born neurons as they become integrated into the established, functioning circuitry of *Xenopus laevis* optic tectum, we used photoconversion of Kaede protein to fluorescently-tag neurons that were born later in development. Whole-cell patch clamp electrophysiology was used to measure the biophysical and synaptic properties of later-born neurons. We show that neurons born in later development mature and become integrated into the tectal circuitry over a period of 5-7 days. When we recorded from newly born neurons that were exposed to chemically-induced seizures following their birth, we observed that seizure-exposed newly born neurons were more excitable and received less inhibitory transmission compared to naïve newly born neurons. This observation correlated with an increased seizure susceptibility in tadpoles exposed to seizures during development. We also describe how seizure activity during development effects the morphology of newly born neurons as they mature. Finally, we explore the contribution of seizure-exposed newly born neurons to later seizure behavior.

Disclosures: A.C. Thompson: None. **C.D. Aizenman:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

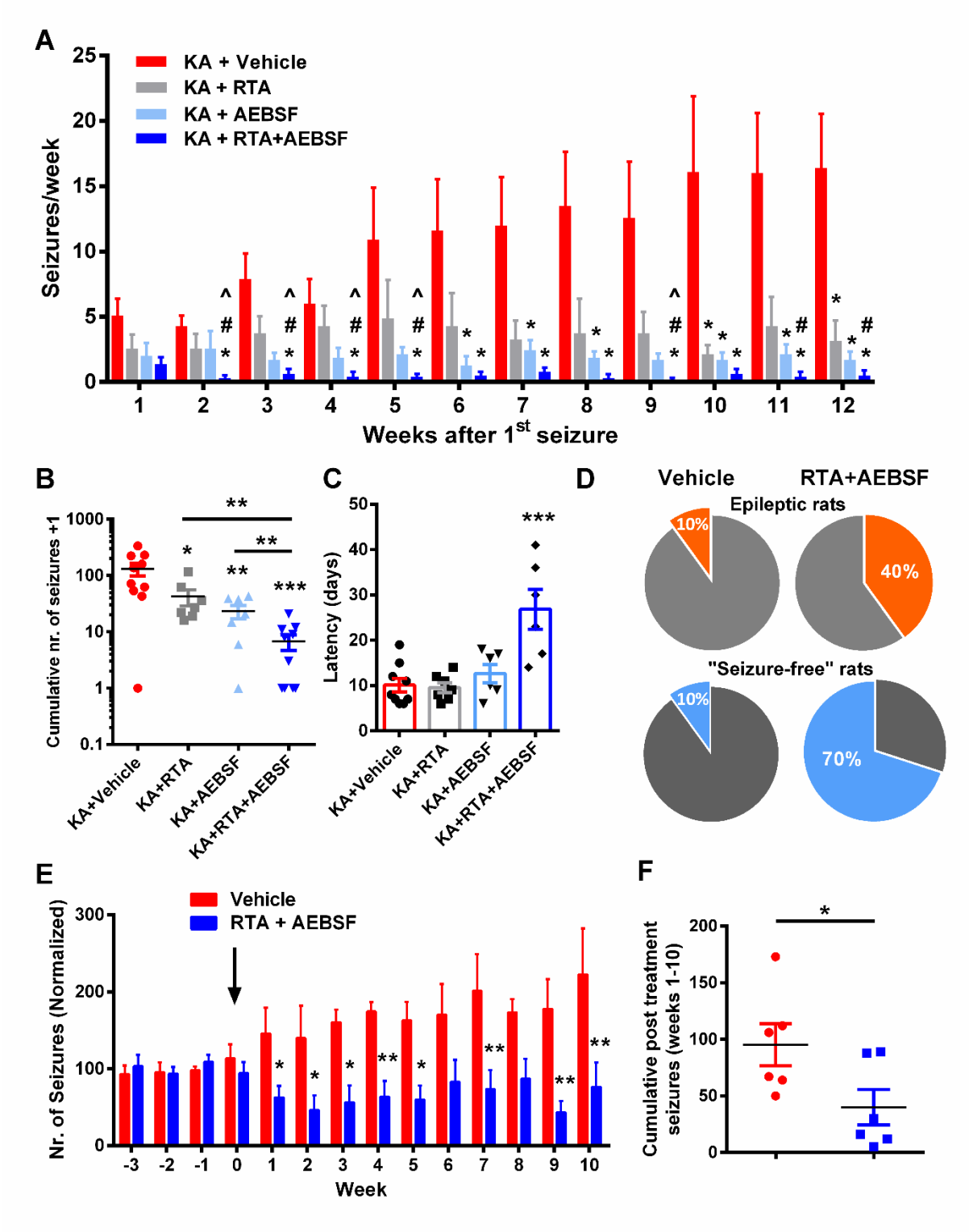
Program #/Poster #: P145.04

Topic: B.10. Epilepsy

Title: Nrf2 activation is neuroprotective and suppresses the development of epilepsy

Authors: *T. SHEKH-AHMAD;
Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Many epilepsies are acquired conditions following a brain insult such as a prolonged seizure, traumatic brain injury or stroke. Following such brain insults, excessive generation of reactive oxygen species (ROS) and induction of oxidative stress has been proposed to contribute to neuronal death and the development of epilepsy. Here we use a combinational strategy of 1) increasing the endogenous antioxidant defences by upregulating the Nrf2 transcription factor via Omaveloxolone, and 2) inhibiting NADPH oxidase (NOX) enzyme, found as a major source of ROS in epilepsy, using AEBSF. We first show that the combination of both drugs had a greater effect (versus each drug alone) on reducing ROS generation as well as on low Mg^{2+} induced cell death. We next determined the effect of this combination antioxidant therapy on Total Antioxidant Capacity (TAC) following kainic acid (KA) induced status epilepticus (SE) in rats. Following 2 h of SE, Omaveloxolone completely restored TAC in both plasma and hippocampus. In rats treated with the combination of Omaveloxolone and AEBSF, TAC was increased to supranormal levels, and was 2-3 times higher in plasma and hippocampus compared to the vehicle group. We next asked if the combination therapy can suppress the development of epilepsy following SE. Vehicle treated animals developed a progressive increase in seizure frequency over time. Rats treated with a single administration of either AEBSF or Omaveloxolone had a decrease in seizure frequency at 10-12 weeks after the first spontaneous seizure. Importantly, seizure frequency in rats treated with both drugs was dramatically decreased from 2 to 12 weeks after the first seizure. From weeks 8-12, 7 of 10 animals treated with combination therapy were seizure-free, compared to only 1 of 10 animals treated with vehicle. For the combination therapy, the odds ratio for being seizure-free (weeks 8-12) compared to vehicle treatment was 21. Thus, a combination of Nrf2 activation and NOX inhibition following SE exerts a neuroprotective and disease-modifying effect and can prevent the development of epilepsy.



Disclosures: T. Shekh-Ahmad: None.

Poster

P145. Epilepsy: Post-Seizure Modifications

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Topic: B.10. Epilepsy

Support: CONACyT 893823

Title: Effect of type-2 diabetes mellitus on neurodegeneration and oxidative stress induced by status epilepticus in adult rats.

Authors: *K. P. RAMOS RIERA[1], C. V. MÉRIDA PORTILLA[1], P. E. MARTÍNEZ GOPAR[2], L. BELTRÁN PARRAZAL[1], F. PÉREZ SEVERIANO[2], M. L. LÓPEZ MERAZ[1];
[1]Brain Res. Inst., Univ. Veracruzana, Xalapa, Mexico; [2]Mol. neuropharmacology and nanotechnology, Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico

Abstract: Effect of type-2 diabetes mellitus on neurodegeneration and oxidative stress induced by *status epilepticus* in adult rats.
Evidence shows that type-2 diabetes mellitus (DM2) facilitates status epilepticus (SE) incidence. SE characterizes by continuous epileptic activity associated with neurodegeneration and high mortality. The main goal of this study was to analyze the effect of DM2 on the severity of SE and the subsequent neurodegeneration and brain oxidative stress (OE) in adult rats. DM2 was produced in male Wistar rats with streptozocin (STZ 100 mg/kg, s.c., n= 18) on postnatal day (P)3; control rats (CTRL, n = 19) were administered with the vehicle (0.1 M citrate buffer, pH 4.5). Glycemic levels were analyzed at P30, P60, and P90. At P90, SE was induced in both groups with the lithium-pilocarpine model (LiCl 3 mEq/kg, i.p.; pilocarpine hydrochloride 30 mg/kg, s.c). Seizure severity was evaluated with Racine´s scale (1972). To stop the seizures, rats were injected with diazepam (10 mg/kg, i.p) 1 h after SE onset. Neurodegeneration was evaluated 24 h after SE with fluoro-Jade B (F-JB) staining. Brain OE was determined 6 and 24 h after SE, through the analysis of lipid peroxidation and the formation of reactive oxygen species (ROS). Neurodegeneration and OE were evaluated in the hippocampus, the piriform cortex, the thalamus, and the amygdala.At P90, STZ rats showed augmented blood glucose levels compared with CTRL rats. We found that STZ rats showed increased latency to the first generalized seizure and SE, and a higher number of generalized seizures of longer duration when compared with CTRL rats. STZ rats also showed an increased number of F-JB positive cells in CA3 and CA1 fields, dentate gyrus, and the hilus of the hippocampus, the piriform cortex, the dorsomedial nucleus of the thalamus, as well as in the medial and cortical amygdala nuclei, in comparison with CTRL rats. Lipid peroxidation and ROS levels were similar in both experimental groups for all the analyzed brain regions.Our results suggest that DM2 increases SE severity and neurodegeneration, but it does not modify brain OE in adult rats.
Supported by CONACyT (doctoral scholarship No. 893823 to KPRR)

Disclosures: K.P. Ramos Riera: None. **C.V. Mérida Portilla:** None. **P.E. Martínez Gopar:** None. **L. Beltrán Parrazal:** None. **F. Pérez Severiano:** None. **M.L. López Meraz:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

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Program #/Poster #: P145.06

Topic: B.10. Epilepsy

Support: NIH Grant 1R37NS115439-01A1

Title: Tracking the evolution of synaptic dysplasticity after early life seizures

Authors: *B. XING[1], A. BARBOUR[2], B. BABROWICZ[1], Y. SONG[1], M. HANDY[1], F. E. JENSEN[1]; [1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsylvania, Neurology, PA

Abstract: Rationale: Multiple lines of clinical and experimental evidence suggest that seizures in early life can be associated with long lasting cognitive and behavioral deficits. Despite the evidence for ELS being associated with long lasting behavioral changes and impaired plasticity at a network level, far less is known about the evolution of changes at a single neuron level that occur following a seizure through the lifespan. **Methods:** Using activity-dependent genetic labeling (TRAP, which relies upon the detection of Cre-induced permanent tdTomato expression, which is driven by the immediate early gene Fos, a widely used marker of activated neurons), we identified and characterized a specific subgroup of neurons activated by ELS in the hippocampus. **Results:** The mice with tonic-clonic seizure induced by postnatal day 10 (P10) intraperitoneal injection of chemoconvulsant kainate (KA) showed a robust neuronal activation in CA1 region. The TRAPed cells in CA1 included mainly glutamatergic neurons (93.517± 8.9, $p < 0.0001$ vs. saline) with little astrocytes (6.9% ± 2.1%). Whole-cell patch clamp recording revealed that the ELS-activated CA1 neurons (tdtomato+, td+) during early development have persistent increases of postsynaptic AMPAR function (spontaneous EPSC amplitude at P30 38.6 ± 8.9, $p < 0.05$ vs. saline and Td- cells, Kruskal-Wallis test) and rapid diminishment of NMDAR-only silent synapses (fraction of silent synapse at P15 of td+ cells was 25.5%, much less than Td- 63.8% and saline 73.8%; the fraction of silent synapse were comparable among groups at P30, $p > 0.05$, one-way ANOVA), a process that involved synaptic insertion of calcium-permeable AMPARs (CP-AMPARs) (rectification index at P30 td+: 3.58 vs td-: 1.84 and saline: 1.64, $p < 0.05$, one-way ANOVA). *In vivo* pharmacological treatment following the ELS with a selective GluA2-lacking receptor blocker specifically reversed the long lasting deficits in the subsets of neurons initially recruited by the ELS (rectification index at P30 IEM: 1.31 vs saline 2.34, $p < 0.01$, unpaired t test). **Conclusion:** Our findings indicate that AMPAR-mediated synaptic dysplasticity is critical for persistent developmental dysregulation induced by ELS, and this mechanism may facilitate a more comprehensive understanding of ELS-induced long-term epileptogenesis and cognitive impairment, shedding light on the new therapeutic strategies in this clinical space where no current cure exists.**SOURCES OF FUNDING:** This work was supported by the National Institutes of Health (1R37NS115439-01A1 to F.E.J.)

Disclosures: B. Xing: None. **A. Barbour:** None. **B. Babrowicz:** None. **Y. Song:** None. **M. Handy:** None. **F.E. Jensen:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

Location: Virtual Only

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Program #/Poster #: P145.07

Topic: B.10. Epilepsy

Support: Wesleyan University Dean's Fund

Title: Augmented adult neurogenesis in the dentate gyrus of naïve and epileptic mice following transplantation and integration of medial ganglionic eminence-derived GABAergic progenitors

Authors: *M. ARSHAD, S. OPPENHEIMER, J. JEONG, J. R. NAEGELE;
Dept. of Biol., Wesleyan Univ. Neurosci. and Behavior Program, MIDDLETOWN, CT

Abstract: GABAergic interneurons are vulnerable to seizures in the pilocarpine model of temporal lobe epilepsy (TLE). Subtypes of GABAergic interneurons located in or near the neurogenic niche of the adult hippocampus also influence stages of adult-neurogenesis in rodents including proliferation and migration of newborn granule cells (GCs) into the granule cell layer (GCL) of the dentate gyrus. In TLE, neurogenesis is severely altered, resulting in an increased number of abnormally-positioned GCs in the hilus, which form hyperexcitable hubs and contribute to seizures. These observations led us to ask in the mouse pilocarpine model of TLE whether replacing GABAergic interneurons via transplantation would restore normal patterns of adult neurogenesis. To address this question, we transplanted fetal medial ganglionic eminence (MGE)-derived GABAergic progenitors into the hilus of the DG in TLE mice and quantified Type 1 and Type 2 progenitors as well as doublecortin+ immature adult-born GCs, focusing on the different stages of adult neurogenesis. We found that MGE transplants reduced the number of Type 1 and Type 2 progenitors in the subgranular zone (SGZ) of the DG in TLE mice. As previously reported, doublecortin (DCX)-positive immature adult-born GCs in ectopic positions in the hilus were significantly increased in TLE mice, and MGE-derived GABAergic transplants significantly reduced the number of ectopic cells, while concomitantly increasing normotopic GCs in the GCL. These results are consistent with the hypothesis that hilar transplants of MGE-derived GABAergic cells normalize the migration of DCX+ adult-born GCs in TLE mice. Prior work showed that pilocarpine-induced TLE in mice is associated with spontaneous seizures that are suppressed by transplants of MGE-derived GABAergic cells (Hunt et al., 2013; Henderson et al., 2014; Arshad MN and Naegele JR 2020). The underlying mechanisms for seizure suppression include increased inhibitory synaptic currents in adult-born GCs (Gupta et al., 2019; Arshad MN et al., 2021). Furthermore, transplant-mediated innervation of adult-born GCs in TLE mice restricts the growth of GC dendritic arbors (Gupta et al., 2019). Our new findings demonstrate that in addition to providing enhanced synaptic inhibition of dentate gyrus GCs, the mechanisms for seizure suppression by GABA transplants may include a reduction in ectopic adult-born GCs.

Disclosures: M. Arshad: None. **S. Oppenheimer:** None. **J. Jeong:** None. **J.R. Naegele:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

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Topic: B.10. Epilepsy

Support: F31NS113479
R01NS095842
AES Predoctoral Fellowship
Iowa Center for Research by Undergraduates Summer Fellowship

Title: Stimulation of DRN serotonergic terminals within the PPT decreases PGES duration in amygdala-kindled mice

Authors: *A. PETRUCCI, A. R. JONES, R. LI, G. F. BUCHANAN;
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Abstract: The leading cause of death in patients with refractory epilepsy is sudden unexpected death in epilepsy (SUDEP). A risk factor for SUDEP may be post-ictal generalized EEG suppression (PGES), a period of reduced EEG amplitude following some seizures. The networks comprising PGES are unknown. Our prior work indicates that increased serotonergic (5-HT) signaling and stimulation of dorsal raphe nucleus (DRN) 5-HT neurons prior to and during a seizure reduces PGES duration. A downstream intermediary may be the pedunculopontine tegmental (PPT) nucleus, a largely cholinergic region associated with arousal and sleep-wake regulation. We hypothesized that excitation of DRN 5-HT terminals in the PPT will reduce PGES duration, whereas inhibition will increase PGES duration. Pet1-Cre (8-16 wks, express Cre recombinase in 5-HT neurons) and WT (n = 8 per sex/genotype/condition) mice were implanted with EEG/EMG and a bipolar stimulating/recording electrode in the right basolateral amygdala (in mm from bregma: AP: -1.3; ML: -2.8; DV: -4.7), and received an AAV injection of Cre-mediated Channelrhodopsin2-mCherry, Archaerhodopsin-YFP, mCherry, or YFP into the DRN (AP: -4.6; ML: 0; DV: -3.0, coupled with an optical fiber in the PPT (AP: -4.46; ML: ± 1.12; DV: -3.5). After 4 weeks, mice underwent afterdischarge threshold determination and were kindled with their threshold current (2x/day, 80-540 μA, 1 s train of 1 ms biphasic square wave pulses at 60 Hz) until stimulation evoked consistent generalized tonic-clonic seizures. During trials, DRN 5-HT terminals in the PPT were stimulated (473 nm, 4 Hz, 10 mW) or inhibited (593 nm, constant, 10 mW) by laser light prior to and during a seizure induced in wake or NREM or at seizure termination. Analysis included seizure and PGES duration and the latency of the EEG (delta, 1-4 Hz; theta, 4-8 Hz; alpha, 8-12 Hz; beta, 12-30 Hz) to recover from PGES. Trials in female mice were conducted in met/diestrus. Viral transfection and implant locations were verified post-hoc. PGES duration was decreased by excitation of DRN 5-HT terminals in the PPT. Inhibition of DRN 5-HT terminals delayed recovery of EEG to baseline from PGES. Seizure duration was unaffected by laser treatment. No significant sex differences were identified or differences among mice that received AAV mCherry or YFP. These results indicate that PGES may be influenced by a DRN to PPT network. However, the PPT neurons and 5-HT receptors mediating our findings are unknown. Future experiments aim to identify these mechanisms utilizing pharmacology and immunohistochemical assays. Elucidating this network could have important implications for developing prophylactic strategies for SUDEP.

Disclosures: A. Petrucci: None. **A.R. Jones:** None. **R. Li:** None. **G.F. Buchanan:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P145.09

Topic: B.10. Epilepsy

Support: DoD Grant W81XWH-19-1-0430

Title: Lateral fluid percussion injury and dysbiosis: implications for post-traumatic epilepsy

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Abstract: Changes in gut microbial composition and function have been documented after traumatic brain injury (TBI). In turn, TBI is a major cause of epilepsy. Using an animal model of the TBI - posttraumatic epilepsy (PTE) continuum, lateral fluid percussion injury (LFPI) in the rat, we examined whether (a) TBI produced changes in microbial composition and (b) whether fecal microbiome transfer (FMT) from post-LFPI animals altered the susceptibility to post-traumatic epilepsy (PTE) in recipients. Microbial composition was analyzed by 16S ribosomal RNA gene sequencing in 60 LFPI and 21 sham LFPI rats prior to, 1 week, 1 month and 6 months after the injury. Time-dependent changes in both alpha diversity (Chao1 and Faith's index) and beta diversity (robust Aitchison distance) were observed in both LFPI and sham-LFPI subjects. Prior to the LFPI/sham LFPI, beta diversity was similar between the animals of the two groups (Adonis p=0.08). One week after LFPI, beta diversity was significantly different between LFPI and sham LFPI rats (Adonis p=0.02), and the difference further increased at 1 month (p=0.0001). For FMT, the following donors were used: naïve; 1 week after LFPI, with subsequent development of PTE; 7 months after LFPI with confirmed PTE; 7 months after LFPI without PTE. Samples from 3-4 donors of each category were combined and administered to recipients (7 per group), 3 weeks after LFPI, and after 2-week treatment with oral antibiotics to suppress commensal microbiota. PTE was examined 7-9 months after LFPI first by monitoring of spontaneous seizures, followed by kindling of amygdala. There were no statistically significant differences in the incidence and frequency of spontaneous seizures between untreated and FMT rats, for any of the donor type. After LFPI, 10 out of 26 rats kindled faster, 8 out of 26 rats kindled slower, and 8 out of 26 rats kindled at a rate similar to sham and naive subjects. After FMT, notwithstanding the type of the donor, no animals had accelerated kindling rate, with 4-6 rats per group having normal, and the remaining- slow kindling. Antibiotics alone had no effects. The observed differences in kindling were statistically significant as compared to untreated rats, but similar among the different types of recipients (Kruskal Wallis + Dunn's). In conclusion, our data show that both LFPI and sham LFPI alter gut microbiome; however, LFPI-specific changes are also present. Judging by the results of FMT on kindling, these changes may counteract the increased susceptibility to epilepsy after TBI.

Disclosures: A. Mazarati: None. **J. Medel-Matus:** None. **V. Lagishetty:** None. **C. Santana-Gomez:** None. **D. Shin:** None. **J. Jacobs:** None. **R. Staba:** None. **R. Sankar:** None.

Poster

P145. Epilepsy: Post-Seizure Modifications

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P145.10

Topic: B.10. Epilepsy

Support: ERUK Grant
BBSRC Student Funding

Title: Characterization of interactions between seizures and cortical spreading depression using calcium imaging and multisite DC-coupled electrographic recordings in vivo.

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Abstract: Cortical seizures are often accompanied by cortical spreading depression (CSD), but the relationship between these two phenomena remains enigmatic. CSD, the physiological correlate of migraine aura, arises from a propagating destabilization of ion homeostasis, resulting in prolonged suppression of subsequent neuronal activity. While this suppression of activity has been linked to the termination of epileptic paroxysms, many reports also indicate increased excitability and epileptiform discharges immediately after a CSD. However, most experimental studies to date have been limited to recording from single, or few, cortical sites with DC-coupled electrodes, failing to capture the circuit relationship between CSD and seizures.

To capture the interactions between ictal discharges, seizures and CSD waves, we developed a method to characterise the spatial propagation and interaction of these events in the cortex of awake mice. We expressed the calcium indicator GCaMP7a in both cortical hemispheres, and recorded the propagation of picrotoxin-induced seizures and associated CSDs across different cortical regions using wide-field imaging. Moreover, we placed transparent, 16-channel graphene solution-gated field effect transistor (gSGFET) arrays on the dura, which allowed simultaneous recording of full-bandwidth electrophysiological signals.

To examine the temporal relationship between seizures and CSD, we developed an automated analysis pipeline to classify and characterize events based on cortical origin and propagation properties. For each CSD event, we extract multiple properties (such as amplitude, waveform, co-occurring hyperpolarization, duration and laterality) and perform unbiased statistical testing with seizure-relevant parameters. Using gSGFET-acquired data, we resolve the full-bandwidth electrophysiology signals into physiologically-relevant frequency components and compare the power of each during different events. This allows us to correlate cortical oscillations with the activity throughout both hemispheres. Using these methods, we are able to perform high-throughput event analyses to examine the diversity of ictal-associated infraslow events and resolve these based on the role they play in epileptic paroxysms.

Altogether, the methodology presented in this study provides a previously unseen view into the relationship between CSD and cortical seizures. We envision that combined application of calcium imaging and gSGFET recordings will provide unparalleled insights into the understanding of seizure initiation and termination, and will facilitate the development of novel therapeutic avenues.

Disclosures: D. Rathore: None. **A. Smith:** None. **E. Masvidal-Codina:** None. **L.F. Rossi:** None. **A. Guimerà-Brunet:** None. **Y. Timofeeva:** None. **R.C. Wykes:** None. **K.E. Volynski:** None.

Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P168.01

Topic: B.11. Glial Mechanisms

Support: NIH Grant NS083858 (SAK)
FPU16/06368, MCIU, Spain (IAM)

Title: Novel mechanism of hypoxic injury mediated by non-excitatory amino acids

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Abstract: One of the major pathogenic events causing acute brain damage during head trauma and hemorrhagic stroke is bleeding and release of plasmatic content, including amino acids (AA), into cerebral parenchyma. Consequently to the decrease in blood flow, abrupt tissue hypoxia-anoxia develops. However, little is known about non-excitotoxic AA contribution to hypoxic cellular injury. Recently we have shown in hippocampal slices that hypoxia-induced synaptic depression becomes irreversible in the presence of non-excitatory AA, coinciding with their intracellular accumulation and increased tissue electrical resistance (Álvarez-Merz *et al.*, 2021). Here, we hypothesize that transporters-mediated uptake of non-excitatory AA promotes cell swelling and exacerbates hypoxia-induced neuronal injury by releasing excitotoxins through volume-regulated anion channels (VRAC). A combination of four AAs (AGQS: L-alanine, glycine, L-glutamine, and L-serine) at plasmatic concentrations were applied to brain slices from 42 male and female adult mice expressing EGFP in pyramidal neurons (Thy1/EGFP) or astrocytes (GFAP/EGFP). Simultaneous high-resolution 2-photon imaging and field electrophysiological recordings in hippocampal CA1 *st. radiatum* were used to monitor astroglial and neuronal swelling concurrently with signs of injury to synaptic circuitry signified by dendritic beading and loss of synaptic transmission. Imaging changes in light transmittance (LT) were used for global monitoring of tissue swelling and shrinking. Data were analyzed blind to conditions. We find that during normoxia, AGQS-induced increase in LT is due to astroglial but not neuronal swelling (n=13 slices). In contrast, an increase in LT during 30-min hypoxia and AGQS manifests irreversible neuronal and astroglial swelling. AGQS-induced permanent loss of synaptic transmission during hypoxia develops alongside dendritic beading, indicating structural damage (n=15). Interestingly neuronal damage is not caused by spreading depolarization, which does not occur in our experiments. Blockade of NMDA receptors prevents neuronal damage and irreversible loss of field potentials (n=10). Control 30-min hypoxia without AA does not cause changes in cell volume, leaving dendrites intact (n=19). Deleterious effects of AGQS during

hypoxia are avoided by alanine-serine-cysteine transporter 2 (ASCT2) and VRAC blockers (n=7 and 8). Our results suggest that extracellular volume reduction induced by intracellular accumulation of non-excitotoxic AA through neutral AA transporters and the resulting glutamate release through swelling activated VRAC aggravate deleterious hypoxia outcomes.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P168.02

Topic: B.11. Glial Mechanisms

Support: PICT 2018-01685

Title: Glucose and oxidative stress as modulators of retinal Müller cells pluripotency capacity. Involvement of histone deacetylase SIRT6.

Authors: F. SANHUEZA SALAS[1], A. GARCÍA VENZOR[2], N. BELTRAMONE[3], C. CAPURRO[3], D. TOIBER[4], ***D. SILBERMAN**[1];
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Abstract: Müller glial cells (MGs) play a critical role in retinal metabolism and are among the first cells to demonstrate metabolic changes in retinal stress or disease. In response to a harmful stimulus they can rapidly dedifferentiate acquiring neural stem cells properties, proliferate and migrate to the damaged retinal layer and differentiate into lost neurons making them candidates as a potential source of regenerative cells in this tissue. However, how this process is regulated in mammals remains unknown.Somatic reprogramming and pluripotency are characterized by a transition from oxidative metabolism into anaerobic glycolysis. Interestingly, the NAD+ dependent histone deacetylase SIRT6 has been shown to act as a key modulator of glucose homeostasis, to be a direct regulator of the expression of core pluripotent genes and to play a role in retinal function. In this work we aimed to study the effect of glucose variations in MGs reprogramming capacity and analyze the participation of SIRT6 as a potential epigenetic modulator of this process. The retinal Müller glial derived cell line MIO-M1 was cultured with different glucose concentrations and under oxidative stress conditions. We found that glucose variations do not exert an effect in the glial cell marker glutamine synthetase (GS) levels nor in the migration capacity of MGs but the combination of high glucose concentrations and oxidative stress induced a decrease in GS levels ($p<0.05$) as well as an increase in the migration capacity ($p<0.05$) suggesting that these experimental conditions could induce some degree of dedifferentiation and favor the migration ability. High glucose also induced an increase in the levels of pluripotent factor SOX9 ($p<0.05$) and a decrease in SIRT6 ($p<0.05$) levels accompanied by the increase in the acetylation levels of one of its

substrates (H3K9) ($p<0.001$). Notably, inhibiting SIRT6 expression by siRNA rendered an increase in SOX9 levels. A moderate increment of SOX9 levels was also observed in retinas from mice with a conditional deletion of SIRT6 in the CNS (Nes-Cre) suggesting that this enzyme, as shown for other reprogramming factors, may be a modulator of this transcription factor. Further studies will help us to understand the mechanisms that regulate MGs response under metabolic impaired conditions.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

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Program #/Poster #: P168.03

Topic: B.11. Glial Mechanisms

Support: R21NS102911
Pick Grant

Title: Astrocyte secreted factors drive microglial activation in SMA patient iPSC cultures

Authors: *R. L. ALLISON[1], G. KHAYRULLINA[2], B. G. BURNETT[2], A. D. EBERT[1];
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Abstract: Spinal muscular atrophy (SMA) is the leading genetic cause of infant mortality and is caused by a mutation or deletion of the survival of motor neuron 1 (SMN1) gene, resulting in reduced expression of the ubiquitous SMN protein. Motor neurons are particularly impacted by decreased SMN protein levels, and motor neuron loss is the primary phenotypic outcome in SMA patients. SMN deficient motor neurons show intrinsic deficits in splicing and electrophysiological function, but these defects alone are not sufficient to induce overt motor neuron loss. Data from us and others indicate that there are significant non-cell autonomous astrocyte and microglia influences on motor neuron health and survival, raising the possibility that glia directly contribute to the vulnerability of neurons in SMA.
Our lab has previously found that astrocytes in SMA undergo morphological and functional changes early in the disease and are capable of inducing motor neuron pathology. Additionally, others have shown that microglia in SMA exhibit activation later in the disease process and are involved in synapse engulfment. However, the mechanisms of glia-mediated neuron dysfunction and the temporal contributions of astrocyte-microglia crosstalk to SMA pathology have not been elucidated.
We hypothesize that early SMA astrocyte dysfunction induces motor neuron pathology and simultaneously drives microglial activation. In support of this, we found that astrocytes differentiated from SMA patient-derived induced pluripotent stem cells (iPSCs) express high levels of pro-inflammatory cytokines IL1β and IL6 as well as complement factors C1q and C3 compared to healthy (unaffected) astrocytes. Moreover, we found that SMA iPSC-derived microglia upregulate the receptors for these ligands, suggesting several avenues of glial crosstalk. Exposure of SMA microglia to SMA astrocyte conditioned medium (ACM) increased reactive morphology and phagocytic ability compared to

control ACM. Interestingly, lentiviral knockdown of the upregulated transcription factor GATA6 in SMA astrocytes abrogated these effects. No differences in astrocyte activation were found after exposure to SMA microglia conditioned media.
These data indicate the significant role of astrocyte secreted factors in contributing to disease phenotypes and suggest an astrocyte-to-microglia timeline of glial activation in SMA. Gaining a better understanding of glial contributions to SMA pathology can help identify additional SMN-independent targets for therapeutic intervention.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

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Program #/Poster #: P168.04

Topic: B.11. Glial Mechanisms

Support: NIH Grant AG061775

Title: Ab40 and Ab42 adopt distinct fibril structures that differentially stimulate astrocytes and microglia

Authors: *X. ZHU[1], J. SCHRADER[2], B. IRIZARRY[3], A. STANISAVLJEVIC[2], S. SMITH[3], W. VAN NOSTRAND[2];
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Abstract: Aβ40 and Aβ42 adopt distinct fibril structures that differentially stimulate astrocytes and microglia
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Fibrillar amyloid β-protein (Aβ) deposits in brain, which are primarily composed of Aβ40 or Aβ42 peptides, are key pathological features of Alzheimer's disease and related disorders. Structural studies on mature Aβ40 fibrils formed in solution have suggested they adopt a two stranded (U-shaped) structure whereas studies on Aβ42 fibrils typically show a three-stranded structure. Fibrillar amyloid deposits in brain promote activation of astrocytes and microglia although the underlying mechanisms are still not clear. Here, we prepared Aβ40 and Aβ42 fibrils and NMR analysis confirmed the distinct two-stranded structure of Aβ40 fibrils and three-stranded structure of Aβ42 fibrils. Primary astrocytes and microglia were isolated from neonatal rat brains and treated with Aβ40 or Aβ42 fibrils. RNA sequencing was performed on cells treated with the different amyloid fibril preparations. The expression data were analyzed and set with limits of ≥5-fold increase in expression and $p < 0.05$. Results show that Aβ40 fibrils stimulated the expression of 180 genes in microglia but >1700 genes under Aβ42 fibrils stimulation. In contrast, Aβ40 fibrils only stimulated 35 genes in astrocytes and 38 genes under Aβ42 fibrils treatment.

Immunohistochemical analysis was performed in an AD rat model with parenchymal fibrillar Aβ42 deposits confirming the expression of MMP9, MMP12, PAI-1 and C1r in plaque-associated microglia supporting the RNAseq results in the treated cultured glial cells. Together, these studies show that the distinct structures of Aβ40 and Aβ42 fibrils differentially stimulate the gene expression profile of astrocytes and microglia and that Aβ42 fibrils are more potent stimulators. These findings indicate that different types of amyloid fibrils can promote distinct gene expression signatures in glial cells that may participate in the pathogenesis of AD and related amyloid-depositing disorders. Work was supported by NIH grant AG061775.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

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Topic: B.11. Glial Mechanisms

Support: NIH-T32-NS007453
Children's Tumor Foundation Young Investigator Award
NIH-R01-NS28840
NIH-R37-NS083580

Title: P2ry14 modulates Schwann cell precursor self-renewal and tumor initiation in mouse model of neurofibromatosis type 1.

Authors: *J. PATRITTI CRAM[1], J. WU[2], S. KUNINAKA[3], R. A. COOVER[4], R. F. HENNIGAN[2], T. A. RIZVI[2], K. E. CHANEY[2], J. A. CANCELAS[2], R. J. SPINNER[5], N. RATNER[6];
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Abstract: Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by tumors in peripheral nerves called neurofibromas. We found that the purinergic receptor P2RY14 is expressed in human and mouse neurofibroma Schwann cell precursor-like cells (SCPs) and in Schwann cells (SCs). Neurofibroma $P2RY14^{+}$ SCP-like cells were enriched in cells with the potential to self-renew. Conversely, SCP self-renewal was blocked by pharmacologic or genetic targeting of P2RY14 in mouse *Nf1* mutants. Downstream of P2RY14, G_{i}-mediated cAMP signaling contributed to these effects. *In vivo,* in a mouse model of NF1, P2RY14 loss delayed neurofibroma initiation, normalized nerve architecture, rescued the reduced cAMP characteristic of neurofibromas and normalized neurofibroma cell proliferation. Thus, the purinergic receptor P2RY14 regulates SCP self-renewal and neurofibroma initiation, and to a lesser

extent, contributes to later stages of tumorigenesis. These gain and loss of function experiments suggest roles for P2RY14 signaling in peripheral nerve that are perturbed by loss of the NF1 tumor suppressor.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P168.06

Topic: B.11. Glial Mechanisms

Support: NS0432577

Title: Critical role of Hv1 and zinc in microglial inflammatory neurotoxicity

Authors: *D. HERNÁNDEZ ESPINOSA, E. AIZENMAN;
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Abstract: Although an inflammatory response is necessary for moderating injurious processes, the dysregulation of microglial activation can directly cause neuronal death, a term we define as inflammatory neurotoxicity. The Hv1 (HVCN1) proton channel participates in the regulation of microglia activation, although its precise roles are not completely defined. In the CNS, this channel is expressed exclusively in microglia, and its activity is strongly regulated by zinc. The present work focuses on defining the widespread consequences of the pharmacological inhibition of Hv1 during microglial activation, as well as the effect of zinc in this process. We used a model of chronic activation in a rat microglia cell line (HAPI cells) as well as in a primary cortical neuronal-microglial coculture. Microglia were treated with LPS/IFNγ for 24 h in the presence or absence of 2-Guanidinobenzimidazole (2GBI), an Hv1 inhibitor, as well as under conditions that increase (ZnPyR) or decrease (TPEN) intracellular zinc. To confirm microglial activation, we quantified phagocytic activity, ROS, NOX and iNOS activity, as well as cytokine production. We also quantify microglial intracellular pH (ipH) changes and neuronal viability in our coculture preparation. During microglia activation, 2GBI causes a dramatic fall in microglial ipH, decreased phagocytic activity, and stunted reactive species production. Hv1 inhibition also reduces NOX and iNOS activity as well as reactive species production by nearly 50%. LPS/IFNγ treatment normally produces a 10-fold increase in IL-6, also partially blocked by Hv1 inhibition. Interestingly, microglial activation produced a discrete increase in IL-10, which is totally blocked by Hv1 inhibition. Regarding inflammatory neurotoxicity, the viability of cortical neurons decreases approximately 40% when cocultured for 24h with activated microglia, while if activation occurs during Hv1 inhibition the neuronal viability only decreases by 15%. When we added ZnPyR during microglia activation, IL-6 production and neurotoxicity increases by 20%, an effect absents in 2GBI-treated cells. In contrast, administration of TPEN increases IL-10 production and decreases neurotoxicity, but only during Hv1 inhibition. In summary, activation of the Hv1 proton channel is necessary for microglial activation and resulting inflammatory neurotoxicity, while zinc chelation during Hv1 inhibition can further restrict

microglial neurotoxicity. These results suggests that the inhibition of Hv1 together with the administration of intracellular zinc chelators could represent a therapeutic option for the control of inflammation-associated neurotoxicity

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

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Program #/Poster #: P168.07

Topic: B.11. Glial Mechanisms

Support: SEP-CONACYT 221092

Title: Glial cell activation of c-Fos marker under aversive conditions

Authors: A. N. AGUILAR DELGADILLO[1], ***L. F. CRUZ MENDOZA**[1], G. S. QUINTERO RUBIO[1], G. I. BARRIENTOS GUTIERREZ[1], L. A. SARAS VILLALPANDO[1], Y. RUVALCABA-DELGADILLO[1], M. S. LUQUIN DE ANDA[1], F. JÁUREGUI HUERTA[2];
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Abstract: The c-fos gene was first described as a proto-oncogene responsible for the induction of bone tumours. In brain sciences, the protein product c-Fos has been studied as an activity marker restricted to neuronal cells. However, according to reports of c-fos expression in astrocytes, microglia, and oligodendrocytes, it is necessary to reconsider this specificity in order to generate a wider vision of c-fos utility in cellular studies. Here, we show that intense stress induces a robust c-Fos protein expression in most of the glial phenotypes residing in brain. We used the immunohistochemical approach to evidence that c-Fos marker may colocalize with other phenotypical markers such as GFAP, Iba1, Olig2 or NG2 proteoglycan. Then, we believe that c-Fos expression may also be useful to evidence activation changes involving glial cells.

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Poster

P168. Glia-Neuron Interactions in Injury and Disease: Cellular Mechanisms

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Program #/Poster #: P168.08

Topic: A.05. Axon and Dendrite Development

Support: NIH R21MH105746
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NIH P20GM113131
NIH R15MH126317

Title: Primary cilia regulate and stabilize neuronal positioning in compact neural structures

Authors: *J. YANG[1], L. QIU[1], X. CHEN[2];
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Abstract: Primary cilia are rigid, centriole-derived, surface protrusion present in most mammalian cells including neurons. It is known that primary cilia regulate early neurodevelopment such as neural tube patterning. Nevertheless, it is not clear how primary cilia are engaged in neuronal positioning. We compared the morphological dynamics of neuronal primary cilia in the hippocampus, cortex and adrenal medulla during development. Here we show that neuronal primary cilia emerge only after hippocampal pyramidal neurons have migrated to reach the pyramidal cell layer, but before the final neuronal positioning. Primary cilia in the pyramidal cell layer undergo marked changes in morphology and orientation postnatally, which coincide with pyramidal neuronal positioning to the deep and superficial sublayers. Moreover, primary cilia of deep-sublayer neurons mostly point to the ventricle zone, whereas those of superficial-layer neurons point to the opposite direction. Calbindin staining show the opposing cilia pointing in the deep and superficial sublayers is in line with the inside-out lamination pattern. Surprisingly, we also found that the centriole/cilia movement during neuronal positioning is different from that of saltatory migration. Overexpression of Arl13B not only elongates primary cilia length, but also promotes earlier cilia emergence, slightly changing the ratio of the opposing cilia pointing in the pyramidal cell layer. Similarly, primary cilia of cortical pyramidal neurons emerge after the completion of migration, and their cilia orientation aligns with the migration direction and inside-out lamination. In contrast, chromaffin cells in the adrenal medulla, which migrate collectively, have different timing of ciliation. Their primary cilia are prominent at embryonic stage and during neuronal migration, and apparently well-positioned to stabilize the functional unit, but do not point to the migration direction. Together, these data suggest that neuronal primary cilia may function like “mechanical anchors” to regulate and stabilize neuronal positioning in compact neural units.

Disclosures: J. Yang: None. **L. Qiu:** None. **X. Chen:** None.

Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P191.01

Topic: C.01. Brain Wellness and Aging

Support: NIH R21AG065606

Title: Aged-dependent microbiome dysbiosis and BBB dysfuction in postoperative delirium pathogenesis

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Abstract: Introduction: Delirium, a syndrome of confusion and inattention, is the most common postoperative complication in senior patients and is associated with accelerated cognitive decline, such as Alzheimer's disease. Senior patients are more likely than younger ones to develop postoperative delirium (POD). However, the neuropathogenesis of POD remains mostly unknown. Gut microbiota dysbiosis, a condition of microbiota imbalance or maladaptation inside the gut, which could lead to altered immune functions and associated with disorders of the immune, endocrine, and central nervous systems, including with POD. Aging is associated with changes in the gut microbiota and microbiota dysbiosis. Our previous studies demonstrated that anesthesia/surgery causes age-dependent gut microbiota dysbiosis and the POD-like behavior in mice. Meanwhile, anesthesia/surgery induce blood-brain barrier(BBB) dysfunction and cognitive impairment in mice. We hypothesized that the aged-dependent gut microbiota dysbiosis associated with the BBB permeability changes lead to POD-like behavior in mice. Therefore, our hypothesis that anesthesia/surgery causes age-dependent changes in the BBB permeability dysfunctions and POD-like behavior in mice that is attenuated by probiotics. Methods: Female 3 or 18 months old mice received abdominal surgery under 1.4% isoflurane for two hours. We employed a battery of natural and learned behavioral tests to determine the POD-like behavior, assessed BBB permeability by tail vein injection with dextran and levels of brain IL-6. For intervention, intragastric administration of probiotic was used to mitigate the anesthesia/surgery-induced above changes. Results: Firstly, we found that anesthesia/surgery induces age-dependent POD-like behaviors and cognitive impairment between the 18 and 3 months old mice.The anesthesia/surgery-induced greater POD-like behavior, increased brain IL-6 levels, and significant BBB permeability dysfunction in 18 than 3 months old mice. Treatments with probiotics mitigated the anesthesia/surgery-induced above changes. Conclusion: We demonstrated that anesthesia/surgery induces age-dependent changes in BBB permeability dysfunction, increases brain levels of IL-6, while also promoting the development of POD-like behaviors in the mice. Treatment with probiotics prior to anesthesia/surgery mitigated these detrimental effects, strongly suggesting that abnormalities in the gut microbiota contribute to the development of postoperative delirium.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Program #/Poster #: P191.02

Topic: C.01. Brain Wellness and Aging

Support: University of Georgia Franklin Foundation Imaging grant
DoD grant number W81XWH-16-1-0586
NIH grant number T35OD010433-14

Title: Longitudinal assessment of structural brain alterations following short-term, Gulf War-related chemical exposure

Authors: J. M. CARPENTER[1], S. H. NGUYEN[2], K. M. MASON[2], N. M. FILIPOV[1];
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Abstract: Gulf War Illness (GWI) affects nearly 30% of veterans from the 1990-1991 Gulf War as a multi-symptom illness characterized by neurological and immunological effects that are attributed to in theatre war-time chemical overexposures. Numerous imaging studies have revealed structural and functional neurological alterations in GWI veterans, such as reduced hippocampal and cerebellar volumes, connectivity, and signaling that highly correlate to poor performance in tasks evaluating cognition and motor function. Symptomology has been recapitulated in GWI rodent models as aberrations in behavioral performance (i.e. cognition/memory, motor, and mood) and biological parameters (i.e. neuroinflammation). While these models produce similar GWI behavioral and biological phenotypes, structural imaging studies remain limited. Thus, this study aimed to longitudinally characterize the progression of brain structural alterations over the course of 9 months following GW chemical exposure to a nerve agent prophylactic (pyridostigmine bromide; PB) and pyrethroid insecticide (permethrin; PM). Male C57BL/6J mice (8-9 weeks) were co-administered PB/PM (0.7/200 mg/kg IP, respectively) or DMSO control daily for 10 days. Using a Varian 7T Bore MRI System, structural (coronal T1- and sagittal T2-weighted) scans were performed at 3, 6, and 9 months post chemical exposure. Regions of interest (ROIs) including the cortex, hippocampus, cerebellum, lateral ventricle, and third ventricle were delineated in the open source Aedes Toolbox in MATLAB, followed by volumetric analysis in ImageJ. Of the data analyzed to date, there were no observed treatment effects on ROIs within 3 or 6 months. However, hippocampal volume was decreased in PB/PM mice from 3 to 6 months; ventricular volumes remained unaffected, suggesting the hippocampal volume decreases precede and/or are independent of ventricular volume changes at this state. In the cerebellum, significant decreases in cerebellar volume were present within both groups from 3 to 6 months, suggesting age related rather than treatment related effects within this region. The observed alterations in brain structures thus far align with GWI clinical reports and neurobehavioral deficits previously characterized in this model; the cerebellar data hints that this brain region may be amongst the earliest affected by age. Overall, the effects seen here further add translational validity to this model for future GWI therapeutic interventions. This research was supported by the University of Georgia Franklin Foundation Imaging grant awarded to JMC, DoD grant number W81XWH-16-1-0586 awarded to NMF, and NIH grant number T35OD010433-14.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Topic: C.01. Brain Wellness and Aging

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Title: The effect of manganese on synaptic transmission and its impact on various physiological processes

Authors: *C. L. PANKAU[1], J. NADOLSKI[2], H. TANNER[3], C. CRYER[1], J. DI GIROLAMO[1], C. N. HADDAD[1], R. E. WILSON[1], D. M. NEELY[1], M. MILLER[1], M. J. LANNING[1], B. WHITTINGHILL[1], R. L. COOPER[1];
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Abstract: Manganese (Mn^{2+} as present within $MnSO_4$ and/or $MnCl_2$) is an element that is essential to various cellular processes, for example, the functioning of essential enzymes such as superoxide dismutase (SOD). Manganese is present within soil, fresh waters, and marine waters; however, overexposure to manganese can be toxic and is often associated with a variety of neurological issues. Overexposure to manganese is often attributed to working within the mining or metal processing industry, being exposed to $MnSO_4$ that had been added to soil for agricultural purposes, or being exposed through other food sources such as infant formula. Research has demonstrated that hypermagnesemia can be associated with the onset of Parkinson's disease-like symptoms and acute cardiovascular disorders in mammals. This impact seems to occur as a result of the blockage of dopaminergic neural circuits by manganese. In order to investigate these effects further, this study was intended to examine the effect of hypermagnesemia on not only dopaminergic synapses, but also on development, behavior, survival, cardiac function, and glutamatergic synaptic transmission through experimentation with *Drosophila melanogaster*. In addition, the effect of manganese on sensory neurons in marine and freshwater crustaceans, glutamatergic neuromuscular junctions in freshwater crayfish, and the shape of neuronal action potentials in freshwater crayfish was also examined. The results from this study indicated a dose-response effect where higher Mn^{2+} has an adverse effect on development, survival, and cardiac function in *D. melanogaster* larvae and survival in adults. It was also shown that $MnSO_4$ and $MnCl_2$ block stretch-activated responses in primary proprioceptive neurons in a dose-response manner. Glutamatergic synaptic transmission at the neuromuscular junction of both crayfish and *D. melanogaster* indicate that Mn^{2+} blocks evoked responses but not glutamate receptors, which suggests that these effects may result from a presynaptic block of voltage-gated Ca^{2+} channels. The effects of manganese on glutamatergic synaptic transmission and the shape of action potentials in axons will also be reported on. The effect of Mn^{2+} is multi-faceted, so learning about its impact on various physiological functions is relevant in order to gain a better understanding about the acute and long-term consequences of overexposure.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Program #/Poster #: P191.04

Topic: C.01. Brain Wellness and Aging

Support: DA039253
DA051450
AG070962

Title: Chronic methamphetamine administration induces degeneration of locus coeruleus neurons and monoamine oxidase inhibition is neuroprotective

Authors: *Y. DU, A. PILSKI, S. CHOI, Y. LEE, S. M. GRAVES;
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Abstract: Methamphetamine (meth) is an addictive psychostimulant with the capacity to induce neurodegeneration. Meth causes dysfunction of vesicular monoamine transporter 2 proteins resulting in increased cytosolic monoamine concentrations. In substantia nigra pars compacta (SNc) dopamine neurons this leads to increased axonal mitochondrial stress due to monoamine oxidase (MAO) metabolism (Graves *et al., Nat Neurosci*, 23:15 2020). Chronic administration of meth results in SNc degeneration which is prevented by MAO inhibition, suggesting that meth-induced MAO-dependent mitochondrial stress is a causal factor (Graves *et al., Neurobiol Dis*, 156:105409 2021). Meth also targets noradrenergic systems and MAO enzymes metabolize norepinephrine. To determine whether locus coeruleus (LC) norepinephrine neurons are also vulnerable to chronic meth-induced degeneration we first assessed mitochondrial stress in these neurons. The redox biosensor roGFP was expressed in the mitochondrial matrix of LC neurons; both somatic and axonal mitochondrial stress was measured in *ex vivo* mouse brain slices as previously described (Graves *et al., Nat Neurosci* 23:15 2020). Similar to that observed in SNc neurons (Graves *et al., Nat Neurosci* 23:15 2020), meth (10 μM) had no effect on somatic but increased axonal mitochondrial stress in LC neurons. The increase in axonal mitochondrial stress was attenuated by MAO inhibition (1 μM rasagiline). To ascertain whether chronic meth was neurotoxic to LC neurons mice were administered saline or meth (5 mg/kg; i.p.) for 28 days, sacrificed, and tissue collected for immunohistochemistry. LC axons in the motor cortex were stained for the norepinephrine transporter (NET); cells in the LC were stained for tyrosine hydroxylase (TH) and counterstained for NeuN, a non-specific neuronal marker. Stereological quantification indicated that chronic meth decreased the length of NET^+ axons in the motor cortex and number of TH^+ cells in the LC. To confirm that these findings reflected degeneration and not phenotypic suppression, NeuN stained cells in the LC were also counted; meth similarly decreased the number of NeuN stained cells in the LC confirming degeneration. Lastly, to determine whether MAO activity contributes to LC degeneration as it does in the SNc (Graves *et al., Neurobiol Dis*, 156:105409 2021), mice were administered the MAO inhibitor rasagiline (1 mg/kg; i.p.) 30 min prior to meth for 28 days. Consistent with the SNc, MAO inhibition also prevented chronic meth-induced LC degeneration. These results suggest that meth-induced MAO-dependent mitochondrial stress is necessary for chronic meth-induced LC degeneration.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Program #/Poster #: P191.05

Topic: C.10. Brain Injury and Trauma

Support: NIAAA T32 AA027488
NIAAA 3R44AA025804-03S1

Title: Ethanol exaggerates cell death at high but not low impact force in an organotypic hippocampal slice culture mechanical distension model of traumatic brain injury

Authors: *J. JAGIELO-MILLER[1], S. P. PATEL[2], C. S. BAILEY[1], C. COUNT[1], A. G. RABCHEVSKY[3], M. A. PRENDERGAST[1];
[1]Psychology, [2]Spinal Cord & Brain Injury research Center, Dept. of Physiol., [3]Spinal Cord & Brain Injury Res. Ctr. (SCoBIRC) & Dept. of Physiol., Univ. of Kentucky, Lexington, KY

Abstract: Every year more than 2.8 million people sustain a traumatic brain injury (TBI) in the United States. A large percent (25-50%) of individuals of are intoxicated at the time of their injuries. Despite the prevalence of TBIs that occur under the influence of alcohol (EtOH), it is not well understood how EtOH impacts the cellular cascades of secondary injury which are triggered by the initial injury, or how EtOH impacts patient outcomes. Research on TBI patients has shown a mixture of findings from EtOH improving, worsening and not changing TBI outcomes. This prompts further investigation into the effects of EtOH on these secondary injury mechanisms. Organotypic slice cultures serve as a useful tool to study these biochemical phenomena in a tightly controlled manner while minimizing the number of animals used. Hippocampal tissue was taken from 8-day old Sprague Dawley pups (n=12) and cultured for five days prior to treatment on culture inserts. Culture inserts were then transferred into new culture media (+/- 50 millimolar ethanol) for an additional 2 days. Following the 2 days of EtOH exposure, tissue in the injury groups were subjected to an indirect stretch injury used to model axonal damage associated with TBIs. Infinite Horizon Impactor was used at two different forces (50 kilodyne (kD) or 100kD) for two different dwell times (0 seconds or 5 seconds) to stretch the culture membranes (4 slice cultures per membrane) which in turn stretched the tissue, causing injury. All tissue inserts were then transferred to new culture media containing propidium iodide (PI), a crude fluorescent marker of cell death in which more PI uptake indicates higher levels of cell death. Tissue was imaged 24 hours post injury for PI uptake. Tissue in all the injury groups showed an increase in PI uptake compared to tissue in the control condition. The EtOH group did not show an increase in PI uptake compared to the Control group. Following lower impact (50kD), there was no effect of EtOH on PI uptake at either dwell times. However, tissues in higher impact (100kD) groups that were exposed to EtOH showed an increase in PI uptake compared to their control injury counterparts at both the 0 second and 5 second dwell times. There was a sex difference (n= 186, 97 females) in both the cornu ammonis 1 (CA1) and cornu ammonis 3 (CA3) regions of the hippocampus, such that male tissue showed an increase in PI uptake compared to female tissue, but this was not found in the dentate gyrus. The findings of this study are preliminary and require future replication with the addition of immunohistochemical staining; however, they indicate that the models used offer a promising paradigm for further understanding of how EtOH use impact TBIs.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Program #/Poster #: P191.06

Topic: C.10. Brain Injury and Trauma

Support: U.S. Air Force FA8650-17-2-6H10

Title: Hippocampal vulnerability to hyperhomocysteinemia worsens mild traumatic brain injury pathological outcomes in rats

Authors: *F. TCHANTCHOU[1], C. MILLER[2], G. FISKUM[1];
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Abstract: Mild traumatic brain injury (mTBI) interpatient pathological variability hinders our ability to develop effective therapeutic agents. The accumulation of the non-proteinogenic amino acid homocysteine called hyperhomocysteinemia (HHCY) has substantial neurotoxic properties. HHCY can be caused by stress, aging, lifestyle, or genetic predisposition and is implicated in the pathogenesis or influence the pathological progression of several neurological disorders, including stroke. We recently reported on the detrimental impact of HHCY on mTBI cortical pathological outcomes. Here, we investigated the effects of pre-existing HHCY on TBI-associated hippocampal neuropathology and related behavioral deficits in rats. Hyperhomocysteinemic male Sprague Dawley rats (250-300g) were subjected to mTBI by controlled cortical impact (CCI) method under anesthesia with 3.5% isoflurane and body temperature maintained at 37°C. CCI was performed over the left parietal cortex with a 4 mm diameter piston, a magnetic impact of 5 m/s, and a penetration depth of 1.5 mm. Rats were assessed for working memory, euthanized on days 1, 7, or 30 post-surgery, and brain collected for histological and biochemical analyses. Statistical analysis was performed by one-way or repeated ANOVA with Tukey-Kramer post-test. There were 5-12 rats/group, and UMB IACUC approved the study. The assessment of the effect of HHCY on the oxidative stress marker nitrotyrosine found an 11-fold increase in nitrotyrosine positive cells in the dentate gyrus (DG) of HHCY-shams compared to normohomocysteinemic (NHCY)-shams ($p < 0.01$). Furthermore, there was also a 2.5-fold increase in nitrotyrosine positive cells in HHCY-CCI rats versus NHCY-CCI rats ($p < 0.01$). HHCY also caused a 35% reduction of occludin expression in the hippocampus of HHCY-CCI rats versus NHCY-CCI rats ($p < 0.05$). Changes in occludin expression were associated with Electron microscopy determined significant elongation and enlargement of the endothelial cell nucleus in HHCY-CCI rats. Significant neuronal cell loss was found in the ipsilateral and contralateral DG of HHCY-shams and HHCY-CCI rats compared to NHCY-CCI. There was also an increased expression or proteolysis of pro-apoptotic proteins BAX and α-ii spectrin parallel with decreased phosphorylation of cell survival-promoting proteins ERK and AKT in HHCY-CCI rats. These mTBI hippocampal pathological alterations were associated with significant deficits in working memory in HHCY-CCI versus NHCY-shams ($p < 0.01$). In summary, HHCY exacerbated working memory deficits in mTBI rats associated with HHCY-induced oxidative stress, BBB disruption, and neuronal cell loss.

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Poster

P191. Brain Injury: Molecular-Cellular Mechanisms and Neurotoxins

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Program #/Poster #: P191.07

Topic: C.10. Brain Injury and Trauma

Support: NIH 5R37NS077908-07

Title: Death of hippocampal neurons after acute injury to the developing brain: neurotoxicity, neuroprotection, and delayed neuronal death

Authors: *T. BALENA[1], L. A. LAU[4], K. P. LILLIS[2], N. RAHMATI[5], K. J. STALEY[3];
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[4]Neurol. Res., MGH, Boston, MA; [5]Harvard Med. School/Massachusetts Gen. Hos, Boston, MA

Abstract: Neuronal death terminates with microglial engulfment of apoptotic neurons or necrotic neuronal debris. Many studies of neurotoxicity and neuroprotection are predicated on changes in the number of visibly dying neurons or their effluent cytoplasmic enzymes. This number is a function of three variables: the rate at which neurons enter the death process; the visibility of neurons during the process (which depends largely on the membrane permeability delimiting the rate of biomarker uptake); and the rate at which they exit the process via microglial engulfment. We describe our initial findings in an in vitro preparation in which this process can be studied.
We evaluated the death of neurons in a chronically epileptic in vitro preparation in which multiphoton microscopy could be performed over a period of several days. Organotypic hippocampal slice cultures were made from wild-type C57BL/6J mice on P6, incubated in vitro, and imaged serially.
We report the following sequence of events in delayed neuronal death following the substantial trauma involved in brain slice preparation. Neurons entering the death process quenched fluorescent proteins concurrent with elevated caspase activity. Due to their increased membrane permeability these neurons rapidly took up AM ester dyes, shrank, and exhibited evidence of DNA degradation. The membrane transporters of dying neurons remained active for as long as two weeks after entering this pathway. Throughout this period, the permeability of the neuronal membranes gradually increased, as evidenced by a progressive increase in $[Na^+]_i$, and eventually reached the point where polar dyes entered the nucleus. The death process ended with microglial engulfment. Neurons were also exposed to conditions in the developing nervous system considered to be neurotoxic (ethanol) or neuroprotective (kynurenate). Ethanol did not affect fluorescent protein quenching or PI positivity but did alter $[Na^+]_i$, whereas kynurenate did not affect $[Na^+]_i$ but did alter PI positivity and microglial engulfment.
Using serially imaged organotypic hippocampal slice cultures we found that the effects of widely accepted neurotoxic maneuvers such as perinatal ethanol exposure, as well as neuroprotective strategies such as seizure blockade, were primarily mediated by confounding effects on microglial activity and membrane permeability, with either no or opposing effects on healthy neurons identified by ongoing fluorescence emission of transgenic proteins. Accordingly, longitudinal assessment of neuronal health is an important additional assay for the assessment of acute neurotoxic and neuroprotective effects.

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Poster

P358. Peripheral Nerve Injury: Methods of Repair

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Topic: C.10. Brain Injury and Trauma

Support: Rowan University Camden Health Research Initiative to DF and RJB

Title: Rna sequencing documents polyethylene glycol induced gene expression changes that accompany inhibition of Wallerian degeneration in a rat sciatic nerve injury model.

Authors: *S. N. WEISS[1], J. M. LEGATO[2], Y. LIU[3], C. N. VACCARO[3], H. HAKONARSON[3], R. J. BUONO[1], D. A. FULLER[2];
[1]Cooper Med. Sch. of Rowan Univ., Camden, NJ; [2]Bone and Joint Inst., Cooper Univ. Hosp., Camden, NJ; [3]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Application of polyethylene glycol (PEG) to a peripheral nerve injury at the time of primary neurorrhaphy is thought to prevent Wallerian degeneration via direct axolemma fusion. The exact mechanism of nerve fusion is unclear. This study aims to investigate the molecular basis of the protective effect of PEG during primary neurorrhaphy in traumatic peripheral nerve injuries via analysis of differential gene regulation in both the neural and muscular environments. Lewis rats underwent unilateral sciatic nerve transection with immediate primary repair. Subjects were randomly assigned to receive either PEG treatment or standard repair at the time of neurorrhaphy. Samples of the sciatic nerve and tibialis muscle were harvested at 24 hours and 4 weeks postoperatively. Total RNA was extracted and depleted of rRNA with subsequent preparation and sequencing of cDNA libraries using Illumina technology. Three tissue samples were used from separate animals per cohort (N=3). Differential gene expression was defined as a two-fold increase or decrease in PEG-treated subjects compared to controls. Correction for multiple testing was performed by the Benjamini method and p-values lower than 0.05 were considered significant. Gene Ontology (GO) Ingenuity Pathway Analysis (IPA) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) were used for bioinformatics analyses. Our results demonstrate an inverse relationship in differential gene expression among tibialis muscle and sciatic nerve at both time points. At 24 hours, 1,480 genes pertaining mainly to inflammation are differentially regulated within the PEG-treated tibialis muscle compared to control, whereas no genes are differentially regulated within the PEG-treated sciatic nerve compared to control. Conversely, at 4 weeks, only 3 genes continue to be differentially regulated within the PEG-treated tibialis muscle compared to control, whereas 918 genes are differentially regulated within the PEG-treated sciatic nerve compared to control. These genes lead to the differential regulation of pathways supporting peripheral nervous system embryogenesis only expressed during fetal development. Our findings indicate that PEG application during primary neurorrhaphy leads to differential gene regulation in both the neural and muscular environment associated with inhibition of Wallerian degeneration. A more complete understanding of PEG activity may facilitate amplification of its effect through either systemic or focal treatments at the time of neurotmesis. A closer examination of these data is underway to identify key molecules or pathways that could be targeted to accelerate recovery after nerve damage.

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Poster

P358. Peripheral Nerve Injury: Methods of Repair

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Querrey Simpson Institute for Bioelectronics at Northwestern University
NUFAB facility of Northwestern University's NUANCE Center

Title: Implantation and control of wireless, battery free systems for peripheral nerve interfacing

Authors: *H. WANG[1,2], D. D'ANDREA[2], Y. CHOI[3], Y. BOURICHA[2], G. WICKERSON[3], H.-Y. AHN[3], H. GUO[3], Y. HUANG[3], M. S. SANDHU[2], S. W. JORDAN[1], J. A. ROGERS[3], C. K. FRANZ[2]; [1]NORTHWESTERN UNIVERSITY, Chicago, IL; [2]Shirley Ryan AbilityLab, Chicago, IL; [3]Northwestern Univ., Evanston, IL

Abstract: Peripheral nerve interfaces are frequently used in experimental neuroscience and regenerative medicine for a wide variety of applications. Such interfaces can be sensors, actuators, or both. Traditional methods of peripheral nerve interfacing must either tether to an external system, or rely on battery-power that limits the time frame for operation. With recent developments of wireless, battery-free and fully implantable peripheral nerve interfaces, a new class of devices can offer capabilities that match or exceed those of their wired or battery-powered precursors. Here we demonstrate methods to (i) surgically implant, and (ii) wirelessly power and control this system in adult rats. To highlight the versatility of our approach, we select as examples the sciatic and phrenic nerve models. We show how the peripheral nerve interface can evoke compound muscle action potentials, deliver a therapeutic electrical stimulation protocol, and incorporate a conduit for the repair of peripheral nerve injury.

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Poster

P358. Peripheral Nerve Injury: Methods of Repair

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Program #/Poster #: P358.03

Topic: C.10. Brain Injury and Trauma

Title: Intraneural topography of rat sciatic axons: Implications for polyethylene glycol fusion peripheral nerve repair.

Authors: *E. HIBBARD[1], D. R. SENGELAUB[2];
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Abstract: Peripheral nerve injuries are the most common type of nerve trauma, and results in the rapid degeneration of the distal nerve segment and immediate loss of motor and sensory function. Behavioral recovery is typically poor. We have been working with a novel repair technique using a plasmalemmal fusogen, polyethylene glycol (PEG), to re-fuse the membranes of severed axons. PEG-fusion repair allows for immediate re-innervation of distal targets, prevents axonal degeneration, and improves behavioral recovery. PEG-fusion of severed axons is non-specific, and we have previously reported that following injury and PEG-fusion in either single-cut or allograft repairs of the sciatic nerve, misconnections between spinal motoneurons and their distal targets were present, and more common in animals with allograft repairs. Surprisingly, appropriately paired proximal and distal motor axons were observed in all PEG-fused animals, regardless of repair type. We hypothesized that a topographic organization of axons contributing to the sciatic nerve could explain the incidence of appropriate connections. In this study, we traced the course of specific axon populations contributing to the sciatic nerve in young adult rats. Following intraneural injection of Fast Blue (2 µl; 2.5%) into the tibial branch, labeled axons were confined to a centralized location along the course of the sciatic nerve from the distal trifurcation to the proximal sciatic notch, and occupied approximately 53% of the transverse area of the nerve. Following intramuscular injection of cholera toxin-conjugated horseradish peroxidase (2 µl; 0.2%) into the anterior tibialis, labeled axons were confined to a discrete lateral position throughout the nerve, and occupied approximately 12% of the transverse area. In both cases, the relative locations of labeled axons were consistent bilaterally within animals, as well as across animals and sexes. Thus, the presence of specific axon populations that occupy a relatively consistent location throughout the nerve could underlie the appropriate re-established connectivity previously seen in PEG-fused animals. Misalignment of these axon populations through rotations of the original nerve stumps during repair, or sizing differences in allograft repairs, could account for the pattern of misconnection observed after PEG-fusion repair. Knowing the organization of axons within the sciatic nerve promotes accurate territory realignment during repair, therefore aiding in recovery outcomes.

Disclosures: E. Hibbard: None. **D.R. Sengelaub:** None.

Poster

P358. Peripheral Nerve Injury: Methods of Repair

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P358.04

Topic: C.10. Brain Injury and Trauma

Support: NIH 7R44NS097113-05

Title: Biomechanical validation of a novel nerve coaptation device

Authors: *G. S. BENDALE[1], M. SONNTAG[2], I. P. CLEMENTS[2], J. E. ISAACS[1];
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Abstract: Despite decades of research, the functional outcomes of peripheral nerve repairs remain suboptimal. While significant focus has been placed on enhancing axon regeneration, the technical quality of the coaptation has received less attention. Although microsuture neurorrhaphy is the clinical standard, repair quality varies based on microsurgeon training and frequently suffers from poor alignment. Nerve Tape is a novel nerve coaptation device designed to precisely align and entubulate nerve ends for a mechanically secure repair. Epineurium-grabbing nitinol microhook arrays arranged in multiple rows are integrated within a thin and flexible biologic substrate. The resulting construct quickly and easily wraps around severed nerve ends for a mechanically precise and stable repair. Groups of small (1.5 to 2mm) and large (6.5 to 8mm) diameter cadaveric nerves were transected and repaired utilizing either microsutures or appropriately sized Nerve Tape devices. Free ends of the nerves were clamped onto a custom testing stage consisting of metal clamps, a force gauge and a motorized actuator. The repairs were distracted at a set rate of 40mm/min until failure while measuring and recording load forces. Both Nerve Tape groups exhibited markedly higher repairs strengths vs. the microsuture repair groups with significant difference ($p<.05$) observed in the small size nerve groups. Microsuture repairs tended to fail by rupture of the nerve while Nerve Tape failures resulted from microhook pull-out, without apparent damage to internal fascicles. Our novel coaptation device, Nerve Tape, provides mechanical repair strength comparable or superior to the clinical standard of microsuture neurorrhaphy.

Disclosures: G.S. Bendale: None. **M. Sonntag:** A. Employment/Salary (full or part-time):; Research Engineer. **I.P. Clements:** A. Employment/Salary (full or part-time):; Chief Technology Officer. **J.E. Isaacs:** None.

Poster

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P358.05

Topic: C.10. Brain Injury and Trauma

Support: NIH NINDS R44NS097113

Title: Design and development of a novel microhook-based device for suture-free repair of peripheral nerves

Authors: *M. SONNTAG[1], G. S. BENDALE[2], J. MCNEICE[1], J. ISAACS[2], I. CLEMENTS[1];
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Abstract: Although microsuturing is the current clinical standard practice for coapting the ends of a transected nerve in direct repairs, it is fundamentally flawed due to the inherent complexity to control the depth of penetration and tension of microsutures. Even with specialized microsurgical training, this method remains challenging to perform, frequently resulting in lengthy operating times and suboptimal repair outcomes. Further drawbacks of suturing include induced focal tension and persistent tissue

reactivity. Entubulation strategies, including wraps and cuffs, offer technical and biological advantages over microsuturing alone, but conduit-assisted repairs are still limited by the need for microsuturing to mechanically fixate the device to the transected nerve. Here, we describe the engineering design, development, and optimization of a biologic wrap with integrated microhooks for suture-free coaptation of peripheral nerves. Microhook geometries and densities were varied to accommodate multiple size ranges of nerves. Materials were selected to closely match the native tissue to create a composite structure with floating microhook columns which by design provide radial conformability and axial strength. Handling experiments and biomechanical testing on cadaver nerves demonstrated excellent handling properties, ease of use, and coaptation strength while significantly reducing the complexity and repair time. Microhooks were demonstrated to bind firmly, safely, and reversibly to the superficial nerve tissue, providing a means to distribute tension evenly across an array of hooks while also controlling the penetration depth. These results demonstrate the promise of a mechanical, suture-free means of nerve coaptation, for quick, consistent, repairs of high technical quality.

Disclosures: M. Sonntag: A. Employment/Salary (full or part-time):; BioCircuit Technologies. **G.S. Bendale:** None. **J. McNeice:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. **J. Isaacs:** None. **I. Clements:** A. Employment/Salary (full or part-time):; BioCircuit Technologies.

Poster

P358. Peripheral Nerve Injury: Methods of Repair

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P358.06

Topic: C.10. Brain Injury and Trauma

Support: NSF Grant OIA-1457888

Title: Application of mesenchymal stem cell-derived exosomes and TEMPO cellulose membrane for neuroregeneration in rats with sciatic nerve injury

Authors: *K. D. SHARMA[1], R. D. HILL[2], V. WALLEY[3], S. DACHAVARAM[5], J. P. MORE II[7], J. A. HESTEKIN[7], P. A. CROOKS[6], J. Y. XIE[4];
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Abstract: Exosomes possess therapeutic potential in various diseases including nerve injury. Exosomes are nanoscale vesicles released by many kinds of cells that contain a variety of RNAs and proteins to change the extracellular milieu and impact the functions of adjacent cells. We tested the effects of exosomes secreted by human bone marrow-derived mesenchymal stem cells on neuroregeneration of sciatic nerve after crush injury. TEMPO cellulose film, an oxidized form of micron cellulose with enhanced stability, was used to constrain exosomes at the injury site. Adult female rats received left sciatic nerve crush for 30 s. TEMPO cellulose film and/or exosomes were grafted directly onto the injured nerve segment. Locomotion and tactile allodynia were assessed at various days post-injury. Animals in the film+exosome and film only groups showed accelerated recovery of the ipsilateral hindlimb

locomotion and deterred development of tactile allodynia compared to the injury control group. Immunohistochemical studies showed better regeneration of axons in the film+exosome-treated group as well. No observable side effects were noticed. These results suggest that the combination of TEMPO cellulose and exosomes could be very useful to promote neuroregeneration induced by peripheral nerve trauma.

Disclosures: K.D. Sharma: None. **R.D. Hill:** None. **V. Walley:** None. **S. Dachavaram:** None. **J.P. More II:** None. **J.A. Hestekin:** None. **P.A. Crooks:** None. **J.Y. Xie:** None.

Poster

P358. Peripheral Nerve Injury: Methods of Repair

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Program #/Poster #: P358.07

Topic: C.10. Brain Injury and Trauma

Support: BMBF INOPRO project, 16SV7656
DFG EXC 1086

Title: Postural control and gait dynamics in unilateral transfemoral amputees

Authors: *T. KRAUSKOPF[1], F. PELKE[1], B. MEYER[1], P. MAIER[3], L. KLEIN[3], M. MUELLER[4], G. W. HERGET[3], P. DEIBERT[3], W. BURGARD[2], T. STIEGLITZ[1], C. F. PASLUOSTA[1];
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Abstract: The loss of a lower limb is accompanied by an increased difficulty to maintain balance and posture during walking. Gait instability caused by the lack of sensory feedback from the amputated limb and by neuromuscular adaptations to the use of the prosthesis leads to altered muscle synergies, gait asymmetry, and increased energy consumption during walking. To improve post-amputation therapies that restore sensory feedback, it is crucial to understand the neuromuscular mechanisms behind these motor output adaptations. The aim of this study was to investigate gait stability and dynamics in unilateral lower limb amputees. We focused on two aspects of postural control during gait, the stability of the pelvis and the dynamics of its stride-to-stride variability. Five unilateral transfemoral amputees and five age-matched able-bodied controls were recruited. Participants were instructed to walk for two minutes on a treadmill at 1, 2, and 3 km/h. Three-dimensional angular velocity and acceleration of the pelvis and of the upper and lower legs were recorded using a motion capture system based on inertial measurement units. Stride times were calculated by computing the time between peaks in the vertical acceleration of the intact/dominant foot. To assess pelvis stability, we computed the short-term (SLE) and long-term (LLE) Lyapunov exponents of its angular velocity, which quantifies the rate of divergence of neighboring trajectories in the state space, providing a measure of the stability of the postural system. The Entropic Half-Life (EnHL) method was used to measure the dynamics of the stride-to-stride fluctuations of the angular velocity of the pelvis. To avoid the influence of the periodicity of the gait cycle in the estimation of the stride-to-stride dynamics, a high-pass filter at the maximum frequency content of the angular velocity was applied previous to computing the EnHL. We compare outcomes of the SLE, LLE and the

EnHL between amputees and controls to explain how motor output adaptations caused by the amputation influence the complexity and stability of gait.

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Poster

P358. Peripheral Nerve Injury: Methods of Repair

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P358.08

Topic: C.08. Ischemia

Support: NIDDK Grant K23DK113119-02

Title: The Role of Cerebrovascular Reactivity in Maintaining Cerebral Oxygenation during Hemodialysis

Authors: *W. T. RICHERSON[1], B. D. SCHMIT[2], D. F. WOLFGRAM[3];
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Abstract: Background: Hemodialysis (HD) patients demonstrate significant white matter hyperintensity burden on neuroimaging which is thought to be a byproduct of cerebral ischemia. During hemodialysis treatments, patients are at risk for cerebral hypoperfusion due to rapid and large declines in systemic blood pressure. The risk for cerebral hypoperfusion may be greater if cerebrovascular reactivity is impaired. A recent study showed that HD patients have a decreased cerebrovascular reactivity (CVR) when measured by transcranial doppler ultrasound, even when compared to chronic kidney disease patients not receiving HD. We hypothesized that CVR combined with intradialytic blood pressure changes are associated with declines in cerebral oxygen saturation during HD. Study Methods: We collected demographic data, comorbidities, intradialytic measurements of blood pressure and cerebral oximetry, as well as resting state fMRI and anatomical MRI for participants on HD. CVR was determined using a resting state CVR pipeline developed to calculate regional CVR without a gas challenge. Regression analysis was used to examine the relationship between intradialytic oxygenation, intradialytic blood pressure changes and resting state CVR in different gray matter regions in the Harvard Oxford Brain Atlas.Results: MRIs were collected from 26 HD patients, mean age of 65.3 years old. CVR in the Anterior Cingulate Gyrus ($p=.0278$, $r^2=.186$) and Insular Cortex ($p=.026$, $r^2=.191$) regions negatively correlated with decline in intradialytic cerebral oxygenation. Multiple linear regression models using CVR and blood pressure as predictors of oxygenation drops demonstrated that the Anterior Cingulate Gyrus CVR and intradialytic systolic blood pressure changes were associated with oxygenation drops during HD ($p=.0075$, $r^2=0.346$). The Insular Cortex CVR and intradialytic systolic blood pressure changes were also associated with oxygenation decreases ($p=.0319$, $r^2=.259$). No other gray matter regions tested were significant and models using diastolic blood pressure changes and CVR were not

significant.Conclusions: We found significant relationships between resting state CVR measured in several different regions of the brain and decline in intradialytic cerebral oxygenation. In particular, CVR in the Anterior Cingulate Gyrus and systolic blood pressure changes explained about 35% of the variance in cerebral oxygenation deficits. This analysis shows that there is a relationship between the cerebral small vessels' ability to increase blood flow and cerebral oxygenation desaturation during HD.

Disclosures: W.T. Richerson: None. **B.D. Schmit:** None. **D.F. Wolfgram:** None.

Poster

P369. Spinal Cord Injury: Training, Rehabilitation, and Repair I

Location: Virtual Only

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Program #/Poster #: P369.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYSDOH SCIRB Contract C32248GG
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NICHD/NIH Grant R01HD100544

Title: Improvements in flexion reflex modulation in complete SCI after combined transspinal stimulation and step training

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Abstract: Spinal cord injury (SCI) severely impairs coordinated spinal reflex modulation and locomotor muscle activity and thus compromises walking ability and mobility. Locomotor training is a potent rehabilitation tool for stepping recovery that restores spinal reflex modulation and coordinated locomotor muscle activity. Excitingly, non-invasive spinal (termed here transspinal) stimulation may augment locomotor training benefits by enhancing the responsiveness of spinal locomotor networks to descending and sensory inputs that contribute to neurorecovery. Recent work has highlighted that higher frequency (e.g. > 100 Hz) spinal stimulation may be more advantageous than conventional spinal stimulation frequencies (5 to 40 Hz). Despite the therapeutic potential of interventions combining high-frequency transspinal stimulation and locomotor training little is known about the neurophysiological effects. Therefore, in this study we aimed to establish neurophysiological changes of spinal flexion reflexes following high frequency transspinal stimulation during robot assisted step training in individuals with chronic motor complete SCI. Four individuals with motor complete SCI received an average of 18 sessions of transspinal stimulation over the thoracolumbar region with a pulse train at 333 Hz during robotic assisted step training. Each session consisted of 60 min of walking, with an average of 240 stimulations delivered during each training session. Before and after the combined intervention, we measured the phase-dependent modulation of the long-latency tibialis anterior (TA) flexion reflex and transspinal evoked potentials(TEP) recorded from flexors and extensors during assisted stepping, and the TEP input-output recruitment curves at rest. The long-latency TA flexion reflex was depressed in all phases of the step cycle and the phase-dependent amplitude modulation of TEPs was altered during

assisted stepping, while spinal motor output based on TEP recruitment curves was increased after the combined intervention. This study shows that non-invasive high-frequency transspinal stimulation coupled with locomotor training depresses flexion reflex excitability and concomitantly increases motoneuron output over multiple spinal segments for both flexors and extensors in people with motor complete SCI. Our current findings support the use of transspinal stimulation to augment locomotor training induced neuroplasticity. However, combined interventions, such as transspinal stimulation and locomotor training, for rehabilitation of neurological disorders need to be systematically assessed.

Disclosures: M.O. Zaaya: None. **T.S. Pulverenti:** None. **M. Knikou:** None.

Poster

P369. Spinal Cord Injury: Training, Rehabilitation, and Repair I

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Program #/Poster #: P369.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Infrastructure Grant (SRALab)

Title: Inflammatory predictors of functional improvement following acute intermittent hypoxia in individuals with incomplete spinal cord injury

Authors: A. BARRY, R. BIBI, L. SIBLEY, W. Z. RYMER, A. DOMENIGHETTI, *M. SANDHU; Shirley Ryan AbilityLab, Chicago, IL

Abstract: An injury to the spinal cord (SCI) impairs motor control and mobility by disrupting the pathways between the brain and spinal cord. Current therapeutic strategies are mainly focused on improving preserved motor function, but they are ineffective. Acute intermittent hypoxia (AIH) is an emerging strategy to enhance neuroplasticity and recovery in SCI patients. It involves exposure to moderate levels of hypoxia (9% O_2), which has been shown to increase synaptic strength and motor neuron excitability in the animal models. AIH has been shown to be safe and effective for enhancing voluntary lower limb function in people with an incomplete SCI. In most published studies, about a third of individuals with SCI do not respond to AIH therapy. An increase in systemic inflammation, common among SCI patients, may be linked to some individuals not responding to AIH therapy. This study aimed to identify inflammatory or neuroplasticity biomarkers associated with responsiveness to AIH in individuals with chronic, incomplete SCI. In a randomized, double-blinded, placebo controlled study, ten subjects with incomplete SCI (ASIA C or D) visited the laboratory twice, at least a week apart, and received both AIH and sham AIH in a randomized manner. During AIH, the subjects were exposed to 15 60-second periods of hypoxia (9% O2) alternating with 60 seconds of normoxia (21% O2), for a total of 30 minutes. Sham AIH consisted of alternating exposures to normoxia. Maximal voluntary torque at the ankle joint was assessed prior to, and at 60 minutes post-AIH. We found 8 out of 10 patients responded to AIH as demonstrated by at least 10% increase in plantarflexion ankle strength. Ankle plantarflexion torque increased by 37.2 ± 11.1% following AIH, compared to 6.9 ± 3.8% change after sham AIH ($p < 0.05$ vs sham AIH). We measured plasma levels of pro-inflammatory markers IL-1β, IL-10, and TNF-α before and after AIH using enzyme-linked immunosorbent assays. In addition, plasma BDNF

concentrations were quantified. The levels of IL-1β and IL-10 were too low to be detected. Our preliminary data suggest a moderate association ($R^2 = 0.57$) between TNF-α levels and responsiveness to AIH therapy (i.e. change in plantarflexion strength after AIH). The relationship between baseline levels of plasma BDNF and strength change after AIH was weak ($R^2 = 0.15$). Consistent with previously published literature, our study found that a single session of AIH significantly improved a participant's ability to generate strength. Further, ongoing experiments indicate that inflammatory biomarker analyses may be used to target SCI patients who are most likely to respond to AIH therapies.

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Poster

P369. Spinal Cord Injury: Training, Rehabilitation, and Repair I

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Program #/Poster #: P369.03

Topic: C.11. Spinal Cord Injury and Plasticity

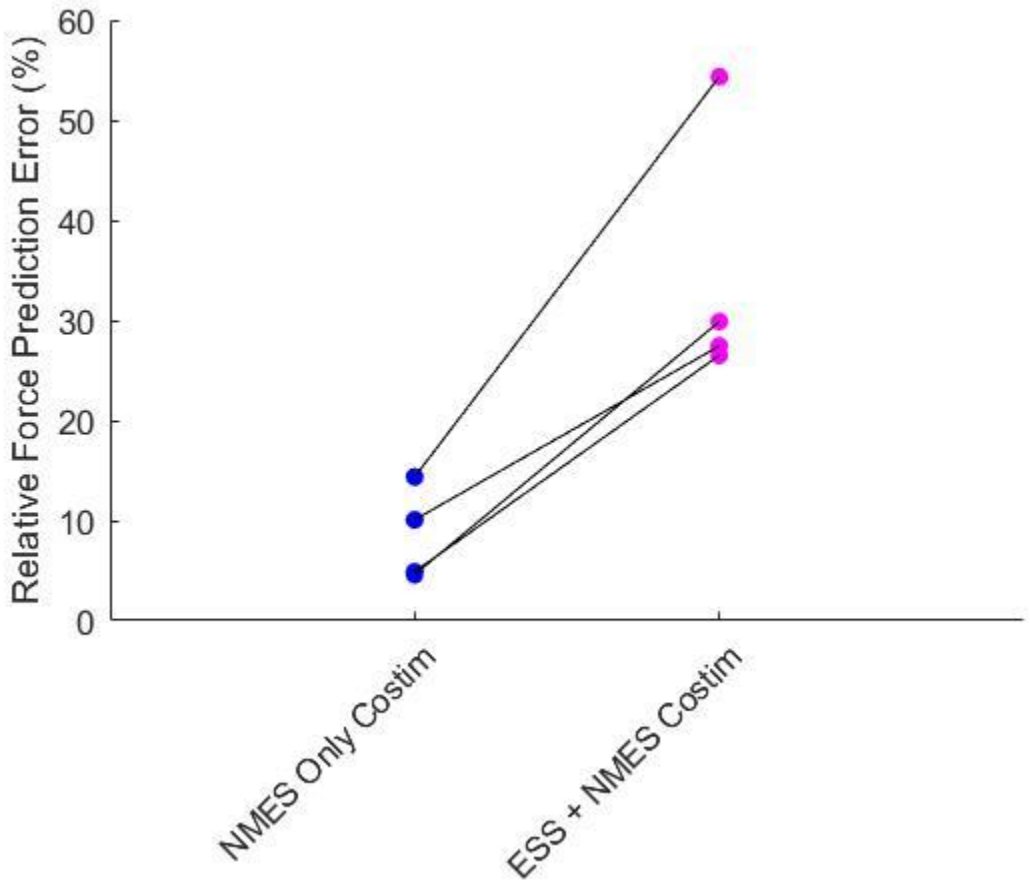
Support: NIH Grant 5R01NS112535-02

Title: Assessment of rat lower limb responses to combined epidural spinal cord and neuromuscular electrical stimulation for movement control

Authors: *D. SONG[1], M. C. TRESCH[1,3,2];
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Abstract: Electrical stimulation techniques such as epidural spinal cord stimulation (ESS) or neuromuscular electrical stimulation (NMES) are two commonly used approaches to restore lower limb movements after paralysis from spinal cord injury (SCI). However, using both techniques simultaneously has not been explored. A combined approach could potentially generate several complementary benefits. ESS can produce generic extension or flexion type movements, but granular control of these actions is difficult. Neuromuscular stimulation (NMES), on the other hand, can evoke more fine-tuned movements by selective muscle stimulation. Additionally, the fast fatigue motor units that are typically recruited by NMES may complement the more fatigue resistant motor units recruited by ESS potentially producing more energetically efficient movements. To develop control schemes using a combined ESS and NMES approach, we need to understand whether simultaneous stimulation produces predictable responses. One common assumption of NMES controllers is that forces produced by simultaneous stimulation of multiple muscles can be predicted by the forces produced by each muscle individually. Whether this holds true for combined ESS and NMES stimulation is unknown. To assess this, we evoked various hindlimb forces in anesthetized rats (n = 4) using different pairs of ESS and NMES inputs. A variety of current amplitudes as well as spinal cord and muscle stimulation sites were tested. We found that the average relative force prediction errors for combined ESS and NMES trials was higher than force prediction errors for muscle costimulation trials (paired t test, p = .013). This suggests that ESS and NMES, unlike muscle costimulation, interacts nonlinearly and may produce larger or smaller than expected forces.

Characterizing these interactions will be necessary to develop movement control schemes in spinal cord injured rats.



Disclosures: D. Song: None. **M.C. Tresch:** None.

Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
Kentucky Spinal Cord and Head Injury Research Trust
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Title: Interpretation of pedal reaction forces during motorized cycling in a rat model of spinal cord injury

Authors: *G. J. R. STATES[1], A. H. SHUM-SIU[2], T. ROUSSEL[3], D. M. ROUFFET[4], D. S. K. MAGNUSON[2];
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Abstract: As an alternative to traditional exercise, passive leg cycling (PLC) is often utilized with human patients with limited lower-limb function. Despite its widespread application, cardiovascular benefits of PLC reported in the literature are inconsistent. Passive hindlimb cycling (PHLC) in rodent models of SCI, however, has been shown to dramatically improve multiple indices of cardiac function, revealing an obvious and interesting discrepancy between the effects of PLC in humans and PHLC in rats. The mechanisms underlying the robust post-cycling improvements seen in rats are poorly understood. One potential mechanism is increased return of peripheral blood to the heart through spinal reflex activation of hindlimb muscles and the resulting effects of the skeletal muscle pump. Movement frequency directly influences the rate of muscle length change, which in turn may alter muscle activation through spinal reflexes and ultimately the force applied to the pedals. We hypothesized that stretch reflex pathways will be activated during PHLC causing activation of the muscles during their lengthening phase and resulting in pedal forces of detectable magnitude. To validate these hypotheses, we have developed a motorized rodent cycling ergometer that incorporates an embedded uniaxial force sensor in one pedal and a corresponding instrumentation system that allows the synchronization of recorded hindlimb kinematics and pedal reaction forces. Previous studies in our lab investigating rats with contusion and transection injuries demonstrated that a low frequency component of the pedal forces was associated with the motion of the pedal, while a high frequency component was presumably associated to spasticity. To differentiate between the low and high components of pedal forces, we created a frequency-domain method for separating forces developed with the motion of the pedal and the remaining high-frequency forces. Preliminary results from rats withT2-35 g-cm contusion injuries (n=5) cycled at cadences of 5, 10, 15, 30, 45, and 60 RPM suggest that low frequency component of the pedal forces increases for movement frequencies ranging from 30 RPM to 60 RPM, with the magnitude of this component typically ranging from10 to 30 percent body weight. Conversely, high frequency component of the pedal force was larger for movement frequencies below 30 RPM while the limb is in extension, with the magnitude of this component can range from 20 to over 100 percent body weight. Additionally, we are currently investigating how both components of this force influence instantaneous blood pressure and heart rate responses during PHLC using implantable telemetry devices.

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Poster

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Support: Craig H. Neilsen Foundation
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NIH (NINDS) (R01-NS104291

Title: Respiratory Training with Intermittent Hypercapnia to Enhances Supraspinal and Interneuronal Plasticity After Cervical Spinal Cord Injury

Authors: M. L. RANDELMAN[1], L. ZHOLUDEVA[2], T. FORTINO[1], H. KING[1], D. BILAS[1], M. LANE[1];
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Abstract: Cervical spinal cord injury (SCI) frequently leads to severe respiratory dysfunction due to damage of the phrenic circuit responsible for diaphragm innervation - the primary muscle of respiration. While some spontaneous functional plasticity occurs following cervical SCI, the extent is limited, and respiratory deficits persist. The goal of this ongoing research is to test whether a novel activity-based therapy – daily acute intermittent hypercapnia (IHc) – can enhance respiratory plasticity and diaphragm recovery sub-acutely (1wk) after mid-cervical contusion injury in the adult female rat. We hypothesized that rehabilitation with this respiratory-specific therapy will stimulate anatomical and functional phrenic plasticity and improve diaphragm function post-SCI. Anatomical plasticity following injury and treatment was investigated using anterograde tracing of descending respiratory axons with biotin dextran amine (BDA) and transsynaptic retrograde tracing with pseudorabies virus (PRV) to label phrenic circuitry within the cervical spinal cord. Immunohistochemistry was used to assess changes in phrenic interneuron integration and supraspinal (serotonergic and bulbospinal respiratory axons) onto phrenic circuitry. Functional plasticity and respiratory recovery following IHc training were assessed with terminal diaphragm electromyography (dEMG). Hypercapnia trained animals showed a greater density of serotonergic and bulbospinal respiratory axons within denervated phrenic circuitry below the lesion epicenter compared with air-treated control animals. It was also found that four weeks of IHc training resulted in a greater recruitment of interneurons - including cholinergic interneurons - into ipsilateral and contralateral phrenic circuitry when compared to controls. Diaphragm EMGs of the IHc trained animals resulted in a significant improvement in diaphragm inspiratory amplitude and response to a respiratory challenge. Correlating anatomy and function changes revealed a significant, positive correlation between the number of phrenic interneurons that were connected to the phrenic network and recovered diaphragm function. These results, therefore, suggest that IHc can promote plasticity within the phrenic network and improve breathing following cervical SCI.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Department of Defense CDMRP W81XWH1810718

Title: Acute Intermittent Hypoxia and Respiratory Strength Training to Improve Respiratory Function in Individuals with Chronic Spinal Cord Injury: Preliminary Outcomes

Authors: *A. K. VOSE[1], J. WELCH[1], J. NAIR[1], K. CAVKA[2], L. DEMARK[2], G. BRUNETTI[2], C. WAUNEKA[2], H. SNYDER[2], G. MITCHELL[1], E. FOX[1];
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Abstract: Background: Spinal cord injury (SCI) disrupts neural pathways to respiratory motor neurons, causing paralysis and decreased breathing capacity. Since respiratory impairment is a major cause of illness and death in SCI, it is critical to devise new strategies to restore breathing function. Acute intermittent hypoxia (AIH) is a promising therapeutic modality that elicits spinal synaptic plasticity, improving breathing in animal models of SCI. AIH also elicits plasticity in limb motor systems in both rodent models and humans with chronic SCI, where functional gains are greatest when paired with task specific training. The impact of similar combinatorial treatments on breathing ability is unknown. Here, we report breathing outcomes in four adults with chronic SCI who received AIH and task specific training (respiratory strength training; RST).
Subjects: Four males with chronic SCI (36.3 ± 18.5 yrs of age; 1.5-15 yrs post-SCI; 3 cervical, 1 thoracic injury; C4-T6 AIS A-D). Respiratory function was 39% ± 10% of the age predicted normative function for expiratory pressure generation and 88% ± 23% of normative values for inspiratory function.
Methods: Participants completed two random ordered 5-day protocols AIH+RST and Sham, 3+ weeks apart. AIH consisted of 15, 1-minute episodes of breathing a hypoxic gas mixture (9% oxygen), interspersed with 1.5-minute episodes breathing room air (21% oxygen). Thirty minutes after AIH, RST involved both inspiratory and expiratory training; 4 sets of 6-12 breaths with the pressure threshold device set to 80% of each individual's maximum. Sham treatments replicated AIH but used room air. Maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and forced vital capacity (FVC) were assessed prior to and 1-day post-intervention.
Results: MIP increased 9% and MEP increased 5% 1 day after AIH+RST but not after Sham. MIP (AIH+RST: pre 118 ± 24 cmH20, post 129 ± 27 cmH20; Sham: pre 123 ± 36 cmH20, post 123 ± 36 cmH20). MEP (AIH+RST: pre 77 ± 18 cmH20, post 81 ± 21 cmH20; Sham: pre 74 ± 23 cmH20, post 74 ± 17 cmH20). No changes in FVC were evident (AIH+RST: pre 4.1 ± 1.0L, post 4.1 ± 1.1L; Sham: pre 4.15 ± 1.1L, post 4.2 ± 1.2L) given ≤1% change pre/post. Following AIH+RST, MIP increased 6-21% in 3/4 participants with a 1% decrease in 1 participant, and MEP increased 1-11% in 3/4 participants with a 6% decrease in 1 participant.
Conclusions: Preliminary outcomes suggest AIH+RST may improve respiratory function in adults with SCI. Next steps will be to test in more individuals and compare this combinatorial treatment to AIH and RST alone to determine if effects are synergistic. Research examining individual response variations is also warranted.

Disclosures: A.K. Vose: A. Employment/Salary (full or part-time):; University of Florida. **J. Welch:** A. Employment/Salary (full or part-time):; University of Florida. **J. Nair:** A. Employment/Salary (full or part-time):; University of Florida. **K. Cavka:** A. Employment/Salary (full or part-time):; Brooks Rehabilitation. **L. DeMark:** A. Employment/Salary (full or part-time):; Brooks Rehabilitation. **G. Brunetti:** A. Employment/Salary (full or part-time):; Brooks Rehabilitation. **C. Wauneka:** A. Employment/Salary (full or part-time):; Brooks Rehabilitation. **H. Snyder:** A. Employment/Salary (full or part-time):; Brooks Rehabilitation. **G. Mitchell:** A. Employment/Salary (full or part-time):; University of Florida. **E. Fox:** A. Employment/Salary (full or part-time):; University of Florida.

Poster

P369. Spinal Cord Injury: Training, Rehabilitation, and Repair I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P369.07

Topic: C.11. Spinal Cord Injury and Plasticity

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Pictet foundation

Title: Decoding lower limb movements from cortical activity towards a brain spine interface for spinal cord injury patients

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Abstract: We aim to establish a neuroprosthetic bridge between the sensorimotor cortex and the dormant neurons located in the spinal cord that are deprived of brain inputs due to a spinal cord injury (SCI). These dormant neurons located in the lumbosacral spinal cord can be reactivated by electrical epidural stimulation (EES) of the spinal cord. This digital bridge, also called a brain-spine interface, aims to restore mobility and promote neurological recovery in people who are chronically paralyzed.
We determined the potential and limitations of electroencephalography (EEG) and electrocorticography (ECoG) signals to control a brain-spine interface. We developed a computational framework for decoding gait events from features using high-density EEG or ECoG recordings. Our EEG framework is based on the accurate source localization to extract time-frequency features from sensorimotor cortical areas. This analysis was conducted on signals recorded from 6 healthy participants, 6 participants with SCI with different injury classification (ASI A-D) and two participants with chronic pain who were implanted with ECoG electrodes over the sensorimotor cortex as part of paint treatment. The people with SCI were implanted with neurostimulation system to reactivate the lumbar spinal cord (EES) as part of an ongoing "STIMO" clinical trial.
In EEG signals, we identified beta band modulations time-locked with gait events during different walking tasks. The average decoding accuracy between right and left stepping achieved using these features in healthy volunteers was 64% SD 7.3. In people with SCI this performance was reduced despite state-of-the-art denoising methods. However, decoding performance was significantly higher (90% SD12.2) in a more controlled, single-joint movement task. Therefore we enabled 4 people with SCI to control their EES spinal stimulation using these EEG features while seated. The output probability of the decoder was mapped to the EES amplitude. This brain-spine interface allowed all people with SCI to regain graded control over single joint movements. Our analysis of ECoG signals reaffirmed the beta band modulations previously found in EEG signals, additionally we identified features in the gamma band

which substantially increased the accuracy of decoding of gait events rising to 90% on average. We demonstrated the feasibility of EEG-based decoders for lower-limb neurorehabilitation therapies in a controlled environment but also highlighted the limitations of this approach to operate a gait prosthesis. Our results indicate that epidural ECoG may provide a good trade-off in between invasiveness and efficacy when controlling gait prostheses.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS104194
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Title: Impacts of epidural spatial stimulation effects on recovery and spasticity in combined bionic and biological SCI therapies

Authors: *A. P. BORISYUK, K. J. DOUGHERTY, S. F. GISZTER;
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Abstract: Spinal cord injury (SCI) is a debilitating condition without a cure. Our lab has previously demonstrated enhanced locomotor outcomes in rats with complete T9/10 SCI after combining viral BDNF treatment and pelvis-based robot training. Combining epidural stimulation (ES) with viral BDNF and pelvis-based rehabilitation further enhanced these outcomes. Interestingly, a combined treatment with robot rehabilitation at the ankle and ES didn't result in outcomes to levels as high as viral BDNF treatment with pelvic-based robot weight-supported treadmill training alone (no ES). Relative to the viral BDNF effects, our prior work has demonstrated the possibility of a critical period during the initial two weeks of training where ES likely helps prevent development of some spasticity side effects of the viral BDNF treatment on motor function, in the experiments using pelvic centered rehab. These cumulative side effects can result in the eventual collapse of gained motor function in ~40% of rats. This collapse was completely prevented when broad current spread ES centered at L2 and S1 was combined with viral BDNF and pelvic-based robot training. We hypothesized that the combined treatment of viral BDNF with localized ES and pelvic based robot training would result in improvement in weight-supported stepping throughout therapy due to the better selectivity. The current study aims to measure the changes in modularity and compare the improvement in functional outcomes in rats with complete SCI through rehab combining viral BDNF, pelvic-based training, and (a) broad versus (b) local ES. Our data so far show that the more focused local ES does not prevent spastic collapse later in BDNF treated rats if used alone. In

contrast to the broad current spread ES, more focused current delivery at L2 and S1 did not mitigate spastic collapse. While our best combination treatment utilized broad ES (broad ES centered on L2 and S1 spinal segments), we next aim to improve the therapy with the combined use of intense but more local ES in parallel to the broad ES current delivery, most intensely stimulating only segments containing central pattern generators for locomotion and extensor support by (focusing intense current locally to L2 and S1, in parallel with a broader delivery to avoid the spastic effects). We hypothesize that modularity analysis of the hindlimb muscles will help reveal the patterns of change during an initial period of reorganization of spinal circuit and then a subsequent stabilization in the different ES and rehabilitation treatments.

Disclosures: A.P. Borisyuk: None. **K.J. Dougherty:** None. **S.F. Giszter:** None.

Poster

P369. Spinal Cord Injury: Training, Rehabilitation, and Repair I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS RO1 NS109552

Title: Electrical stimulation of intact spinal cord activates broader range of muscles than anatomical motor pool

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Abstract: Background: Direct electrical spinal cord stimulation shows promise as a therapy for patients with motor impairments after spinal cord injury. The anatomical location of the motor pools for muscles used in locomotion has been identified. However, the map of surface electrical stimulation of the spinal cord and its functional output to different muscles is still relatively unknown and represents a significant gap in knowledge in spinal cord injury rehabilitation. Objective: Our goal was to determine what hindlimb muscles are activated by surface electrical stimulation of the lumbar spinal cord of the cat. Methods: In 8 decerebrate cats with intact spinal cords, eleven locations were stimulated starting from the caudal portion of lumbar segment L3 to the border of sacral segments S1 and S2. Stimulation was done 15 times at each location at 1 Hz with stimulation amplitudes high enough to evoke muscle responses without causing tissue injury. EMG was measured in 9 hindlimb muscles: soleus, tibialis anterior, lateral gastrocnemius, sartorius, medial gastrocnemius, vastus lateralis, biceps femoris posterior, gluteus medius, and pectineus. EMG peak to peak amplitude of the short-latency response (presumably monosynaptic) was used to assess muscle response. Results: For most muscles, the most effective stimulus was at or near the center of the anatomical location of the motor pool. However, some muscles, including the sartorius, and medial and lateral gastrocnemius, were strongly activated outside of their motor pools. Additionally, stimulation at most locations activated multiple muscles with diverse, even antagonistic functions.

Conclusion: These results suggest that surface electrical stimulation of the spinal cord can activate some muscles outside the anatomical location of their motor pools. This broader range of muscles activated by stimulation likely further expands following spinal cord injury. This indicates that surface spinal stimulation used for treatment of spinal cord injury is unlikely to generate specific movement patterns, and thus must be approached with a more holistic understanding of the broad array of muscles and even their antagonists that may be activated by specific stimulation.

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Poster

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Title: Spinal stimulation for motor rehabilitation differentially modulates nociceptive and non-nociceptive sensory transmission

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Abstract: Spinal cord injury (SCI) leads to radical physiological changes at and below the lesion. SCI usually results in dysregulation of spinal reflexes, reduction of voluntary motor output below the lesion, and neuropathic pain. Spinal stimulation-based therapies intended to enhance motor rehabilitation after SCI often fail to consider modulation of neural transmission in spinal sensory pathways, including pathways integral to SCI-related neuropathic pain. Here, we used spike train analyses to characterize the effects of intraspinal microstimulation of the ventral horn (vISMS) on the firing dynamics of sensory neurons (e.g., nociceptive specific, NS; and wide dynamic range, WDR) in the dorsal horns *in vivo*. All experiments were approved by the Institutional Animal Care and Usage Committees of Florida International University and Washington University in St. Louis and were conducted in adult male Sprague-Dawley rats under urethane anesthesia (n=6). After T13-L2 laminectomy, microelectrode arrays were implanted at the L5 dorsal root entry zone. Electrode locations for spinal stimulation targeted the ventral horn region, whereas their locations for quantifying neural transmission in sensory pathways spanned the superficial and deep dorsal horns. Prior to, during, and after vISMS, we mechanically stimulated the L5 dermatome by applying controlled forces ranging from non-painful to painful. Primary outcome measures included the number of sensory neurons in the dorsal horns, changes in the temporal profile of their neural activity (assessed via peristimulus time histograms of single-neuron spike times), and changes in their temporal features (e.g., mean frequency, and mean intra-burst frequency). The

threshold for detecting a change after vISMS was ≥20% difference in a given parameter.
We found that even short periods of vISMS (≤10min) could modulate neural transmission in pain and non-pain-related pathways of the dorsal horn. Our results showed that 45% of NS (n=60) and 29% of WDR (n=452) neurons reduced their mean intra-burst frequency (number of spikes during painful mechanical stimulation of the dermatome over the duration of the stimulus) after vISMS, whereas 18% of NS and 23% of WDR neurons increased their mean intra-burst frequency after vISMS.
Our results suggest that vISMS paradigms may reduce transmission in spinal pain pathways while continuing to enhance spinal motor output. Future work is required to elucidate potential mechanisms behind the modulation of spinal pain transmission by vISMS, and to optimize the therapeutic effects of vISMS in motor output and pain transmission.

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Poster

P388. Treatments for Persistent Pain I

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS102850

Title: Assessment of spinal cord stimulation-based modulation in the spontaneous hyperexcitability model of neuropathic pain

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Abstract: Spinal cord stimulation (SCS) is used clinically for relief of chronic neuropathic pain. The gate control theory presents a theoretical framework of the therapy's mechanism of action associated with Aβ sensory afferent recruitment, but the true mechanisms remain unclear. Preclinical studies frequently investigate mechanisms leading to modulation of stimulus-evoked pain, despite the primary function of therapeutic SCS being modulation of chronic, stimulus-independent pain. Here, we utilized an *ex vivo* spinal cord-dorsal root ganglia preparation to generate a model of spontaneous hyperexcitability in sensory nociceptive circuits using 4-aminopyridine (4-AP). Applied 4-AP selectively increased Fos immunolabeling in superficial dorsal horn neurons - consistent with selective recruitment of pain circuitry (n=2). We characterized spontaneous activity by recording from sensory afferents in lumbar dorsal roots (DR), Lissauer's tract (LT), and neurons in the superficial dorsal horn (DH). 4-AP led to the emergence of spontaneous activity manifesting as rhythmic dorsal root potentials with superimposed burst firing, and coincident rhythmic field potentials with superimposed spikes in LT and the subjacent DH (n=4). To investigate modulation of spontaneous nociceptive activity by gate control theory mechanisms we assessed the effects of clinically analogous SCS at dorsal column (DC) and dorsal root (DR) recruitment threshold intensities. We observed that 50 Hz SCS at DC threshold intensity depressed spiking activity in LT/DH during SCS, but it could not modulate field potentials or produce prolonged modulation following cessation of stimulation (n=4). These results demonstrate the utility of a 4-AP model of spontaneous

hyperexcitability and the limitations of presumed selective Aβ recruitment as underlying SCS modulation of spontaneous nociceptive activity.

Disclosures: S. Idlett-Ali: None. **M. Sawchuk:** None. **S. Hochman:** None.

Poster

P388. Treatments for Persistent Pain I

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Program #/Poster #: P388.02

Topic: D.03. Somatosensation – Pain

Title: Spinal cord stimulation (SCS) evokes irregular activity from dorsal column (DC) axons

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Abstract: Conventional tonic SCS generates pain relief by activating DC axons but also generates concomitant paresthesias. Recent SCS paradigms reduce the amplitude of stimulation to subperception amplitudes to avoid these uncomfortable paresthesias, but the mechanisms underlying pain relief with these approaches remains unclear. We hypothesized that low-amplitude, low-frequency SCS activates DC axons at frequencies less than the SCS frequency, thereby producing asynchronous spiking. We tested this hypothesis *in vivo* by placing a bipolar electrode paddle under the T10-T11 vertebrae and recording from single DC axons underneath the T12-L1 vertebrae in urethane anaesthetized male rats. We recorded the responses of 24 axons across 8 rats to symmetric biphasic 90 Hz SCS at amplitudes just above each axon's activation threshold (AT). Stimulation amplitudes from 1-1.4x AT resulted in axonal spiking at frequencies <90 Hz. Stimulation at 1-1.1x AT evoked spikes from approximately 25-65% of axons per pulse, and stimulation at 1.1-1.2x AT evoked spikes from approximately 65-90% of axons per pulse. On average, full axon entrainment to the stimulation frequency, i.e., following at 90 Hz, occurred at 1.21x AT, and no axons were entrained by stimulation <1.1x AT. Additionally, we found that axonal spiking at <90 Hz generally consisted of "bursts" of spikes at 90 Hz interspersed with short gaps of quiescence with varying length, in contrast to our expectation that responses would be regular firing at some divisor of 90 Hz (e.g. 10, 30, or 45 Hz). The "bursting" responses were generally characterized by two dominant frequencies: the intraburst frequency equal to the stimulation frequency and the gap frequency, which defined the interval between bursts (typically 1-8 stimulation pulses). The number of spikes per burst varied greatly from a few spikes to hundreds. Increasing or decreasing the SCS amplitude increased or decreased, respectively, both the burst length and gap frequency, but did not affect the intraburst frequency. These results demonstrate that amplitudes of SCS just above AT can generate axon spiking at frequencies less than the stimulation frequency and confirmed that low-amplitude, low-frequency stimulation produced asynchronous axonal responses. Additionally, low-amplitude, tonic SCS can evoke "bursting" patterns from DC axons. The asynchronous and bursting nature of axonal responses to low-amplitude, low-frequency SCS may help to determine the mechanism through which sub-perception SCS paradigms produce analgesia without generating paresthesia.

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Poster

P388. Treatments for Persistent Pain I

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Topic: D.03. Somatosensation – Pain

Support: Conacyt (Grant A-S1-40015)
SEP-Cinvestav (Grant 127)
IASP early career research grant (PB-I)

Title: Antiallodynic effect of α-lipoic acid is associated with the reduction of the integrated stress response in a model of neuropathic pain in mice.

Authors: *S. MUÑOZ-LOMBARDINI[1], P. BARRAGAN-IGLESIAS[2], V. GRANADOS-SOTO[1]; [1]Dept. De Farmacobiología, CINVESTAV, Mexico City, Mexico; [2]Dept. of Physiol. and Pharmacol., Univ. Autónoma de Aguascalientes, Aguascalientes, Mexico

Abstract: Painful diabetic neuropathy is a complication generated by chronic hyperglycemia, a condition of patients with Diabetes mellitus. Diabetic patients with pain have elevated concentrations of plasma methylglyoxal (≥600 nM). By itself, methylglyoxal (MGO) generates mechanical hypersensitivity by the activation of the integrated stress response (ISR) in mouse dorsal root ganglion (DRG) neurons. Preclinical pain models and clinical trials have shown that α-lipoic acid (ALA) reduces mechanical hypersensitivity in diabetic rodents and humans, respectively. Interestingly, ALA reduces the phosphorylation of eukaryotic initiation factor 2α (eIF2α) (main marker of ISR activation) in cell cultures pretreated with high doses of glutamate or other drugs that activate ISR. However, the effect of ALA on the ISR in tissues involved in pain transmission is unknown. The purpose of this study was to investigate the effects of ALA on tactile hypersensitivity and phosphorylation of eIF2α in DRG and spinal cord in MGO-induced model of neuropathic pain in mice. Tactile allodynia was assessed with Von Frey filaments and phosphorylation of eIF2α was determined by western blotting. Intraplantar (0.72 [0.4], 7.2 [4], 72 [40], and 720 [400] ng (μM) or intraperitoneal injection (2 mg/kg) of MGO induced tactile allodynia in female and male Swiss Webster mice. MGO generated tactile hypersensitivity in female mice starting the first hour post-administration and returning to baseline on different days depending on the dose. Oral (100-300 mg/kg) and intraperitoneal (5.6-30 mg/kg) administration of ALA, but not vehicle,

partially reversed MGO-induced tactile allodynia in female mice. Intraperitoneal administration of ALA (10 mg/kg) produced a similar effect in male and female mice on MGO-induced neuropathy. ALA (10 mg/kg) had no effect *per se.* These results suggest that the antiallodynic effect of ALA is associated with the mechanisms that generate the pronociceptive effects of MGO in mice. Accordingly, MGO enhanced phosphorylation of eIF2α, while ALA blocked MGO-induced effects on eIF2α at DRG but not spinal cord. Data suggest that antiallodynic effect of ALA is associated with a reduced phosphorylation of eIF2α in peripheral sensory neurons.

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Poster

P388. Treatments for Persistent Pain I

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant U18 EB029251
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Title: Electrophysiological effects of dorsal root ganglion stimulation on C-type neurons

Authors: *A. S. JHAND[1,3], R. D. GRAHAM[1,3], S. F. LEMPKA[1,3,2];
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Abstract: Dorsal root ganglion stimulation (DRGS) has shown promise for managing chronic pain, but fails to provide pain relief in some patients. We do not understand the mechanisms of action of DRGS, preventing us from optimizing the outcomes of this therapy. Low-pass filtering has been observed at the bifurcation (T-junction) of C-type dorsal root ganglion (DRG) neurons, preventing some action potentials (APs) in high frequency trains from propagating into the central axon from the periphery. Animal models have shown that this filtering ability is diminished in chronic pain states. It has been hypothesized that DRGS may restore this low-pass filtering ability by modulating C-type neuron activity, but computational and experimental studies have reported conflicting findings on the activation of C-neurons during DRGS. Therefore, we developed a computer model to investigate the possible biophysical mechanisms of DRGS-induced C-neuron activation and low-pass filtering at the T-junction.
We constructed a three-dimensional finite element method (FEM) model of a human L5 DRG using published data from experimental and cadaver studies. We developed a multi-compartment model of a nonmyelinated C-type neuron. The model included Hodgkin-Huxley style representations of voltage-gated sodium (Nav1.7, Nav1.8, Nav.19), potassium (KDR, KA, KCNQ), and calcium (L-type) channels. We also included a small-conductance calcium-dependent potassium channel.
The C-type neuron model reproduced previously published *in vitro* somatic calcium traces (amplitude and decay time). The model also produced following frequencies (i.e., the maximal frequency at which all pulses in an afferent train propagate into the central axon) in the range observed experimentally. We then

coupled the multi-compartment C-type neuron model to the FEM model of DRGS to simulate the effect of DRGS on unmyelinated C-type neurons. Activation thresholds (i.e., the stimulation amplitude needed to induce an AP) of this novel C-type neuron model were in the range observed in previous computer modeling studies.
We are currently investigating the mechanisms by which DRGS may augment the low-pass filtering behavior at the T-junction and the effects of cell morphology and stimulation parameters on C-type neuron dynamics during DRGS. These results may provide further insights into the mechanisms by which DRGS produces pain relief. A clear understanding of the mechanisms of action of DRGS will help to optimize the therapy to improve patient outcomes.

Disclosures: A.S. Jhand: None. **R.D. Graham:** None. **S.F. Lempka:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Medtronic, Inc, Presidio Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hologram Consultants, LLC, Presidio Medical. F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation.

Poster

P388. Treatments for Persistent Pain I

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Topic: D.03. Somatosensation – Pain

Support: DoD Grant MR141214
Miami Project to Cure Paralysis
Lois Pope Fellowship Award

Title: Multidimensional chronic neuropathic pain phenotypes after traumatic brain injury

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Abstract: Chronic pain is a debilitating condition that affects more than 50% of people following traumatic brain injury (TBI), yet effective treatment is still lacking. Characterizing pain phenotypes may lead to a better understanding of underlying pain mechanisms and contribute to developing effective treatment approaches for TBI-related chronic pain. Thus, in the present study, we 1) evaluated up to three different pains in individuals with TBI-related chronic pain (N = 25, males = 14, females = 11), 2) identified neuropathic pain phenotypes in nineteen (N = 19) of these participants, based on neuropathic pain symptom inventory (NPSI) scores, and 3) compared the phenotypes on somatosensory and psychological function, and psychosocial impact of pain. Our results showed that individuals with TBI-related chronic pain experienced multiple simultaneous pains characterized by nociceptive and neuropathic pain symptoms. A two-step cluster analysis indicated two pain phenotypes: high neuropathic

pain symptom severity (HNP, N = 11) and low neuropathic pain symptom severity (LNP, N = 8). The HNP phenotype experienced significantly more severe pressing, paroxysmal, evoked pain, and paresthesia/dysesthesia than the LNP phenotype. Regarding somatosensory function, assessed by quantitative sensory testing (QST), the HNP phenotype exhibited cold hyperalgesia and vibration hypoesthesia on the forehead, possibly due to spinal or supraspinal sensitization, reduced inhibition, or deafferentation. In contrast, the LNP phenotype exhibited pressure hypoalgesia on the right medial calf suggesting neuronal dysfunction. These findings indicate an altered somatosensory function in both phenotypes compared to healthy, pain-free individuals. In addition, the HNP phenotype scored significantly higher on overall pain severity ($t(1,17) = 4.14$; $p = 0.001$), post-traumatic stress disorder ($t(1,17) = 3.66$; $p = 0.002$), anxiety ($t(1,17) = 4.28$; $p = 0.001$), depression ($t(1,17) = 4.01$; $p = 0.001$), and affective distress ($t(1,17) = 4.14$; $p = 0.001$) than the LNP phenotype. These results indicate that more severe neuropathic pain symptoms are associated with greater somatosensory alteration, psychological dysfunction, and affective distress that negatively impact the quality of life after TBI. Collectively, our findings further the understanding of pain phenotypes associated with TBI-related chronic pain. Future work is required to fully characterize the underlying mechanisms of this condition and ultimately develop phenotype-based treatment approaches.

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Poster

P388. Treatments for Persistent Pain I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P388.06

Topic: D.03. Somatosensation – Pain

Support: NIH Grant GM115384 (J.W.)

Title: Disrupted population coding in the prefrontal cortex underlies pain aversion

Authors: A. LI[1,5], Y. LIU[1], Q. ZHANG[1,5], I. FRIESNER[1,5], ***H. JEE**[1], Z. S. CHEN[5,2,3,4], J. WANG[1,5,2,4]; [1]Dept. of Anesthesiology, Perioperative Care, and Pain Med., [2]Dept. of Neurosci. and Physiol., [3]Dept. of Psychiatry, [4]Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; [5]Interdisciplinary Pain Res. Program, New York Univ. Langone Hlth., New York, NY

Abstract: The prefrontal cortex (PFC) regulates a wide range of sensory experiences, and recent studies indicate that neurons in the PFC can increase their firing rates in response to noxious stimuli. Chronic pain is known to impair the endogenous neural response to these noxious inputs, leading to enhanced pain aversion. However, it remains unknown how nociceptive responses in the cortex are processed at the population level, and whether such processes are disrupted by chronic pain. We, therefore, sought to investigate whether the PFC utilizes population coding to process pain information, and if so, how chronic pain affects this coding scheme. Using *in vivo* endoscopic calcium imaging, we tracked calcium activity in the prelimbic PFC (PL-PFC) of freely-behaving rats before and after delivering a noxious mechanical stimulus or a control, non-noxious stimulus. We identified increased population activity in

response to noxious stimuli, and using the graph-theoretic functional connectivity analysis, found stable patterns of functional connectivity among neurons in the PL-PFC. We also discovered that persistent inflammatory pain, modeled by injecting Complete Freud's Adjuvant (CFA) to the rat's hind paw, disrupts PL-PFC neurons' functional connectivity and reduces the overall nociceptive response. Interestingly, a single sub-anesthetic dose of ketamine, a neuromodulator used to treat a number of neuropsychiatric diseases including chronic pain, restores the functional connectivity among PL-PFC neurons in the chronic pain state to produce anti-aversive effects. These results suggest a dynamic resource allocation mechanism in the prefrontal representations of pain, and indicate that population activity in the PFC critically regulates pain and may serve as an important therapeutic target in chronic pain management.

Disclosures: A. Li: None. **Y. Liu:** None. **Q. Zhang:** None. **I. Friesner:** None. **H. Jee:** None. **Z.S. Chen:** None. **J. Wang:** None.

Poster

P388. Treatments for Persistent Pain I

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Program #/Poster #: P388.07

Topic: D.03. Somatosensation – Pain

Support: NIH SPARC Grant U01 NS113873
NIH Grant R01 DK120824
NSF CAREER Award 1844762

Title: Blocking peripheral drive from colorectal afferents by sub-kilohertz DRG stimulation

Authors: *B. FENG[1], L. CHEN[1], T. GUO[1], S. ZHANG[1], P. P. SMITH[2];
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Abstract: Clinical evidence indicates dorsal root ganglion (DRG) stimulation effectively reduces pain without the need to evoke paresthesia. This paresthesia-free anesthesia by DRG stimulation can be promising to treat pain from the viscera, where paresthesia usually cannot be produced. Here, we explored the mechanisms and parameters for DRG stimulation using an *ex vivo* preparation with mouse distal colon and rectum (colorectum), pelvic nerve, L6 DRG, and dorsal root in continuity. We conducted single-fiber recordings from split dorsal root and assessed the effect of DRG stimulation on afferent neural transmission. We determined the optimal stimulus pulse width by measuring the chronaxies of DRG stimulation to be below 216 μsec, indicating spike initiation likely at attached axons rather than somata. Sub-kilohertz DRG stimulation significantly attenuates colorectal afferent transmission (10, 50, 100, 500 and 1000 Hz), of which 50 and 100 Hz show superior blocking effects. Synchronized spinal nerve and DRG stimulation reveals a progressive increase in conduction delay by DRG stimulation, suggesting activity-dependent slowing in blocked fibers. Afferents blocked by DRG stimulation show a greater increase in conduction delay than unblocked counterparts. Mid-range frequencies (50-500 Hz) are more efficient at blocking transmission than lower or higher frequencies. In addition, DRG stimulation at 50 and 100 Hz significantly attenuates *in vivo* visceromotor responses to noxious colorectal balloon

distension. This reversible conduction block in C- and Aδ-type afferents by sub-kilohertz DRG stimulation likely underlies the paresthesia-free anesthesia by DRG stimulation, thereby offering a promising new approach for managing chronic visceral pain.

Disclosures: B. Feng: None. **L. Chen:** None. **T. Guo:** None. **S. Zhang:** None. **P.P. Smith:** None.

Poster

P388. Treatments for Persistent Pain I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P388.08

Topic: D.03. Somatosensation – Pain

Support: Consortium for Medical Marijuana Clinical Outcomes Research

Title: Assessing synergistic pain-reducing potential of cannabis components cannabidiol and β-caryophyllene using a rat SCI pain model

Authors: *A. PACHECO-SPIEWAK, A. EESWARA, S. GROSS, S. JERGOVA, J. SAGEN; Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: Medical marijuana is most frequently reported to be used for pain relief, however there is a paucity of preclinical studies evaluating the effects of cannabis components in chronic pain models. Anecdotal observations show patients with spinal cord injuries (SCI) experience significant pain relief using marijuana and its medicinal extracts. Thus, the goal of this study was to evaluate the effects of two cannabis components, cannabidiol (CBD) and β-caryophyllene (BCP), and their potentially synergistic pain-relieving combination. Male and female Sprague-Dawley rats received spinal cord injuries using a clip compression model at mid-thoracic levels. First, we conducted dose-response analyses for both CBD and BCP using a battery of behavioral tests including the Von Frey test, the acetone evaporation test, and the Hargreaves test. Animals were evaluated for the presence of tactile and cold hypersensitivity every 30 mins up to 2 hours, at 5 hours and 24 hours post drug administration, starting at 4 weeks post SCI. Drugs were administered by i.p injection (CBD, saline) or oral gavage (BCP). Dose response analyses were conducted to determine A50 doses for individual drugs to be used in the combination. Possible synergism between drugs was evaluated by isobologram. Both males and females developed hypersensitivity to tactile and cold stimuli by week 4 post SCI. Injection of CBD at dose 0.1-1-3-5 mg/kg showed dose-dependent effect with A50 determined for males as 3.02 for tactile and 1.23 for cold, for females as 7.5 for tactile and 1.8 for cold. BCP was injected at doses 10-20-50 mg/kg with A50 values for males as 22.6 for tactile and 19.03 for cold, for females as 35.2 for tactile and 20.7 for cold. For the assessment of the combined effect, drugs were administered at the A50 values as a starting dose, with 50% reduction for the other 2 doses in dose-response experiment. Data from this experiment were used to create isobolograms to evaluate possible synergism. Data shows a synergistic effect of the drugs for reducing cold allodynia in males and females. Additive effects were observed for tactile allodynia. The effects of both compounds and the combination appeared less potent in females compared to males, suggesting that sex differences will need to be considered when developing cannabinoid pain-reducing strategies. We observed no overt

side effects from combining CBD and BCP. These findings support the further development of cannabis extracts as potentially safe and effective therapeutics in the management of chronic SCI pain.

Disclosures: A. Pacheco-Spiewak: None. **A. Eeswara:** None. **S. Gross:** None. **S. Jergova:** None. **J. Sagen:** None.

Poster

P388. Treatments for Persistent Pain I

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Program #/Poster #: P388.09

Topic: D.03. Somatosensation – Pain

Support: Department of Defense OR170276

Title: Evaluation of recombinant gene therapy with serine-histogranin and endomorphin-1 in a model of phantom limb pain in male and female rats

Authors: *S. GROSS, A. EESWARA, A. PACHECO-SPIEWAK, K. LIEBMANN, S. JERGOVA, J. SAGEN;
Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: Limb amputation, either from direct traumatic injury or medically indicated due to injury severity and inability to adequately repair extremities, often results in the emergence of phantom limb pains (PLP). Local targeting of pain processing centers using gene therapy can provide analgesic substances directly where they are needed and avoid the off-target effects of systemically administered drugs. A key mechanism thought to underlie nerve injury pain is enhanced excitatory N-methyl-D-aspartate (NMDA)-mediated signaling in the spinal dorsal horn. The naturally-derived NMDA antagonist peptide, [Ser^{1}]histogranin (SHG), demonstrates inhibitory properties at the NMDA receptor and can reduce pain in other models. Recent studies in our lab using male rats have shown that injection of viral vectors producing SHG can reduce pain symptoms following peripheral and CNS injury. The addition of a potent mu-opioid peptide, endomorphin-1 (EM-1), provided additional synergistic antinociception. Since pain responses can differ between sexes, both female and male Sprague-Dawley rats were evaluated for PLP using a pre-injury complete nerve transection model. AAV_SHG, AAV_SHG/EM1 or AAV_GFP constructs were administered via dorsal root ganglion injection, intrathecally, or intraspinally either on the same day as transection or a week later, with pre-amputation nerve injury induced at 1 to 14 days prior to transection. Animals were scored daily for PLP autotomy behaviors including onset, severity and location. Several pain-related biomarkers were evaluated using CSF and tissue to discover possible underlying pathological changes. Our data shows slightly reduced severity of PLP-like behavior in females compared to males. In both groups, significant attenuation in the severity and onset of PLP-like behavior was observed in animals treated with SHG and SHG/EM1 compared to GFP. SHG and SHG-EM1 outcomes showed that animals treated with SHG/EM1 presented lower autotomy scores, indicating that simultaneous activation of mu-opioid receptor by EM1 may generate more potent PLP alleviation than inhibition of glutamate signaling by SHG alone. The most potent effect of both constructs was observed after intraganglionic injection when conducted on the same day as transection, with intrathecal

delivery yielding the most consistent results across all time points. CSF samples and immunocytochemistry showed downregulation of inflammatory mediators IL-1β and TNF-α and reduction in reactive glial markers GFAP and Iba-1 in correlation with the severity of the behavior. These findings suggest that combination gene therapy strategies can attenuate chronic PLP in both sexes.

Disclosures: S. Gross: None. **A. Eeswara:** None. **A. Pacheco-Spiewak:** None. **K. Liebmann:** None. **S. Jergova:** None. **J. Sagen:** None.

Poster

P388. Treatments for Persistent Pain I

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P388.10

Topic: D.03. Somatosensation – Pain

Support: Nevro Corp.

Title: Inhibitory interneuron activity is increased during combined 10 kHz and low frequency spinal cord stimulation

Authors: K. LEE, D. C. LEE, D. WANG, ***Z. B. KAGAN**, K. BRADLEY;
Nevro Corp., Redwood City, CA

Abstract: 10 kHz spinal cord stimulation (SCS) is believed to operate by causing inhibitory interneurons in the superficial dorsal horn (SDH) to substantially increase their action potential firing rate, while only minimally changing the firing rate of excitatory interneurons in the same area, without activation of dorsal column fibers. In contrast, low frequency (LF) SCS (40-60 Hz) is believed to operate by generating action potentials in large diameter dorsal column fibers. Based on this difference, these types of SCS are often applied at different locations along the spinal cord, with 10 kHz SCS applied more caudally and LF SCS applied more rostrally. We hypothesized that simultaneously applying 10 kHz SCS more caudally and low frequency SCS more rostrally would produce synergistic effects as measured by the relative firing activity of interneurons in the SDH.
Adult male Sprague-Dawley rats (n=7) were anesthetized with urethane and a spinal-segmental (ss) L1-L4 laminectomy was performed. A 4-shank, 16-channel microelectrode was implanted at the L5 level to record from neurons in the SDH with a receptive field of the left hind paw. All recordings were digitized at 40 kHz before band-pass filtering between 500 and 10k Hz. Individually identified unit firings were categorized as belonging to either inhibitory or excitatory interneurons on the basis of their response (non-adapting or adapting, respectively) to mechanical stimulus to the left hind paw. SCS was applied caudally (ss L5-L6) and rostrally (ss L1-L2) with two inline tripolar isodiametric electrodes. SCS strategies included (a) 10 kHz applied at 30% of motor threshold (MT) alone or LF stimulation at 70% MT alone through either the rostral or caudal electrode, (b) applying an interleaved 10 kHz SCS and LF SCS to either electrode, or (c) simultaneously applying 10 kHz SCS to the caudal electrode and LF SCS to the rostral electrode. Firing rates of each neuron type in response to stimulation was used to determine whether a given strategy had a significant effect.
In total, 25 inhibitory and 30 excitatory neurons were identified. Simultaneously delivering 10 kHz

caudally and 40 Hz rostrally increased the activity of inhibitory interneurons by 26 Hz, while increasing excitatory interneurons by 4 Hz. The next largest difference between inhibitory and excitatory interneurons was observed when 10 kHz alone was applied caudally, with inhibitory and excitatory neurons increasing their activity by 4.7 and 0.7 Hz, respectively. These results suggest that this approach of combining 10 kHz and low frequency SCS at different stimulation locations may be a method of further reducing patients pain compared with current available.

Disclosures: K. Lee: A. Employment/Salary (full or part-time):; Nevro Corp. **D.C. Lee:** A. Employment/Salary (full or part-time):; Nevro Corp. **D. Wang:** A. Employment/Salary (full or part-time):; Nevro Corp. **Z.B. Kagan:** A. Employment/Salary (full or part-time):; Nevro Corp. **K. Bradley:** A. Employment/Salary (full or part-time):; Nevro Corp..

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P450.01

Topic: D.06. Auditory & Vestibular Systems

Support: REGULAR FONDECIT 1160258

Title: Neurophysiological and behavioral correlates of auditory contextual emotional processing in healthy adult women: description of the loudness dependence auditory evoked potential and its role in the description of affective processing

Authors: *R. GAJARDO[1], R. A. HENRIQUEZ[2], F. J. ABOITIZ[2];
[1]Dept. of Psychiatry, Pontificia Univ. Catolica de Chile, Santiago, Chile; [2]Dept. of Psychiatry, Pontificia Univ. Católica de Chile, Santiago, Chile

Abstract: Major depression disorder (MDD) is described as a dysfunction of serotonergic system. Studies have correlated serotonergic activity, psychophysical performance and emotional sensitivity with the modulation of an event-related potential component called Loudness Dependence of the Auditory Evoked Potential (LDAEP), evoked by tonal auditory stimuli.
In this pilot study, we evaluate whether the LDEAP is elicited by a novel version of auditory oddball paradigm using stimuli with emotional valence and if it is correlated with psychophysical indicators and the emotional sensitivity scale of the Inventory of Beck (BDI) in 10 healthy female subject. We sought to describe and explore changes in LDAEP component as well as in psychophysical indicators in a task of detection and recognition of emotional auditory stimuli.Behavioral and electroencephalographic (EEG) data were obtained using a modified auditory oddball paradigm. We used audios (300 ms) with emotional valence (positive-laughs, negative-cries, neutral-vowel) obtained from The Montreal Affective Voices. There were 3 conditions: (1) standard:negative/ distractor:positive (PD); (2) standard:neutral/distractor:positive-negative (OD); (3) standard:positive/distractor:negative (ND). EEG was recorded from 64 non-polarizable Ag/AgCl active electrodes. In addition, the BDI was conducted to assess the emotional sensitivity of the participants.
Behavioral analysis indicates that false alarm percentage presented a statistical difference between PD

and OD condition ($p < 0.001$, one-way ANOVA;bonf. correction). In reaction times and total accuracy, percentage of correct responses between standards and distractors have a significant difference ($p < 0.0001$, Wicoxon test) within their same category. This demonstrates that emotional processing is an early phenomenon that depends on physical properties of the stimuli -intensity/ duration/ emotional information- affecting their behavioral response. EEG analysis describe that LDAEP is elicited with auditory stimuli with emotional valence. The grand average in each condition shows a greater amplitude -not significative- in increasing order in the conditions ND < PD < OD. Sperman correlation between the LDAEP component and BDI scale values show a trend with a $r \geq 0.8$ in the 3 conditions.
This pilot study is the first evidence to date that shows the appearance of the LDAEP component against auditory stimuli of contextual human vocalization with emotional valence. Also suggest that the LDAEP presented with an emotional paradigm is a useful tool for assessing emotional regulation, as well as a tool that can be used for the clinical diagnosis of MDD.

Disclosures: R. Gajardo: None. **R.A. Henriquez:** None. **F.J. Aboitiz:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

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Program #/Poster #: P450.02

Topic: D.06. Auditory & Vestibular Systems

Support: NIH grant R01 DC005216
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NIH grant P30 NS076408
NIH RR026783
W.M. Keck Foundation

Title: Distinct representations of tonotopy and pitch in human auditory cortex

Authors: *E. J. ALLEN[1], J. MESIK[1], K. N. KAY[2], A. J. OXENHAM[1];
[1]Psychology, [2]Radiology, Univ. of Minnesota, Minneapolis, MN

Abstract: Tonotopy is a fundamental organizing principle present at numerous stages throughout the auditory system, from the cochlea of the ear up through the brain. However, it is unclear whether tonotopic maps in cortex reflect physical frequency, inherited from the cochlea, a computation of pitch (reflecting fundamental frequency, F0), or a combination of such features. We used high-resolution, ultra-high field (7T) fMRI to measure BOLD responses in the auditory cortices of 10 normal hearing participants as they listened to sequences of tones in three different conditions: 1) pure tones, traditionally used to estimate tonotopy, that vary in both F0 and spectral content (frequency); 2) complex harmonic tones with a fixed spectral envelope peak but varying F0; and 3) complex harmonic tones with a fixed F0 but varying spectral envelope peak. Encoding models were used to compare representations of pure tones to the representation of tones varying in F0 or spectral envelope. Traditional tonotopic maps were found to be maps of spectral tuning, and bilateral representations of pitch selectivity were found to partially overlap these tonotopic maps, with distinct regions tuned to low, medium, and high F0s distributed

throughout auditory cortex. The data suggest the existence of two cortical representations: one based on spectral tuning (i.e., tonotopy), and the other based on pitch or F0 tuning. Consistent with hierarchical organization, more primary regions (i.e., Heschl's gyri) appear to predominantly exhibit tuning to spectral content, whereas surrounding regions bilaterally exhibit more tuning to pitch. Follow-up work is underway exploring whether and how relative changes in frequency (i.e., musical interval size and direction, irrespective of absolute frequency) are represented in human auditory cortex, as another way to determine the extent to which cochlear tonotopy is simply reflected or reshaped in different regions of the auditory cortex.

Disclosures: E.J. Allen: None. **J. Mesik:** None. **K.N. Kay:** None. **A.J. Oxenham:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P450.03

Topic: D.06. Auditory & Vestibular Systems

Support: Matilda Ziegler Foundation for the Blind

Title: Neural representations of temporal and spectral regularities of reverberant environments

Authors: *H. GARCIA-LAZARO, Y. ALWIS, S. TENG;
Smith Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Auditory scene analysis perceptually segregates complex acoustic inputs into multiple auditory perceptual objects. Among these is reverberation, the aggregate acoustic reflections from multiple nearby surfaces, which both distorts source signals and carries information about the local space. Human listeners are perceptually sensitive to temporal and spectral regularities of reverberation (Traer & McDermott 2016), which facilitates perceptual segregation and enables a separable neural code for sound sources and reverberant spaces (Teng et al., 2017). However, it remains unclear how neural responses represent reverberant acoustic statistics and, importantly, how the neural representations index perception of those acoustics.

To address these questions, we conducted an EEG experiment in which participants (N=14) listened to a 2s excerpt of spoken sentences, unique to each trial and convolved with a reverberant impulse response (IR). The IRs were either "Real" (R), recorded in a real-world environment, or "Fake" (F), synthesized in one of five ways matching or deviating from various statistical features of real environments (Traer & McDermott 2016). On each trial, subjects heard the 2000ms stimulus, followed by a 500ms delay and a visual cue commencing an untimed response period; the task was to ignore the speech signal and judge the reverberant space as R or F.

Perception of R and F IRs was reliably above chance, varying across synthetic conditions consistent with previous findings (Traer & McDermott 2016). Multivariate Pattern Analysis of EEG trials showed reliable decoding between R and F IRs starting at ~500 ms, suggesting that despite irrelevant speech signal information, the neural response reliably captures statistical regularities of physically realistic reverberation across multiple IRs. Classification accuracy increased when trials were filtered for correct

responses, indicating that stimulus representations were enhanced with improved task performance. Subject-wise behavioral performance across conditions correlated significantly with decoding accuracy starting at ~800 ms. Our results suggest that subtle statistics of complex acoustic environments are captured by early cortical responses, and that perception is driven by later responses.

Disclosures: H. Garcia-Lazaro: None. **Y. Alwis:** None. **S. Teng:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

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Program #/Poster #: P450.04

Topic: D.06. Auditory & Vestibular Systems

Support: NIH grant K99DC017472
NIH grant R01DC005216

Title: Investigating the neural correlates of harmonicity in auditory cortex in humans

Authors: *A. H. MEHTA[1], E. J. ALLEN[1], J. MESIK[1], K. N. KAY[2], A. J. OXENHAM[1];
[1]Psychology, [2]Radiology, Univ. of Minnesota, Minneapolis, MN

Abstract: Pitch and harmonicity are central perceptual properties of real-world sounds, including speech and music, and are crucial for the perceptual organization of sounds in an auditory scene. Despite advances in our understanding of how pitch is perceived and coded in the human auditory system, there are still significant gaps in our basic understanding of how pitch is represented in auditory cortex. Regions anterolateral to Heschl's gyrus have been identified as potentially pitch sensitive. However, it is not yet clear whether the activation truly reflects the pitch elicited by harmonically related tones, or whether these cortical regions are sensitive to other spectro-temporal differences between pitch-evoking complex tones and frequency-matched broadband noise. Previous work has suggested that resolved harmonic complex tones have stronger representations in the putative pitch sensitive regions of auditory cortex compared to unresolved harmonic complex tones and frequency matched noise. However, these stimuli differ significantly, not only in their pitch salience but also in other spectro-temporal properties. In this study, we compare 3T fMRI responses for harmonic complex tones (resolved and unresolved) to inharmonic complex tones, which were matched to the harmonic tones in terms of spectral density and frequency range but do not elicit a clear unambiguous pitch. Additionally, we measure responses to frequency matched broadband noise which has traditionally been used as a reference condition for localizing pitch sensitive regions. We also examine the effect of phase manipulation in the unresolved harmonics in order to investigate the responses driven by envelope fluctuations. We observed robust, bilateral, stimulus-driven activity in Heschl's gyrus and surrounding auditory regions for all stimuli. While data collection is ongoing, preliminary data shows minimal differential activation in previously reported pitch sensitive regions for stimuli with and without salient pitch percepts, when controlling for spectral density and bandwidth. We will also investigate whether any harmonicity-driven differences exist outside of primary auditory cortex. This work will help determine which properties inherent to pitch stimuli are represented in the putative pitch center.

Disclosures: A.H. Mehta: None. **E.J. Allen:** None. **J. Mesik:** None. **K.N. Kay:** None. **A.J. Oxenham:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

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Program #/Poster #: P450.05

Topic: D.06. Auditory & Vestibular Systems

Support: NWO grant 864-13-012

Title: Frequency-based attention reduces auditory cortical responses to relevant sounds

Authors: A. LAGE-CASTELLANOS[1], F. DE MARTINO[2], O. GULBAN[3], ***M. MOEREL**[4];
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Abstract: Auditory attention enables prioritizing currently relevant information. Results from animal electrophysiological studies suggest that attention induces rapid changes in auditory neuronal feature preference and selectivity [1]. Functional magnetic resonance imaging (fMRI) studies of human auditory cortex have revealed an increase in BOLD response in neuronal populations tuned to attended sound features [2]. However, as fMRI studies could typically not characterize the influence of attention on neuronal population receptive field properties, it is still largely unclear how the results obtained with fMRI in humans relate to the electrophysiological findings in animal models.We used ultra-high field fMRI to examine auditory processing while participants (N = 10) listen to ripple sounds and natural sounds. Participants performed a detection task on the ripple sounds. By manipulating the chance of target occurrence, participants alternatively attended to low frequency (300 Hz) or high frequency (4 kHz) ripple sounds. Instead, responses to natural sounds were used to compute neuronal population receptive fields (PRFs).In the behavioral data, we observed a faster reaction time to noise bursts in attended compared to unattended ripples indicating a beneficial influence of attention on task performance. In contrast with previous fMRI studies, the auditory cortical response to attended ripple sounds was *lower* than when the same sounds were not attended. This difference decreased with increasing distance between the voxels' best frequency (BF) and the attended sound frequency. Maps of frequency preference (BF) and selectivity (tuning width; TW) were similar across attentional conditions, with the exception of a narrower TW with attention in parabelt locations with a BF close to the attended frequency.Our results suggest that frequency-based attention results in narrower tuning width in voxels whose preferred frequency matches the attended one. This could underlie the observed lower response to attended, compared to non-attended, ripple sounds. The difference between our results and previous fMRI studies [2] may be explained by the difference in experimental design. Previous studies simultaneously presented attended and reference non-attended sounds, while our presentation was sequential. This suggests that fundamentally different mechanisms may underlie these different attentional settings. [1] Fritz et al. R. Nat. Neurosci. 6, 1216-1223 (2003)[2] Riecke et al., Neuroimage 174, 274-287 (2018)

Disclosures: A. Lage-Castellanos: None. **F. De Martino:** None. **O. Gulban:** None. **M. Moerel:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant RF1 MH116978
ERC-2020-Cog no. 101001270

Title: Laminar profile of predictive sound frequency processing in the human auditory cortex

Authors: *L. K. FAES[1], L. VIZIOLI[2], Z. YU[3], I. ZULFIQAR[4], J. N. SHIN[3], K. ULUDAG[5], L. MELLONI[6,3], E. YACOUB[2], F. DE MARTINO[1,2];
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Abstract: Predictive coding postulates that our brains build an internal representation of the sensory world through the comparison of predictions casted by an internal model and the sensory input. Such a process takes place throughout the (sub-) cortical hierarchy attributing a specific role to the different cortical layers in the information flow between top-down predictions and bottom-up sensory evidence [1, 2]. However, in the auditory cortex, the particular role of cortical layers is still debated [3]. We use ultra-high field fMRI (7T) to investigate the role of cortical layers in response to tones that either respect or deviate from contextual cues. In addition, we evaluate the impact of fMRI (thermal noise) denoising using Noise Reduction with Distribution Corrected (NORDIC) PCA [4] for the investigation of submillimeter fMRI responses in temporal regions.We acquired anatomical (0.75 mm iso) and functional (0.8 mm iso) data, while volunteers (N = 8) listened to tone sequences. The sequences consisted of four tones. The last tone was either presented in a predictable context (e.g. a high frequency tone preceded by three ascending ones) or an unpredictable context (e.g. a high frequency tone preceded by three tones whose frequency was not ordered). In the predictable context, in a small proportion of the trials, the last tone could be an oddball (e.g. a low frequency tone following three ascending ones). Preliminary analyses revealed that, in the Heshl's gyrus, a high-low-high frequency gradient [5] is present in the tonotopic maps of all conditions. The tonotopy appears similar between sequences with a predictable and unpredictable context, but slightly altered in response to sequences ending with an oddball. The same gradient was visible in both the original data and the data processed with NORDIC. As expected, NORDIC resulted in clearer responses to sound presentation due to the thermal noise suppression [3]. This preliminary result suggests that NORDIC offers a comparative advantage to the standard reconstruction, while also suggesting that oddball responses are differently represented than the predictable and unpredictable ones.In follow-up analyses we will quantify the spatial correlation between the tonotopic maps of different sequence types. Additionally, we will investigate the (cortical depth dependent) responses to predictable, unpredictable and oddball stimuli and their relationship to the tonotopic representation [6].

1. Bastos et al. (2012) Neuron; 2. De Lange et al. (2018) Trends in Cog. Sci.; 3. Heilbron & Chait (2018) Neuroscience; 4. Vizioli et al. (2020) BioRxiv; 5. Moerel et al. (2014) Front. Neurosci.; 6. Berlot et al. (2018) J. Neurosci.

Disclosures: L.K. Faes: None. **L. Vizioli:** None. **Z. Yu:** None. **I. Zulfiqar:** None. **J.N. Shin:** None. **K. Uludag:** None. **L. Melloni:** None. **E. Yacoub:** None. **F. De Martino:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P450.07

Topic: D.06. Auditory & Vestibular Systems

Support: Phyllis M. Taylor Center for Social Innovation and Design Thinking

Title: Rhythmic priming results in neural entrainment and persistent effects on sensorimotor synchronization

Authors: *M. A. VELASQUEZ[1], K. A. YURGIL[3], L. DOMENECH[2], C. PEARSON[2], J. L. WINSTON[1], P. J. COLOMBO[1];
[1]Psychology, [2]Neurosci., Tulane Univ., New Orleans, LA; [3]Psychological Sci., Loyola Univ., New Orleans, LA

Abstract: Rhythm is an important component in music, and neural entrainment has been proposed as a key mechanism for its perception. Neural entrainment occurs when the frequency of neural oscillations synchronizes to a rhythmic stimulus and reports indicate a positive relationship between rhythm entrainment and sensorimotor synchronization (SMS). The present study examined the role of neural entrainment on SMS and whether the effects of neural entrainment on behavioral and neural responses persist after termination of auditory stimulation. Electrical brain activity was recorded from participants (N=30) while they listened to either a synchronous (2.5 Hz) or asynchronous auditory stimulus for 6 minutes (10 trials of 33s each with 3s intertrial intervals). After presentation of the stimuli, participants in both conditions were instructed to tap their index finger in time with the synchronous stimulus (2.5 Hz) for 33s. After a 15 min delay, all participants listened to the synchronous stimulus for 6 min then completed the finger-tapping task a second time. Participants receiving the initial synchronous stimulus showed higher amplitudes at the beat frequency, indicating neural entrainment, and better tapping accuracy, indicating better sensorimotor synchronization, compared to participants who heard the asynchronous stimulus. Among those who received the synchronous stimulus, there was a correlation between the amplitude at the beat frequency and tapping accuracy, indicating that stronger neural entrainment was related to better sensorimotor synchronization. During the post-delay synchronous stimulation, there was no group difference in amplitude at the beat frequency. However, the synchronous group showed better accuracy and less variability than the asynchronous group, indicating that the effect of either synchronous or asynchronous stimulation was persistent. In both groups, there was a correlation between tapping variability and amplitude at the beat frequency, indicating that the differences in behavioral performance post-delay were most likely influenced by the synchronous stimulus and not the

asynchronous stimulus. Lastly, while there was a difference in tapping performance between groups after the delay, there was no difference in amplitude at the beat frequency, suggesting that this difference was due to a mechanism other than neural entrainment. Overall, the current results show that sensorimotor synchronization can be influenced by the rhythmicity of an auditory prime, and these effects can persist after a delay.

Disclosures: M.A. Velasquez: None. **K.A. Yurgil:** None. **L. Domenech:** None. **C. Pearson:** None. **J.L. Winston:** None. **P.J. Colombo:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P450.08

Topic: D.06. Auditory & Vestibular Systems

Support: Leverhulme Trust Early Career Fellowship ECF-2019-305

Title: Naturalistic Stimulation Reveals the Tonotopic Structure of Human Auditory Cortex

Authors: *N. HEDGER[1], T. KNAPEN[2];
[1]Univ. of Reading, Reading, United Kingdom; [2]Cognitive Psychology, Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: Despite the importance of audition in spatial, semantic, and social function, there is no consensus regarding the detailed organisation of human auditory cortex. Using a novel computational model to analyse a high-powered naturalistic audiovisual movie-watching dataset, we simultaneously estimate spectral tuning properties and category selectivity to reveal the modes of organisation and computational motifs that characterise human auditory cortex. We find that regions more remote from the auditory core exhibit more compressive, non-linear response properties and finely-tuned, speech-selective receptive fields in low frequency portions of the tonotopic map. These patterns of organisation mirror aspects of the visual cortical hierarchy, wherein tuning properties progress from a stimulus category-agnostic 'front end' towards more advanced regions increasingly optimised for behaviorally relevant stimulus categories.

Disclosures: N. Hedger: None. **T. Knapen:** None.

Poster

P450. Auditory Processing: Temporal, Frequency, and Spectral Processing I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P450.09

Topic: D.06. Auditory & Vestibular Systems

Title: Neurofunctional differences when processing subsecond and suprasecond auditory time intervals.

Authors: *N. THIBAULT[1], P. ALBOUY[1], S. GRONDIN[2];
[1]CERVO, Québec, QC, Canada; [2]Univ. Laval, Québec, QC, Canada

Abstract: How does the human brain process time intervals? The perception of subsecond intervals (below 1 sec) is thought to be supported by automatic sensory circuits. In contrast, it has been proposed that suprasecond intervals (above 1 sec) are processed by high-order cortical network such as the central executive network. However, some inconsistencies have emerged in the recent neuroimaging literature when trying to identify the brain networks responsible for the perception of time intervals. In the present study, we investigate whether distinct or common neural resources support the perception of sub and supra second time interval using electroencephalography (EEG) and an auditory oddball paradigm. Twenty participants underwent 12 blocks of 8 minutes of an oddball paradigm on time intervals. In each block, 40 trials of 10 sounds were presented for each condition (subsecond, suprasecond). For each trial, one deviant inter-sound-onset-interval was randomly presented through the standard intervals (800ms for the subsecond condition, and 1600ms for the suprasecond condition). These deviant intervals were either shorter than the standard interval (early condition: 700, 750; 1400, 1500ms) or longer than the standard interval (late condition: 850, 900; 1700, 1800ms). Auditory evoked potentials were studied for each condition at both the sensor and source level. We first show that different event related responses and neural resources support the perception of duration of intervals (suprasecond, subsecond). A positive frontocentral peak at 190ms after stimulus onset, with generators in the right primary auditory cortex, was associated with the detection of subsecond deviants. For the suprasecond condition, a biphasic response was associated with deviance detection. First, a negative peak at 170ms with generators in the right inferior frontal gyrus and right precentral gyrus was observed. This peak was followed by a frontocentral positivity at 350ms with generators in the dorsal pathway including the premotor cortex and the supplementary motor area. Finally, similar brain activity in the central executive network were observed for the processing of late deviants (that occurs after the after the expected timing) as compared to early deviants in both sub and supra second condition. Activity in this fronto-parietal network for detection of late deviants might represent top down and prediction error mechanisms. These results suggest that distinct neural mechanisms support the perception of sub and supra second time intervals in the human brain.

Disclosures: N. Thibault: None. **P. Albouy:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NSERC. **S. Grondin:** None.

Poster

P480. Visual Motion I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P480.01

Topic: D.07. Vision

Title: Spatial summation for motion detection

Authors: *J. A. SOLOMON[1], C. W. TYLER[2];
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Abstract: We used the psychophysical "summation" paradigm to reveal some spatial characteristics of the mechanism responsible for detecting a motion-defined visual target. All stimuli were composed of 256 x 256 pixels, subtending 1.5 degrees of visual angle, with randomly selected graylevels. Graylevels within each 16 (horizontal) x 1 (vertical) group of pixels shifted rightwards with a velocity defined by a noisy, two-dimensional Gaussian function of space. Independent variables were the Gaussian target's space constant and the variance of the velocity noise. The dependent variable was the target's threshold amplitude for (81%-correct, two-alternative forced-choice) detection. To a first approximation, all thresholds were observed to decrease with the square-root of the target's space constant (i.e., the fourth-root of its area). Similarly satisfactory, quantitative fits to the data were obtained with two styles of model: an "uncertainty" model, in which decisions are based on the maximum of many independent signals, and an otherwise-ideal-observer model, subject to intrinsic noise and inefficient sampling, as though a random grid of small elements comprised each receptive field. Both styles of model fit best when the maximum area for any individual receptive field contained between 50 and 100 pixels. Thus, regardless of whether the mechanisms for motion detection integrate information over locally contiguous or sparsely distributed regions of the visual field, it is clear from our results that these regions contain little area. In other words, there is surprisingly little spatial summation for human motion detection.

Disclosures: J.A. Solomon: None. **C.W. Tyler:** None.

Poster

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Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P480.02

Topic: D.07. Vision

Support: NIH Grant U19NS118246

Title: Causal inference in hierarchical motion perception

Authors: *S. SHIVKUMAR[1,2], G. C. DEANGELIS[3,2], R. M. HAEFNER[4,2];
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Abstract: Our subjective percept of an object's motion has been shown to differ dramatically from its retinal velocity in the presence of other moving objects (Johansson 1950). In particular, when an object is part of a larger object, then the perceived motion of the part corresponds most closely to the part's motion relative to the whole. This observation holds even for impoverished visual scenes consisting only of dots, with no semantic information about objects and their relationships, raising the question of how the brain parses and segments such a scene and correctly infers relative motion in a hierarchical fashion. Inspired by recent computational work (Gershman et al. 2016), we have developed a hierarchical Bayesian causal

inference model that can qualitatively account for the findings of prior studies on motion perception (Shivkumar et al. 2020). Our hierarchical model consists of a single recurring motif in which the velocity of each visual element is decomposed into the velocity of the "group" that it belongs to and a velocity relative to the group. Importantly, the prior over the relative velocity is a mixture of a delta function at zero velocity and a Gaussian distribution centered at zero. This modification of the classic slow-speed prior (Stocker et al. 2006) effectively performs causal inference (Kording et al. 2007) over whether the object is stationary or moving and leads to a hierarchical segmentation of the visual scene into groups and supergroups (of groups) when applied to multiple visual elements.Here, we report the results of new psychophysical experiments that quantitatively probe both the hallmark of causal inference in our model, and the hallmark of hierarchical motion perception: the probabilistic transition from cue-integrating dots of sufficiently similar motion to segmenting them into different but connected objects, and perceiving them relative to each other in a hierarchical fashion. Fixating human observers report the perceived direction of a coherently moving "center" group of dots using a dial. This patch of dots is surrounded by coherently moving dots in two concentric annuli of surrounding dots ("S1" and "S2"). Our model predicts that when the motion of the center group is close to that of the motion of S1, then the center and S1 are perceived as one group and its motion is perceived as relative to S2. On the other hand, when the center motion is very different from S1, then the center is segmented from S1 and the center motion is perceived relative to S1, with a probabilistic transition in between both scenarios. Our behavioral data clearly show this transition, allowing us to constrain the parameters of our model in future work.

Disclosures: S. Shivkumar: None. **G.C. DeAngelis:** None. **R.M. Haefner:** None.

Poster

P480. Visual Motion I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P480.03

Topic: D.07. Vision

Title: Design and implementation of an at-home treatment regimen for visual motion hypersensitivity

Authors: *Ó. RÚNARSSON, T. WIBBLE;
Karolinska Institutet, Stockholm, Sweden

Abstract: Patients who suffer from motion-sickness, visual vertigo and other conditions relating to *visual motion hypersensitivity* (VMH) will often feel dizzy when exposed to rapid visual motion or cluttered fields-of-view. Previous studies indicate that attentiveness to these stimuli influence the intensity of discomfort for these individuals. Allowing patients to visualize their attentional levels or cognitive involvement may therefore aid in suppressing VMH.
This study aims to develop a visual biofeedback system for use with a commercial *electroencephalographic* (EEG) headset and a personal computer which may be used for treating motion-sickness and VMH. A neurofeedback program was constructed using MATLAB and a Muse 2 Meditation Device (InteraXon Inc., Toronto, Canada), which functions as a commercial EEG. The program projected a spinning maze-like pattern on a monitor where increase in velocity was proportional to increase in theta wave activity (3.5-6.5 Hz) detected by the Muse. Five test subjects (3M, 2F, avg. age 31) were recruited.

They filled out a *Short-form Motion Sickness Susceptibility Questionnaire* (MSSQ-Short) and were subjected to a proficiency test, where balance and EEG data was collected in a controlled environment while they used the program for the first time. They received a copy of the program and a Muse, and instructed to practice reducing their EEG activity, reflected in the program as a slower spin velocity of the maze. These practice sessions took place daily for seven days. They then returned to the lab for another proficiency test.
Mean spectral power data from the training regimen shows a 23.7% drop in theta wave activity from first session to last ($p = 0.005$). Using Pearson's correlation, no significant results were obtained while comparing training improvements and proficiency test improvements ($r = -0.22$, $p = 0.72$) or reduction in body sway ($r = 0.78$, $p = 0.12$). MSSQ-Short scores correlated significantly with body sway before training ($r = 0.93$, $p = 0.02$) but not after training ($r = 0.68$, $p = 0.21$).
For every subject there was a clear drop in spectral power over the course of the training, indicating that the neurofeedback system works as intended. The high correlation between MSSQ-short scores and body sway during the initial proficiency testing session indicates that the program evokes a balance response. This correlation disappears after the training sessions, however the person who got the highest MSSQ-Short score by far (49.5/54, high susceptibility) was also the one who improved the most. This indicates that the program may be more effective on those who are already susceptible, though a greater sample size is required for validation.

Disclosures: Ó. Rúnarsson: None. **T. Wibble:** None.

Poster

P480. Visual Motion I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P480.04

Topic: D.07. Vision

Title: Biological Motion Perception in Perceptual Decision Making Framework

Authors: *B. AYDIN, B. A. URGEN;
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Abstract: Neurophysiological studies with non-human primates characterize perceptual decision-making with a two-step process: 1) sensory evidence accumulation, 2) decision that leads to response selection (Gold and Shadlen, 2007). These studies commonly use random dot motion stimuli (RDM) and show that the firing rate of the neurons in LIP increases and the behavioral response time decreases as the coherence of the motion stimuli increases. Recently, EEG studies in humans have revealed the CPP component, which shows similar functional properties as LIP neurons, and is associated with the sensory evidence accumulation process (Kelly and O'Connell, 2013). Furthermore, it is distinguished from the LRP component which is associated with response selection. The aim of the present study is to investigate whether these processes would generalize to more complex and socially meaningful stimuli such as biological motion. Sixteen participants did a direction discrimination task with biological motion stimuli as 64-channel EEG was recorded. The coherence of the stimuli was manipulated by embedding noise dots at four different levels. The task was to indicate whether the noise-embedded biological motion walker

moved towards left or right. Our behavioral results show that the reaction times and miss rate decrease as the coherence is increased. Furthermore, we found that the peak rate of the CPP component tracks the coherence of the biological motion stimuli and is distinguished from the LRP component. However, CPP has a later onset compared to the RDM task, probably due to further processing needed for biological motion stimuli. In sum, our results suggest that perceptual decision-making processes can be generalized to more complex and socially important stimuli with some delays in timing.

Disclosures: B. Aydin: None. **B.A. Urgen:** None.

Poster

P480. Visual Motion I

Location: Virtual Only

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Topic: D.07. Vision

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Biotechnology and Biological Sciences Research Council grant (R004765)
Biotechnology and Biological Sciences Research Council Studentship

Title: Distinct neural dynamics underlie the encoding of visual speed in stationary and running mice

Authors: *E. A. B. HORROCKS, A. B. SALEEM;
Univ. Col. London, London, United Kingdom

Abstract: Sensory experiences are often driven by an animal's self-motion. For example, an animal's movement through an environment can drive rapid changes to visual inputs in the form of visual flow. Real-time encoding of visual motion during locomotion is therefore critical for an animal to understand and control its interaction with an environment. Whilst locomotion has been shown to modulate visual responses in the mouse brain, little is known about how it modulates the temporal dynamics (time courses) of these responses. In this study, we compared the temporal dynamics of single neuron and population responses, in stationary and running sessions (n=17 mice), from eight mouse visual areas to dot field stimuli moving at a range of visual speeds using the Visual Coding dataset from the Allen Institute for Brain Science. We found a diverse range of reliable trial-averaged temporal response dynamics, and responses in stationary and running sessions had distinct temporal dynamics - responses recorded during running had less transient stimulus onset and offset response features. We therefore investigated the functional encoding of visual speed by assessing tuning strength over the response period. In running sessions, a combination of increased dynamic range and more reliable temporal response dynamics enabled visual speed tuning to emerge faster (-67ms, $p<0.001$) and persist for longer (+93ms, $p=0.014$). As a result, visual speed could be decoded above chance more quickly (-53ms, $p=0.030$) and until later (+114ms, $p<0.001$). Population activity reflected the temporal dynamics of single neuron responses, including their modulation by locomotor state. We used factor analysis to obtain neural trajectories which evolved over time. Using a geometric measure (the Distance Ratio) we found that neural trajectories in running sessions made more direct transitions between baseline and stimulus steady

states during the stimulus onset and offset periods ($p<0.001$ for both periods). This enabled faster and more persistent encoding of visual speed from population activity. Interestingly, the structure of population coding for visual speed also differed between locomotor states - population activity prioritised the encoding of visual speed in running, but not stationary sessions. Our results reveal a profound influence of locomotion on the temporal dynamics of neural responses. We find that during running, mouse visual areas prioritise the encoding of potentially fast-changing, behaviourally relevant features such as visual speed.

Disclosures: E.A.B. Horrocks: None. **A.B. Saleem:** None.

Poster

P480. Visual Motion I

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Program #/Poster #: P480.06

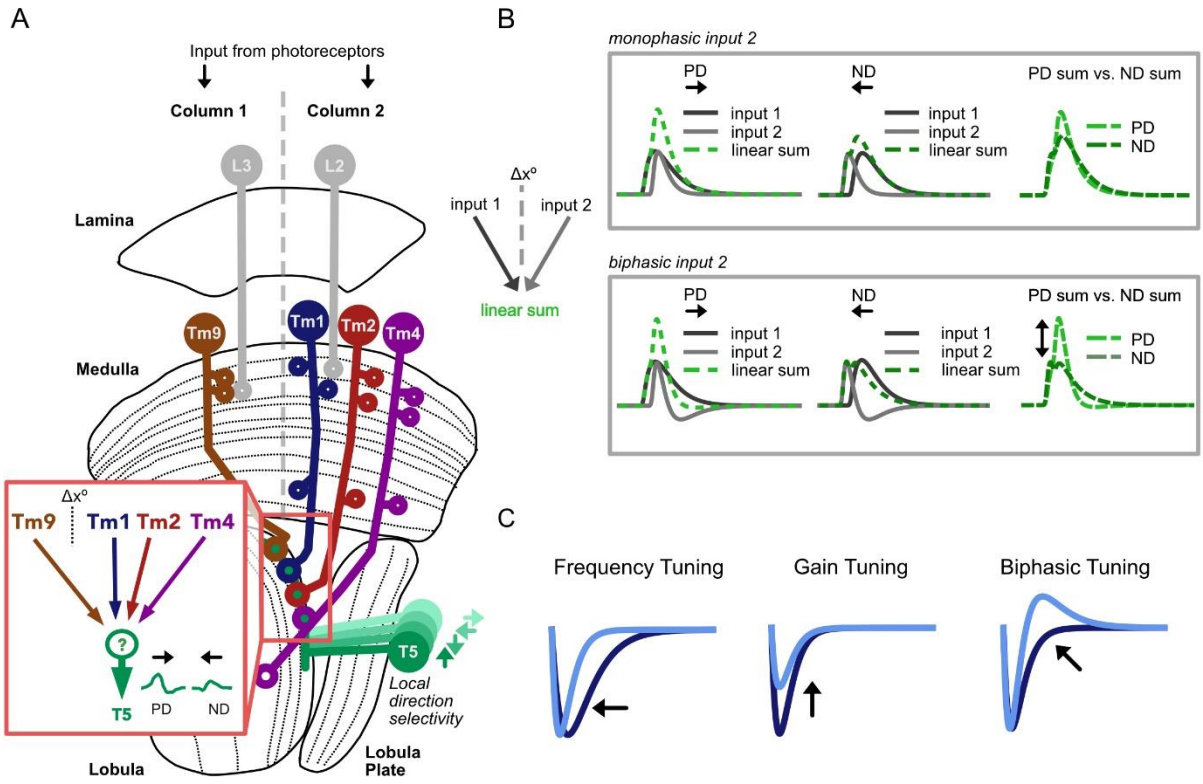
Topic: D.07. Vision

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Title: State and stimulus dependence reconcile motion computation and the Drosophila connectome

Authors: *J. P. PORTES, J. R. KOHN, M. P. CHRISTENSON, L. F. ABBOTT, R. BEHNIA; Columbia Univ., New York, NY

Abstract: Sensory neurons dynamically optimize their tuning to encode stimuli across a wide range of environmental and behavioral conditions. Although such adaptation has been widely studied, its impact on the computations performed by neural circuits is not understood. The well-described and anatomically characterized *Drosophila* motion detection circuit provides a prime opportunity to address this issue. We measured the filtering properties of neural inputs to the OFF motion-detecting T5 cell in *Drosophila* and report state- and stimulus-dependent changes in the shape of temporal responses which, importantly, become more biphasic under specific conditions. Summing these inputs within the framework of a connectome-constrained model of the visual-motion circuit demonstrates that the observed shape changes are necessary and sufficient to explain T5 responses to a variety of motion stimuli. These findings provide a clear example of how a neural circuit can dynamically optimize an important sensory computation.



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Poster

P480. Visual Motion I

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

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Topic: D.07. Vision

Support: NIH Grant EY027023
NIH Grant EY029997

Title: Heterogeneity of direction selectivity and receptive field profile in randomly-wired models of component and pattern cells in visual cortical area MT

Authors: *Z. YAO[1], W. BAIR[2];
[1]Bioengineering, [2]Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Visual receptive fields (RFs) in cortical area MT are conventionally conceptualized and modeled to be homogeneous such that MT neurons prefer the same direction throughout the spatial RF and that sensitivity is relatively even but drops off toward the edge. However, a recent study found that

nearly 50% of macaque MT neurons had multi-peaked RFs with heterogeneous direction preference (Richert et al., 2013, Front Syst Neurosci). This raises basic questions about the spatial structure of MT RFs. To test under what conditions such heterogeneity can arise from simple random connectivity models that achieve realistic spatial integration of V1 inputs, we extended a previous MT model (Baker & Bair, 2016, J Neurosci) and simulated a population of units having architectures that accounted for both component (CDS) and pattern direction selective (PDS) neurons. The spatial structure of the V1-MT connections in the models was controlled by variation of four major factors: (1) the density of V1 connections to the MT unit, (2) the spatial uniformity vs. randomness of the locations of those inputs, (3) the organization of V1 direction channel inputs into coherent local spatial subunits, and (4) the direction bandwidth of the distribution of weights on the V1 inputs (PDS units have wider bandwidth than do CDS units). For comparison to Richert et al., we applied reverse correlation using random dot stimuli like theirs to map the sensitivity profile and direction preference of our model RFs. We found that manipulation of the above model parameters could achieve RF heterogeneity to a limited extent. When V1 inputs of different direction channels were spatially aligned, forming local subunits, both CDS and PDS models with sparse and randomly positioned subunits tended to have heterogeneous sensitivity profiles. Spatially staggering the direction channels did not affect the level of RF heterogeneity for CDS models, but such a configuration significantly reduced the heterogeneity of the sensitivity profile and increased the direction heterogeneity for PDS models. Overall, we observed minimal RF direction heterogeneity in our models: while we were able to simulate irregular RFs with multiple subregions fragmented by low sensitivity gaps, these subfields shared similar preferred directions. Our results suggest that spatial randomness in the wiring of V1 inputs would not be sufficient to produce RF subregions in MT neurons with substantially different direction tuning to the degree reported by Richert et al. Thus, the existence of direction heterogeneity in the RFs of single MT neurons most likely arises from concerted, non-random developmental processes.

Disclosures: Z. Yao: None. **W. Bair:** None.

Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P555.01

Topic: E.05. Brain-Machine Interface

Support: NINDS UH3 NS107714

Title: ICMS-evoked touch sensations are enhanced during attempted grasp

Authors: *T. CALLIER[1], J. E. DOWNEY[2], A. SOBINOV[2], V. KARAPETYAN[4], R. A. GAUNT[4,5,6,7], S. J. BENSMAIA[1,2,3];
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Abstract: Electrical stimulation of somatosensory cortex (SC) elicits artificial touch sensations and can be used to deliver sensory feedback from prosthetic limbs. This feedback improves prosthetic control, underscoring the importance of closing the sensorimotor loop. The perceptual correlates of intracortical stimulation (ICMS) of SC are necessary to determine object properties in real-time, but have almost exclusively been studied under open-loop conditions, in which stimulation is delivered to participants, who then make reports of the perceptual experience. In the present study, we wished to examine the degree to which ICMS-evoked touch sensations are modulated by the behavioral state of the participant. Specifically, we asked whether the sensations would differ if they were paired with a motor act. First, we had participants perform a detection task under two conditions. In one condition ('active'), peri-threshold ICMS pulse trains were synchronized with a hand grasping an object in virtual reality (VR) and participants were instructed to attempt to mimic the observed grasp. In the other condition ('passive'), the same ICMS pulse trains were presented without the VR context. In both conditions, ICMS trials were randomly interleaved with catch trials with no stimulation. We found that participants were better able to detect peri-threshold ICMS pulse trains in the attempted grasp condition compared to the passive condition. Next, we had the participants report the intensity of the sensations evoked by suprathreshold ICMS in the attempted grasp condition and in the passive condition. We found that the evoked sensations were systematically more intense when ICMS was paired with attempted grasp. We conclude that sensations are enhanced when the ICMS-based feedback is congruent with an attempted motor act.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Topic: E.05. Brain-Machine Interface

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Cerebral Palsy Alliance Research Foundation
Wu Tsai Neurosciences Institute
Howard Hughes Medical Institute
Larry and Pamela Garlick

Title: Neural representation of hand gestures in human premotor cortex

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Abstract: High-resolution neuroprosthetic decoding of finger movements and hand gestures could greatly improve the usability of robotic limbs and enable new communication methods such as ten finger typing. Here, we aimed to better understand the geometry of motor cortical neural activity during naturalistic hand gestures, to guide the design of hand motion neuroprostheses.
Simultaneous neural population activity was recorded from two intracortical Utah arrays (192 channels) in the 'hand knob' area of premotor cortex of a human participant with tetraplegia while they attempted different hand gestures. Each trial was cued with an animated hand, with a 1 second preparatory period followed by a 2 second movement period. Trials varied across laterality (left/right hand) and palm position (up/down/sideways). Trials started from a neutral resting position to one of 81 different gestures consisting of an exhaustive combination of three targets (flexion/extension/no movement) for four finger groups (ring and little fingers had the same movement). For the same single finger movement (flexion/extension), changing the hand laterality (left/right), the hand pose (up/down/sideways) or the identity of the finger was largely captured by a uniform, time-independent shift in neural activity for the entire duration of the trial. However, for multi-finger gestures, a decoding analysis revealed a more complex structure. First, a linear classifier was able to distinguish between 81 gestures on four finger groups with 40% accuracy (chance accuracy <2%), confirming that the neural activity was modulated by the movement of each finger. Second, for the same movement of the other fingers (condition), decoding the movement of a particular finger using training data from the same condition had high accuracy (>88% accuracy across all fingers). Third, a classifier trained on one condition had low accuracy when tested on other conditions (varied between 78% for thumb and 57% for middle finger; chance accuracy 50%).
In conclusion, using neural recordings from the hand knob area of the motor cortex, accurate decoding of single finger movements, across hands lateralities and poses, could be achieved using standard linear methods but simultaneous movement of all fingers would likely require non-linear methods.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P555.03

Topic: E.05. Brain-Machine Interface

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Title: Real-time linear prediction of simultaneous and independent movements of two finger groups using an intracortical brain-machine interface

Authors: *S. R. NASON[1], M. J. MENDER[1], A. K. VASKOV[2], M. S. WILLSEY[3], N. GANESH KUMAR[4], T. A. KUNG[4], P. G. PATIL[3], C. A. CHESTEK[1];
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Abstract: Current brain-machine interfaces (BMIs) can return mobility to cervical level spinal cord injury patients (BrainGate), where upper-limb function is of utmost importance (Anderson 2004). A major roadblock to their clinical use is their inability to restore the functionality and naturalism of the native hand. Here, we present a low-power intracortical BMI capable of predicting the simultaneous and independent movements of two finger groups to help close that gap. We implanted two nonhuman primates (N and W) with Utah microelectrode arrays in the hand area of primary motor cortex. We trained them to perform a behavioral task in which they controlled a virtual hand by moving their physical hand or using the BMI. The index finger and the middle-ring-small (MRS) fingers as one group were each presented with their own virtual targets, for two targets total. During the task, we recorded spiking band power (SBP), which is a low-bandwidth signal that accurately captures the firing rate of the highest amplitude unit on each electrode (Nason *et al.*, 2020), and trained ReFIT Kalman filters to predict the simultaneous and independent movements of both finger groups in real-time using their thoughts. We analyzed cortical tuning to these movements in a 2D space made by plotting the 1D index finger movements against the 1D MRS group movements. The ReFIT Kalman filter enabled the nonhuman primates to acquire targets in 1.01s (N) and 2.4s (W) on average. When investigating the cortical activations for these movements, we found that the SBP activity for a given movement could be linearly predicted by the activity for related movements. This enabled us to predict combined finger movements using a decoder model that was trained only on individuated movements, and vice versa, with a 0.04 (N) and 0.08 (W) loss in correlation. Finally, we investigated the tuning of SBP channels to both position and velocity of the fingers across a wide variety of behaviors and found that a channel's preferred position rarely aligns with that channel's preferred velocity. Our results suggest linear models can sufficiently predict complex finger movements during tasks involving two targets. Further, training and testing on mutually exclusive behaviors suggests cortical activity related to fingers is consistent between independent and combined movements, at least up to 2 degrees of freedom. Finally, misalignment in the preferred positions and velocities of cortical units related to finger movements suggests simultaneous encoding of multiple kinematic parameters within individual units. Future work will use this multi-dimensional finger BMI to control an implantable functional electrical stimulation system.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Program #/Poster #: P555.04

Topic: E.05. Brain-Machine Interface

Support: Leibniz Wettbewerb (K265/2019)

Title: How similar are representations of observed and executed grasps in the frontoparietal cortical grasping network?

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Abstract: Neurons in the frontoparietal cortical grasping network respond during both the execution and observation of an action. This has been used to support theories that link motor control and cognition and has offered the tantalizing promise of straightforward observation-based training of decoders for brain-computer interfaces (BCIs). Such observation-related signals have often been described as grasping-related phenomena, further pointing to their potential utility for training grasp decoders. However, the precise link between execution and observation activity remains elusive, specifically the granularity of information shared between both contexts. To address this, chronic multi-electrode arrays were used to record simultaneously from neuronal populations in parietal (AIP), premotor (F5), and primary motor (M1) nodes of the cortical grasping network as animals either grasped a variety of different objects or observed a human subject doing the same. From these data, no distinct class of neuron emerges which is particularly responsive during observed grasps. Instead, neurons in the grasping network span a continuum of relative preference for execution and observation, although on average, AIP or F5 neurons exhibit more activity during observation than M1 neurons. Absent a particular class of neuron to study, targeted dimensionality reduction identifies linear combinations of these neurons that capture shared neuronal activity patterns, some of them being nearly identical during execution and observation. These shared activity patterns are more prominent in AIP and F5 than they are in M1. Linear classifiers and decoders were then used to determine whether this shared activity is sensitive or invariant to object identity and hand kinematics. Initial results suggest that this common activity pattern, reduced to its transient movement-specific component, is largely invariant to both object identity and grip kinematics. Thus, while observation-related signals serve well to localize nodes of the cortical grasping network, they may not be suitable for effective BCI training.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Program #/Poster #: P555.05

Topic: E.05. Brain-Machine Interface

Support: NINDS UH3 NS107714

Title: Effects of intracortical microstimulation in somatosensory cortex across multiple human participants

Authors: *C. HUGHES[1], T. CALLIER[4], V. KARAPETYAN[1], C. VERBAARSCHOT[1], N. BRANTLY[2], E. OKOROKOVA[4], J. E. DOWNEY[5], N. G. HATSOPOULOS[4], M. BONINGER[1], J. L. COLLINGER[1], S. J. BENSMAIA[5], R. A. GAUNT[3];
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Abstract: Intracortical microstimulation (ICMS) of the human somatosensory cortex can evoke sensations from the hands of paralyzed individuals and can improve control of prosthetic arms. While these observations demonstrate proof-of-principle, the real potential of this approach remains uncertain as most of the work on the stability of these devices, as well as the perceptual and functional effects of stimulation, has been conducted in single participants at different study locations. The observed effects, however, can be dependent on the implanted devices, implant location, time since injury, and many other factors that are likely to vary across participants. In Pittsburgh and Chicago, we have implanted multiple participants to begin addressing multi-subject and multi-site factors related to ICMS. One participant has been implanted for over 6 years (P2) and two participants have been implanted for approximately one year (P3 and C1), enabling us to examine the recording quality on stimulated electrodes and the perceptual effects of stimulation across three participants. Although P3 and C1 have been implanted for much less time than P2, we have already observed several differences. First, the signal quality increased initially in all participants as assessed with peak-to-peak voltages and the number of high-amplitude waveforms. Signal quality then declined slowly, but there has been variability in how individual electrode arrays behave over time across participants. Some stimulation arrays have outperformed recording-only arrays in motor cortex, while others have not. Second, we have seen the effect of frequency on evoked sensation is dependent on the stimulated electrode, and the presence and spatial distribution of these relationships are dependent on the participant. Finally, survey data collected in all participants showed evoked sensations that followed an expected somatotopy, but the location of the sensations, distribution of evoked qualities, and reported naturalness of the sensations were different across participants. These effects, particularly on recording and stimulation stability, will need to be observed for longer periods of time in both P3 and C1 for a more direct comparison with data from P2. These results demonstrate the importance of repeating studies in multiple participants As sensory restoration through ICMS becomes more common, establishing standardized or comparable assessment and reporting guidelines will be important to enable multi-site replication across multiple participants to understand the true potential of ICMS to restore somatosensation.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Topic: E.05. Brain-Machine Interface

Support: R01 NS053603

Title: Studying the consistency of neural and muscular representation of stereotypical grasps

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Abstract: Primates can perform a rich repertoire of arm and hand movements with remarkable consistency. Recent studies have hypothesized that the fundamental building blocks underlying this consistent behavioral execution are stable latent cortical dynamics within a low-dimensional manifold of neurons controlling motor activity. The stability of these latent representations over time has been established, but little is known about the consistency of representations across individuals. Such consistency would suggest that behaviors could be inferred from neural activity in a robust manner and that such inference could form the basis of brain machine interfaces that generalize even across individuals. The purpose of this study was to explore the consistency of motor behaviors and their neural representation across animals by assessing the similarity of neural and muscular recordings across monkeys performing a variety of grasping tasks.
We trained three monkeys to perform two types of grasps and recorded neural signals from the hand area of primary motor cortex (M1) and intramuscular electromyographic (EMG) signals from several arm, forearm, and hand muscles. We assessed similarity in both the high-dimensional domain of these signals and in their lower dimensional representations. Results show that the high-dimensional neural recordings of different monkeys are largely uncorrelated but that the similarity increases when these recordings are projected into a low-dimensional space. In contrast, EMG signals from the muscles controlling movement were similar in both the recording space and the lower dimensional latent space. In an attempt to extract a single latent space that represented the activity recorded across monkeys, we implemented Canonical Correlation Analysis (CCA) to align the latent dynamics of M1 signals and the EMG signals from each animal. The similarity between the low dimensional manifolds for both M1 signals and EMG signals increased further after CCA alignment. Consequently, we asked how accurately a decoder trained to predict EMG based on aligned latent dynamics from one monkey would perform on aligned latent dynamics from a different monkey. The across-monkey accuracy of this decoder was higher than that of decoders based on both the recorded neural activity and the unaligned latent dynamics.
Our findings suggest that consistent representations of motor activity exist across animals. Discovering this common representation is a crucial first step in designing generalizable BMI decoders that perform well even in the absence of subject-specific tuning.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: NIH GRANT 5UH3NS107714-03

Title: Intracortical microstimulation of human somatosensory cortex can evoke short-latency responses in motor cortex

Authors: *N. SHELCHKOVA[1], A. SOBINOV[1], J. E. DOWNEY[2], E. OKOROKOVA[1], T. CALLIER[1], C. L. HUGHES[3], V. KARAPETYAN[4], J. L. COLLINGER[4], R. A. GAUNT[5], L. E. MILLER[6], M. L. BONINGER[4], N. G. HATSOPOULOS[1], S. J. BENSMAIA[2];
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Abstract: Closed-loop control of a prosthetic limb involves decoding motor intent from motor cortex (M1) while conveying somatosensory feedback via intracortical microstimulation (ICMS) delivered to somatosensory cortex (SC). Decoders are often trained with the assumption that ICMS to SC evokes only negligible activity in M1. However, the known functional connectivity between M1 and SC implies that some activity in the former may be synaptically transmitted to the latter. To test this possibility, we delivered ICMS pulse trains at varying frequencies and amplitudes to SC while measuring the neuronal activity evoked in M1 in human participants implanted with electrode arrays in both SC and M1. First, we found that individual ICMS pulses delivered to SC could evoke action potentials in M1 with latencies as short as 2 ms. Second, the spatial pattern of activation in M1 depended on the location of the stimulating electrode in SC. Third, multi-channel ICMS evoked stronger and more widespread activity than would be predicted from the linear sum of its single-channel counterparts. We propose that closed-loop control may improve if ICMS-induced activation of M1 is taken into consideration in building decoders.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Title: Intracortical brain-computer interfaces to restore arm and hand function in four human participants

Authors: *N. W. BRANTLY[1], E. V. OKOROKOVA[4], C. L. HUGHES[1], T. CALLIER[5], B. DEKLEVA[2], D. HARRINGTON[2], Q. HE[6], A. J. HERRERA[1], F. LIU[2], O. J. LUTZ[5], D. SATZER[5], N. SHELCHKOVA[5], A. SOBINOV[5], C. SPONHEIM[7], A. VAN DRIESCHE[5], J. M. WEISS[2], S. J. BENSMAIA[6], M. BONINGER[2], R. A. GAUNT[2], J. GONZALEZ-MARTINEZ[3], N. G. HATSOPOULOS[6], E. C. TYLER-KABARA[9], P. WARNKE[8], J. E. DOWNEY[6], J. L. COLLINGER[2]; [1]Dept. of Bioengineering, [2]Physical Med. and Rehabil., [3]Dept. of Neurosurg., Univ. of Pittsburgh, Pittsburgh, PA; [4]Committee on Computat. Neurosci., [6]Dept. of Organismal Biol. and Anat., [7]Organismal Biol. and Anat., [8]Dept. of Neurolog. Surgery, [5]Univ. of Chicago, Chicago, IL; [9]Dept. of Neurosurg., Univ. of Texas at Austin, Austin, TX

Abstract: Intracortical brain-computer interfaces (iBCIs) are a promising approach to restore arm and hand function for people with tetraplegia. Here we report the signal quality recorded from Utah Electrode Arrays (UEAs) implanted in motor cortex and the progress toward restoring arm and hand function across four study participants (ages 52, 28, 28, and 57 at time of implant) at two sites: the Universities of Pittsburgh and Chicago. Three participants are currently active, including one participant who has contributed for more than six years. Neural data recorded at the start of each test session were used to quantify signal quality. Active motor array channels were defined as those recording threshold crossings with firing rates >0.7Hz and peak-to-peak voltage (Vpp) >30uV. In all participants, the number of active channels in motor cortex increased over the first ~100 days post-implant before slowly declining. To assess longevity, we report active channels for the most recent session. P1 was implanted for ~32 months and had 48% active channels at the time of explant (due almost entirely to low firing rates, though the signals were sufficient for BCI control of a robotic arm). P2 had 73% active channels at 74 months post-implant, P3 had 97% active channels at 11 months post-implant, and C1 had 72% active channels at 8 months post-implant. These longitudinal neural recordings enabled all participants to achieve kinematic control of a robotic or virtual arm, including endpoint velocity and hand grasp. All participants achieved at least 90% success in a 4D grasp and carry target acquisition task within six months of training, showing improvements in performance over time. Additionally, participants P1, P2, and P3 were able to control a robotic arm to complete an object transfer task that involved picking up and transporting an object as many times as possible with performance ranging from at least 6 to a maximum of 24 transfers in two minutes. Participant C1 has completed this task in a virtual environment. In addition to kinematic control, all active participants (P2, P3, C1) have successfully controlled grasp force of a virtual hand model to interact with objects. The ability to chronically record neural activity from motor cortex has enabled high-dimensional control of arm and hand movements across four participants indicating that these technologies can work consistently for long periods of time, which is promising for future clinical applications. Future work will focus on robust grasp force decoding for dexterous hand control, generalizability of control across task contexts, and integration of touch feedback via intracortical microstimulation of somatosensory cortex.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant UH3NS107714

Title: Harnessing grasp force signals in motor cortex

Authors: *J. E. DOWNEY[1], E. OKOROKOVA[2], A. SOBINOV[1], B. DEKLEVA[3], N. BRANTLY[4], M. BONINGER[3], R. A. GAUNT[3], J. L. COLLINGER[3], L. E. MILLER[5], N. G. HATSOPOULOS[2], S. J. BENSMAIA[1];
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Abstract: Brain-controlled prosthetic arms can be used by people with tetraplegia to complete functional reach and grasp tasks. To date, this prosthetic control has almost exclusively involved decoding movement kinematics from motor signals. While this strategy has achieved a good measure of success, it does not allow for the straightforward, graded application of isometric forces, critical when grasping objects. Furthermore, during natural interactions with objects, force variation results in continuously varying somatosensory feedback, without which force control is compromised. Previous work has shown that, during imagined grasps, force signals in motor cortex are transient, fading during sustained grasp. We hypothesized that this transience of force-related signals in motor cortex stems from the lack of somatosensory feedback.To investigate this possibility, we monitored the activity evoked in the motor cortex of a human participant during 3 closely related conditions: During the first condition the subject attempted to grasp an object with a consistent amount of force for every trial, but received one of 10 possible stimulation amplitudes during the grasp. During the second condition he attempted to grasp with a specified amount of force and received no ICMS feedback. During the final condition, he attempted to grasp with a specified amount of force and received ICMS feedback with an amplitude proportional to that force. Using these three conditions, we identified separate neuronal subspaces related to ICMS and grasp force. Activity that is directly related to the ICMS is not useful for decoding, because the BCI user does not have direct volitional control of the ICMS. Therefore, in an offline analysis, we used neuronal activity exclusively from the force subspace to decode intended grasp force during ICMS and found that the resulting force predictions were both stronger and longer lasting than their counterpart without ICMS. Applying these findings to online control should result in more dexterous and precise control of grasp force, increasing the number of tasks that a BCI user can complete independently.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs or the United States Government. CAUTION: Investigational Device
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Title: Statistical Measures of Nonstationarity in Simulated Neural Data During BCI 2D Control

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Abstract: Intracortical brain-computer interfaces (iBCIs) are designed to bypass damaged motor pathways and provide new links to assistive technologies for people with neuromotor deficits from conditions such as amyotrophic lateral sclerosis, brainstem stroke, and spinal cord injury. The ongoing BrainGate clinical trials of iBCIs have demonstrated impressive progress of enabling rapid point-and-click control over external devices and reach-and-grasp actions with prosthetic arms. However, in order to translate iBCIs for 24/7 practical use, researchers have to design a stable and reliable iBCI system that is effective for supporting continuous, independent use without the oversight of a technician. One challenge is to maintain stable cursor control for long-term use, especially when the decoder becomes ineffective in handling a large degree of within- and across-day nonstationarity in the relationship between neural activity and intended movements. Neural activity underlying consistent behaviors can vary over time due to changes in recording conditions and individuals' cognitive states.

It is important to systematically investigate how different types of nonstationarity can lead to a drop in decoder performance on cursor control. We first simulated neural data during a center-out-and-back task using a feedback control model described in Willett et al. (2017). We perturbed the neural encoding model to simulate various types and severity of nonstationarity, while not updating the decoder trained on the unperturbed model. By looking at the neural-kinematic pair, we then proposed using the hypothesis test offered by Toyoda and Ohtani (1986) to detect a change in our probabilistic encoding model compared to the unperturbed model. However, in general it is not possible to obtain the true intended movement data in clinical settings with tetraplegic participants, especially during independent personal use of the BrainGate system where targets are not instructed. With only neural data available, we found that Wasserstein distance can be a useful metric to measure change in the neural data resulting from a perturbed model. It correlates nicely with the amount of perturbation introduced in our model as well as the mismatch decoder performance on simulated cursor control.

To summarize, we found that the associated p-values from hypothesis test and Wasserstein distance are

both sensitive to different kinds of perturbation.
Next, we will evaluate these methods for detecting nonstationarity in neural activities in real time, and for quantifying the need for decoder recalibration to maintain steady iBCI performance for reliable continuous use.

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Poster

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Samuel and Betsy Reeves
Simons Foundation Collaboration on the Global Brain 543045

Title: Decoding simultaneous dual-effector movements from human premotor cortex in real-time via recurrent neural networks

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Abstract: Intracortical brain-computer interfaces (iBCIs) aim to restore movement and communication to people with paralysis by decoding movement signals from the brain via microelectrodes implanted in the cortex. To date, most iBCI studies have been limited to the control of a single effector for point-and-click typing (e.g., one cursor) and reaching/grasping (e.g., one arm). Recent work has shown that “arm/hand” area of motor cortex represents all body parts, not just the contralateral arm. This opens the door to creating iBCIs that restore the motion of multiple effectors at the same time. However, it may be more challenging to decode the simultaneous motion of multiple effectors, as recent work has also shown that the neural tuning changes nonlinearly during dual-effector motion (i.e., neural tuning during bimanual movement is not simply the linear sum of neural tuning during unimanual movement). We addressed this problem by designing and developing recurrent neural network decoders (RNNs) to enable real-time continuous bimanual control of two cursors on a computer monitor.

Our research participant (T5) has tetraplegia due to spinal cord injury (C4 AIS-C) and is enrolled in the BrainGate2 clinical trial. He underwent implantation of two 96-channel microelectrode arrays (implanted in the dorsal "hand knob" area of motor cortex) approximately 6 years ago. To train the RNNs, our participant first performed an "open-loop" delayed-movement task in which he attempted to move both of his hands in correspondence with two cursors on a screen that traveled at random speeds to targets at random locations. Trials were interleaved with bimanual movements (both hands) and unimanual movements (either the left or right hand by itself). We found changes in neural tuning depending on the movement type, including changes in preferred direction between bimanual and unimanual movements and tuning suppression during bimanual movement. After training and optimizing RNNs with data collected from multiple session days, we demonstrated online continuous control of two cursors via RNN decoders. Future work will assess performance of these RNN decoders against linear decoders and expand to include additional effectors.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P555.12

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C, A2295R, A2827R)
NIH NINDS (UH2NS095548)
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Robert J. and Nancy D. Carney Institute for Brain Science - Brown University
Brown University School of Engineering
MGH-Deane Institute

Title: Enabling a high quality user experience during independent home use of an iBCI by an individual with tetraplegia

Authors: *T. SINGER-CLARK[1], R. GROSS[2], T. HOSMAN[4,2,3], A. KAPITONAVA[1], J. D. SIMERAL[4,2,3], L. R. HOCHBERG[4,2,1,5,3];
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Abstract: Intracortical brain-computer interfaces (iBCIs) have the potential to improve independence for individuals with tetraplegia resulting from injury or neurological disorders such as spinal cord injury or ALS. Using the BrainGate iBCI, paralyzed individuals have displayed general-purpose point-and-click control of an unmodified consumer tablet computer to, among other things, send and receive email and browse the web. However, for iBCI systems to reach their full potential in positively impacting the lives of users with paralysis and achieve widespread adoption, they will need to be usable independently in the home without expert supervision, be enabled and disabled at the user's discretion, and require minimal recalibration - all while providing high performance control of enabling devices. Such features of the iBCI, although potentially quite technically complex, must be readily accessible to users through an intuitive, unintimidating user interface. Here, we describe an iBCI user interface, called BG Home, that was developed to satisfy many of these requirements and to support consistent, long-term independent use of an iBCI by individuals with tetraplegia at home. Versions of BG Home have been in use at home by a clinical trial participant for over a year, typically 2-3 days per week.

The iBCI system processes neural data transmitted wirelessly from the user's head. Caregivers were trained to don and doff the transmitters so the participant could use the system without research staff present which, critically, enabled usage to continue during the COVID-19 pandemic. Through a remote connection, research staff could power the system on, after which the user was free to use the system independently. The iBCI system performs 2D kinematic decoding and discrete multi-gesture decoding to provide mouse cursor control and actions such as click and scroll, all on the participant's own Windows 10 PC, enabling iBCI control of all their familiar applications. The user could pause and resume control of their device by imagining a sequence of gestures. The system detects when the user moves into or out of range of the wireless receiver system and pauses or resumes decoding and neural control appropriately. The GUI component of BG Home, which appears as a small, relocatable, floating button on the user's screen, allows the user to recalibrate neural decoders, see feedback messages from the system, adjust mouse speed, and more.

These innovations supplement the technical capabilities of the iBCI with user-centered features designed to prioritize user satisfaction and usability of iBCI technology in the home setting.

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Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P555.13

Topic: E.05. Brain-Machine Interface

Support: VA Center for Neurorestoration and Neurotechnology (N2864C)
The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the Department of VA or the US Government. Caution: Investigational Device. Limited by Federal Law to Investigational Use

Title: How many people would benefit from an intracortical brain-computer interface?

Authors: *A. DUFFY[1], D. B. RUBIN[1], R. MARUJO[1], D. A. SCHOENFELD[2], L. R. HOCHBERG[1,3,4,5,6]; [1]Dept. of Neurol., [2]Dept. Biostatistics, Massachusetts Gen. Hosp., Boston, MA; [3]Sch. of Engin., [4]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [5]Dept. of Neurol., Harvard Med. Sch., Boston, MA; [6]Dept. of VA Med. Ctr., VA RR&D Ctr. for Neurorestoration and Neurotechnology, Providence, RI

Abstract: Intracortical brain-computer interfaces (iBCIs) have the potential to restore motor function and communication in individuals with severe brain and spinal cord damage/disease. The BrainGate system uses an intracortical microelectrode array implanted in the arm/hand region of the motor cortex to record, decode and translate neural activity to an effector (e.g. robotic arm, computer cursor) during motor imagery. Quantifying the number of people who would benefit from an iBCI would demonstrate to payors, investors, and government and foundation-based agencies the vast unmet need to expand current iBCI research and treatments. We queried the Massachusetts General Brigham (MGB) Research Patient Data Registry (RPDR) (data from 6.5 million patients: 2 billion medical records) to quantify those who would benefit from an iBCI for upper extremity use and/or communication. Querying 170 relevant diagnosis codes resulted in >190,000 cases. We developed a protocol to review records of the 131 individuals with locked-in state (LIS) to characterize these cases as 1.) Likely to benefit from an iBCI 2.) Unlikely to benefit 3.) Severely dysarthric (only symptom) 4.) Withdrawal of life-sustaining therapy (WLST) within 1-year 5.) Death <1-yr from precipitating event (not due to WLST) 6.) Cognitive impairment 7.) Unable to undergo iBCI surgery or 8.) Uncertain due to lack of data. We established a team of 3 clinicians and one neuroscientist to independently characterize the LIS patients to ensure inter-rater reliability. To characterize iBCI benefit across all 170 diagnoses, we pursued a sampling methodology. We grouped diagnoses by modality (upper extremity/communication), and clustered diagnoses with the same estimated proportion of iBCI benefit (e.g. 2.5%, 50%, 90% etc.). We defined any diagnosis with >10,000 cases as its own cluster, resulting in 14 diagnosis clusters. We used a sampling equation that incorporates the variances of these estimated proportions of people who would benefit from an iBCI. This study provides the methodology to characterize iBCI benefit of a subset of people with locked-in state within the MGB system as well as a sampling methodology to perform a more efficient but still statistically valid review of cases across all 170 chosen diagnoses. Extrapolating these proportions to larger national databases (i.e. private insurance, Medicare and the VA) will demonstrate the importance of developing and financing novel iBCI technologies and resources.The MGH Translational Research Center has a clinical research support agreement with Neuralink, Paradromics, and Synchron, for which LRH provides consultative input.

Disclosures: A. Duffy: None. **D.B. Rubin:** None. **R. Marujo:** None. **D.A. Schoenfeld:** None. **L.R. Hochberg:** Other; Neuralink, Paradromics, Synchron.

Poster

P555. Neuroprosthetics: Control of Real and Artificial Arm, Hand, Other Grasping Devices I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P555.14

Topic: D.04. Somatosensation – Touch

Support: DARPA Award HR001120C0120

Title: Relative timing of vibration and electrically-evoked tactile stimuli

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Abstract: Electrical stimulation of the primary somatosensory cortex (S1) can elicit feelings of touch, which can be used as feedback for people with sensorimotor deficits. Characterizing the timing of this artificial touch feedback is critical for predicting how beneficial sensory neuroprostheses will be, as noticeable lags will impede usability. Previous studies have compared the reaction time (RxT) of artificial touch to cutaneous vibration in humans and monkeys [Caldwell et al. 2019; Godlove et al. 2014; Sombeck & Miller 2019]. Even though cortical stimulation bypasses a great deal of neural circuitry, artificial touch was perceived more slowly than vibration. However, prior studies did not closely match the perceived intensity between stimuli, which can strongly influence RxT. Therefore, one goal of this study was to further characterize the RxT of artificial touch. We also sought to measure the perception of simultaneous artificial and natural touch, which informs how cortical stimulation interacts with existing somatosensory circuits. We worked with a human subject who has microelectrode arrays implanted in S1 and retained tactile sensation. In a RxT task, the subject received vibration or artificial touch and responded when he felt the stimulus onset. In a temporal order judgement (TOJ) task, we sequentially delivered vibration and artificial touch and the subject answered which stimulus came first. Vibration and artificial touch were offset by 0, 50, 100, 200, 300, or 500 ms, with 20 trials per offset. In both tasks, we adjusted stimulation levels until the subject reported that vibration and artificial touch felt equal in intensity. The RxT was 352 $\pm$ 10 ms (mean $\pm$ std error) for vibration and 400 $\pm$ 13 ms for artificial touch. Sigmoidal curves were fit to raw TOJ data to extract the point of subjective simultaneity (PSS), representing the time at which two stimuli are maximally simultaneous. When vibration and artificial touch occurred in the same region of the hand, the PSS was -18 ± 16 ms, meaning that vibration must occur before artificial touch in order for the stimuli to be perceived as maximally simultaneous. In summary, our RxT results agree with prior findings: the RxT to vibration is faster than artificial touch. Interestingly, the PSS was close to zero, implying a dissociation between processing time and tactile event sequencing. Nevertheless, even though artificial touch takes ~50 ms longer to perceive than natural touch, the stimuli can be simultaneously delivered to the same hand region and be perceived as simultaneous. This indicates that somatosensory neuroprostheses have the potential to be used without noticeable lag in sensorimotor rehabilitation.

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Poster

P618. Behavioral Effects I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P618.01

Topic: F.05. Neuroimmunology

Support: NIH Grant DP1AT010416
NCCIH Grant R01-AT009741

Title: A glia-derived antimicrobial peptide mediates a brain-gut-brain axis to sustain lifespan

Authors: *W. XU, J. RUSTENHOVEN, A. FERREIRO, C.-A. BURNHAM, Z. PAPADOPOULOS, G. DANTAS, J. KIPNIS;
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Abstract: As a hallmark protein of Alzheimer's disease (AD), amyloid beta was proposed to be an antimicrobial peptide (AMP), which is involved in AD pathogenesis. However, whether and how other brain-derived antimicrobial peptides regulate aging is largely unknown. Here, we used *Drosophila* and identified an evolutionally conserved AMP as a key modulator of aging. This aging-induced AMP is glia-derived and required to sustain life span via the regulation of sleep quanlity. Furthermore, we found that the sleep modulation by the glial AMP was microbiota-dependent. Glial knockdown of the AMP alters the composition of gut microbiota, and microbiota transfer to germ-free flies phenocopies the sleep deficits. Hence, our study identified a glia-derived immune molecule confers a brain-gut crosstalk, and links neuroinflammation with sleep decline during aging.

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Poster

P618. Behavioral Effects I

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Program #/Poster #: P618.02

Topic: F.05. Neuroimmunology

Support: Busch Biomedical Grant, Rutgers University

Title: Deletion of the N/OFQ peptide or its receptor NOP alters the effects of inflammatory endotoxin LPS on the exploratory response to a novel object and open field

Authors: *M. NISSENBAUM[1], P. PAYNE[1], C. CARDINALE[1], J. E. PINTAR[2], A. W. KUSNECOV[1];
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Abstract: The precursor propeptide for Nociceptin/Orphanin FQ (ppN/OFQ) and the nociceptin receptor (NOP) are widely distributed in the brain, particularly limbic regions like the hippocampus, amygdala, and hypothalamus. The N/OFQ peptide has been linked to a variety of behavioral changes, including nociception, reward, and anxiety regulation. Activation of NOP often acts in opposition to a variety of actions including stress, inflammation and mu-opioid receptor stimulation. Here we examined in

C57BL/6 background NOP-deficient [NOP KO] (16F; 20M) or ppN/OFQ-deficient mice [ppN/OFQ KO] (8F; 11M) and their littermate WT controls (8F; 11M) the behavioral and neural response to an inflammatory stimulus, LPS (200μg/kg IP), which reliably elicits systemic IL-1β, TNFα and IL-6. Mice of each genotype were given Saline (13/genotype) or LPS (11/genotype) and subjected to open field (OF)/novel object behavioral testing after 90 mins. A subset of mice per group remained in the home cage. All mice were killed 90 mins after behavioral testing or home cage for spleen cytokine measures and brain c-Fos IHC (quantification in progress). The OF/novel object test assesses anxiety-like responses to contextual and object novelty and consisted of 5 mins of exploration in an empty OF (Phase 1) followed by 5 mins with a novel object placed in the center of the OF (Phase 2). Object introduction reduced exploration for all parameters (distance travelled in inner and border zones, entries into the inner zone, time spent in each zone, latency to enter the inner zone, and latency to approach the object; $p<0.05$). Compared to WT controls, ppN/OFQ KO mice travelled less total distance ($p<0.05$) in both sexes. For both phases, an interaction effect between treatment and genotype was present in which LPS caused reduced total distance travelled in NOP and ppN/OFQ KO mice, but increased distance travelled in WT mice ($p<0.05$). Across sex, LPS-treated NOP KO mice also spent less time in the inner zone during Phase 2, while LPS female NOP KO mice entered the inner zone less than LPS females of other genotypes ($p<0.03$). WT animals interacted with the object more than NOP KO mice. These data suggest that the NOP/OFQ system may counteract the proinflammatory effects of LPS in anxiogenic/exploratory environments. Limbic brain regions are being analyzed to determine if in NOP or ppN/OFQ KO mice c-Fos expression is enhanced in response to behavioral and/or inflammatory stimulation.

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Poster

P618. Behavioral Effects I

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Topic: F.05. Neuroimmunology

Support: Research Fund KU Leuven (C24/18/067)
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Leuven Kanker Institute
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Kinderkankerfonds

Title: Neuroinflammation and its association with cognition, neuronal markers and peripheral inflammation after chemotherapy for breast cancer

Authors: *G. SCHROYEN[1], J. BLOMMAERT[2], D. VAN WEEHAEGHE[3], C. SLEURS[2], M. VANDENBULCKE[4], N. DEDONCKER[4], S. HATSE[2], A. GORIS[4], M. KOOLE[3], A. SMEETS[2], K. VAN LAERE[3], S. SUNAERT[1], S. DEPREZ[1];

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Abstract: Background: To uncover mechanisms underlying chemotherapy-induced cognitive impairment in breast cancer, we studied new biomarkers of neuroinflammation and neuronal survival. **Methods:** This cohort study included 74 women (47±10 years) from September 22, 2017, until August 20, 2020. Nineteen chemotherapy-treated and 18 chemotherapy-naïve patients with breast cancer were assessed one month after completion of surgery and/or chemotherapy, and 37 healthy controls were included. Assessments included neuropsychological testing, questionnaires, blood sampling for 17 inflammatory and 2 neuronal survival markers (neurofilament light-chain (NfL) and brain-derived neurotrophic factor (BDNF) and PET-MR neuroimaging. To investigate neuroinflammation, translocator protein (TSPO) [^{18}F]DPA714-PET-MR was acquired for 15 participants per group, and evaluated by volume of distribution normalized to the cerebellum. **Results:** Chemotherapy-treated patients showed higher TSPO expression, indicative for neuroinflammation, in the occipital- and parietal lobe when compared to healthy controls or chemotherapy-naïve patients. After partial-volume correction, differences with healthy controls persisted (p_{FWE}<.05). Additionally, compared to healthy- or chemotherapy-naïve controls, cognitive impairment (17-22%) and altered levels in blood markers (F≥3.7, p≤.031) were found in chemotherapy-treated patients. NfL, an axonal damage marker, was particularly sensitive in differentiating groups (F=105, p=4.2E-21), with levels 20-fold higher in chemotherapy-treated patients. Lastly, in chemotherapy-treated patients alone, higher local TSPO expression was associated with worse cognitive performance, higher blood levels of BDNF/NfL and decreased fiber cross-section in the corpus callosum (p_{FWE}<.05). **Conclusion:** These findings suggest increased neuroinflammation is associated with chemotherapy-related cognitive impairment in breast cancer. Additionally, NfL could be a useful biomarker to assess neurotoxic effects of anticancer chemotherapies.

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Poster

P618. Behavioral Effects I

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Program #/Poster #: P618.04

Topic: F.05. Neuroimmunology

Support: National Institute of Mental Health (R21MH117483
University of Cincinnati College of Medicine Research Innovation/Pilot Grant

Title: Ptsd and airway inflammation: a role of t helper 17/il-17a in fear-memory regulation

Authors: *E. ALLGIRE[1], R. AHLBRAND[2], J. MCALEES[3], I. LEWKOWICH[3], R. SAH[1,2];
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Abstract: Posttraumatic stress disorder (PTSD), a trauma associated disorder, is facilitated by maladaptive fear responses that persist beyond typical trauma response. Investigating mechanisms that facilitate persistence of traumatic fear memories will lead to effective screening and treatment regimen for individuals at risk for PTSD. Our lab focuses on the role of asthma-associated airway inflammation (AI) in fear regulation. Of interest, recent evidence supports a synergistic effect of T helper 2 (Th2)/T helper 17 (Th17) mixed response in severe asthma. Higher asthma severity has a greater association with PTSD; thus we have chosen to directly target Th17 signaling. Our recent studies highlight a role of AI and Th17 signaling in regulation of fear extinction, a PTSD relevant behavior. These findings are consistent with strong epidemiological links between severe asthma and PTSD. Using genetic and immunological interventions the current study examined the necessity and sufficiency of IL-17 in regulating extinction. A pilot RNAseq run was conducted to map AI-induced changes in brain transcriptomic signatures. We hypothesized that Th17/IL17A expansion and elevated CNS IL17A will lead to increased fear related behaviors, as well as significant alterations in immune-associated transcripts. Methods: 1) For Th17/Il17A expansion, intratracheal allergen (house dust mite (HDM)) was administered to BALB/c mice with a control antibody (mild) or a C5a receptor-blocking antibody that has been shown to shift the immune response to a mixed Th2/Th17 phenotype. 2) severe asthma prone A/J mice, or A/J mice lacking IL-17 receptor A (IL-17RA KO) were generated. 3) To test sufficiency, recombinant IL17A was administered intracerebroventricularly (ICV) to BALB/c mice prior to behavior. Fear conditioning and extinction was performed in all three manipulations. Consistent with our hypothesis, we found increased extinction freezing in BALBc-C5 mice expressing a mixed Th2/Th17 phenotype, and reduced extinction freezing in IL-17RA knockout mice. Direct administration of lL17A promoted anxiogenic (reduced open arm time) behavior, however, no significant effects on fear extinction were observed. Collectively, these data suggest that Th17A/IL17A expansion and IL17A signaling is necessary for fear extinction deficits associated with airway inflammation, however, indirect mechanisms or other secondary mediators are required for IL17A-mediated fear regulation. Overall, our work provides novel mechanistic information on how airway inflammatory mediators can modulate PTSD-relevant fear behavior and is highly relevant for understanding PTSD association with asthma.

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Poster

P618. Behavioral Effects I

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Program #/Poster #: P618.05

Topic: F.05. Neuroimmunology

Support: T32 MH014276
Charles B.G. Murphy Fund
State of Connecticut Department of Mental Health and Addiction Services

Title: Investigating the persistent impact of developing germ free on reward learning and motivation in adult male and female mice after conventionalization

Authors: *S. L. THOMPSON[1], S. M. GROMAN[1,2], N. W. PALM[1], J. R. TAYLOR[1];
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Abstract: The gut microbiome is a critical factor in the developmental and behavioral mechanisms underlying psychiatric disorders. Mounting evidence indicates that the gut microbiome influences reward-based behavior, but the extent and mechanisms are not fully understood. Here, we assessed the effects of germ free status during development on aspects of instrumental reward learning and motivation for food reward in adult mice after conventionalization (i.e., ex-germ free). C57BL/6 mice were conventional (n = 12 female/11 male) or ex-germ free (n = 12 female/11 male). Ex-germ free mice were bred in sterile isolators and then conventionalized at eight weeks old with stool from their conventional counterparts. In adulthood, mice were food-restricted to 85% of free-feeding weight. Hedonic value was assessed by measuring free-access intake of three concentrations of sweetened condensed milk. Mice were trained in an instrumental task to respond for 10% sweetened condensed milk on a fixed ratio-1 reinforcement schedule to assess reward learning. Next, mice were tested on a progressive ratio schedule and on an effort discounting task to measure aspects of effortful motivation. Data were analyzed with change point analyses, cox proportional hazard models, demand functions, factor analyses, and generalized estimating equations, with alpha = 0.05 and p-values corrected for multiple comparisons. Sweetened condensed milk consumption was unaffected by ex-germ free status. Ex-germ free mice acquired the instrumental response slower than conventional mice ($p<.0001$), and this effect was larger in females. However, all groups ultimately achieved equivalent performance. Ex-germ free mice consistently reached lower breakpoints on the progressive ratio schedule ($p<.01$). In the effort discounting task, ex-germ free mice disproportionately discounted the higher effort, larger reward option in an effort-dependent manner ($p<.0001$) and exhibited a larger global effort discounting parameter than conventional mice ($p<.05$). Overall, females learned faster and exerted more effort to acquire rewards compared to males ($p's<.05$). A factor analysis revealed multiple dissociable aspects of motivation and learning, where the learning factor best predicted group assignment. Together, absence of a microbiome during development caused persistent changes in instrumental reward learning and motivation in adult conventionalized mice, particularly in females, but without disruption of basic hedonic drive for a palatable liquid food reward. These results suggest a critical role for the microbiota in the neurodevelopmental mechanisms that underlie reward learning and motivation.

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Poster

P618. Behavioral Effects I

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Program #/Poster #: P618.06

Topic: F.05. Neuroimmunology

Support: NIH Grant 1R21AG070412-01

Title: Chronic neuroinflammation and behavior changes with continuous allergen exposure in a mouse model of cow's milk allergy

Authors: *A. BRISHTI, D. GERMUNDSON, N. SMITH, K. NAGAMOTO-COMBS;
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Abstract: Cognitive and behavioral changes are often observed in food allergic individuals. Although the mechanism by which food allergy influences cognition and behavior has not been defined, exposure to an allergen is likely the trigger since the removal of suspected food from their diet reportedly improves the associated symptoms. Importantly, these individuals seem capable of consuming offending foods without severe discomfort or anaphylaxis. Consequently, they may not be aware of their food hypersensitivity or necessarily concerned with allergen avoidance, repeatedly placing themselves at risk of allergen exposure and its sequelae. Previously, we demonstrated that inducing cow's milk allergy (CMA) in C57BL/6J mice via sensitization to bovine β-lactoglobulin (BLG) resulted in neuroinflammation with associated anxiety- and depression-like behavior, even though the mice did not display anaphylaxis upon acute allergen challenge. We hypothesized that these allergen-induced peripheral and central inflammatory effects would be prolonged or exacerbated when allergen exposure is recurrent for an extended period. To test this hypothesis, we developed a chronic allergen exposure paradigm by placing BLG-sensitized mice on a whey-containing diet for 3 months to simulate continued dairy consumption by individuals with non-anaphylactic CMA. At the completion of a 5-week sensitization procedure, BLG-sensitized mice showed elevated plasma levels of BLG-specific IgE and IgG1 despite the lack of overt allergic reactions as reported previously, indicating CMA development. After 3 months of whey diet consumption, the allergen-specific immunoglobulin levels and depression-like behavior were comparable in all groups. However, BLG-sensitized mice performed the elevated zero maze test with increased latency to enter the open zones and the cross maze test with decreased number of successful arm alternations, exhibiting anxiety-like behavior and spatial-memory impairment, respectively. In addition, several inflammatory cytokines were elevated in the brains of BLG-sensitized mice on the whey diet, particularly in the hippocampus, compared to respective sham mice or BLG mice placed on a whey-free diet after sensitization. Moreover, BLG-sensitized mouse brains showed increased glial fibrillary acidic protein immunoreactivity. Our results indicated that peripheral and central inflammation and behavioral changes were differentially affected in BLG-sensitized mice by the presence of allergens in their diet and the duration of consumption.

Disclosures: A. Brishti: None. **D. Germundson:** None. **N. Smith:** None. **K. Nagamoto-Combs:** None.

Poster

P618. Behavioral Effects I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P618.07

Topic: F.05. Neuroimmunology

Support: NIH R01NR019531
UCCoM, Research Innovation Grant
UCCoM, PSP, Pilot Award

Title: Early life cancer and chemotherapy exposure results in cognitive deficits: a potential role for brain and gut cytokine responses

Authors: J. P. KONSMAN[1], C. J. LAAKER[2], K. R. LLOYD[3], B. L. SMITH[4], M. A. SMAIL[5], ***T. M. REYES**[6];
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Abstract: Survival rates for acute lymphoblastic leukemia (ALL), the most common childhood cancer, are now close to 90%, but survivors of childhood cancer are at an increased risk for long term cognitive deficits, particularly affecting executive function (e.g., attention, planning, inhibitory control, cognitive flexibility). The chemotherapeutic agent methotrexate (MTX) is used to treat most ALL patients, and is closely associated with executive function deficits. Thus a pressing need exists to define the mechanisms that link MTX exposure to cognitive dysfunction.
To that end, we have developed a translationally relevant mouse model of leukemia survival that combines cancer exposure (mouse leukemic cell line (L1210 cells) with contemporary chemotherapeutic drugs (vincristine and MTX, with leucovorin rescue) administered during early life. Male and female mice were tested several weeks later using novel object recognition (recognition memory) and 5-choice serial reaction time task (executive function). Gene expression of proinflammatory, white matter and synapse-associated molecules was assessed in the prefrontal cortex and gut both acutely after chemotherapy and chronically after cognitive testing. Early life cancer-chemotherapy exposure resulted in recognition memory and executive function deficits in adult male mice. Prefrontal cortex expression of the chemokine Ccl2 was increased acutely, while gut expression of the proinflammatory cytokine tumor necrosis factor-alpha was elevated both acutely (both sexes) and chronically (males only). Inflammation in the gut was related to prefrontal cortical proinflammatory and synaptic gene expression changes, as well as to executive function deficits. Collectively, these data indicate that the current protocol results in a robust mouse model in which to study cognitive deficits in leukemia survivors, and suggest that gut inflammation may represent a novel contributor to adverse CNS consequences of early life chemotherapy.

Disclosures: J.P. Konsman: None. **C.J. Laaker:** None. **K.R. Lloyd:** None. **B.L. Smith:** None. **M.A. Smail:** None. **T.M. Reyes:** None.

Poster

P618. Behavioral Effects I

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P618.08

Topic: F.05. Neuroimmunology

Support: NIH R21MH117482

Title: Microglia Depletion in Adult Female Rats Promotes the Display of Maternal Behavior

Authors: *C. DYE[1], D. FRANCESCHELLI[2], B. LEUNER[1], K. LENZ[1];
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Abstract: The peripartum period is a time of dramatic shifts in the peripheral immune system, particularly significant immunosuppression which allows the fetus to be carried to term. Interestingly, we

and others have also demonstrated significant neuroimmune changes that occur during pregnancy, most prominently a decreased number of microglia across limbic brain regions (Haim, et al., 2017; Posillico & Schwarz, 2016). However, the functional significance of peripartum microglial alterations remains unclear. Given that these microglial decreases emerge in late pregnancy, we hypothesize that they are important for the coordinated onset and display of maternal behavior. To test this, we recapitulated the peripartum neuroimmune profile by depleting microglia in non-mother rats. Adult female virgin rats are typically not maternal but can be induced to behave maternally towards foster pups following repeated exposure, a process called maternal sensitization. BLZ945, a selective colony-stimulating factor 1 receptor (CSF1R) inhibitor, was administered systemically to virgin rats 2 times 48 hours apart, which led to ~75% decreases in microglia number in the brain within 24 hours of the last injection. BLZ- and vehicle-treated females then underwent maternal sensitization via daily exposure to foster pups. We found that BLZ-treated females met criteria for displaying maternal behavior significantly sooner than vehicle-treated females. Moreover, BLZ-treated animals displayed increased pup-directed behaviors including licking and sniffing. BLZ-treated animals also displayed reduced anxiety-like behaviors as measured by increased entries and time in the center of an open field. Ongoing work examining factors that facilitate experience-dependent plasticity, such as perineuronal nets, that are typically upregulated in the absence of microglia, show promise as mediators of the changes we report here. Though previous work suggested that microglial depletion does not significantly affect behavior in adult males (Elmore et al., 2014; Dagher, et al., 2015), our results demonstrate for the first time that microglia are crucial regulators of behavior in the adult female brain, and might be particularly important in the context of maternal care.

Disclosures: C. Dye: None. **D. Franceschelli:** None. **B. Leuner:** None. **K. Lenz:** None.

Poster

P618. Behavioral Effects I

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P618.09

Topic: F.05. Neuroimmunology

Support: NIH Grant AT010416
NIH Grant AG034113
NIH Grant NS096967
NIH Grant AG057496

Title: Il-4 regulates synaptic plasticity and memory through il-4ra on gabaergic neurons

Authors: *J. HERZ[1], Z. FU[2], K. KIM[1], T. DYKSTRA[1], M. WALL[2], H. LI[3], A. SALVADOR[1], B. ZOU[4], N. YAN[4], S. BLACKBURN[1], P. ANDREWS[2], D. GOLDMAN[1], Z. PAPADOPOULOS[1], I. SMIRNOV[1], X. XIE[4], J. KIPNIS[1];
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Abstract: Mechanisms governing how immune cells and their derived molecules impact homeostatic brain function are still poorly understood. Here, we elucidate neuronal mechanisms underlying effects of T cells on synaptic function and episodic memory. Depletion of CD4 T cells led to memory deficits and impaired long-term potentiation. In addition, severe combined immune-deficient (SCID) mice exhibited amnesia, which was reversible by repopulation with T cells from wild-type but not from IL-4-knockout mice. We further demonstrated that the impaired cognition was mediated via IL-4 receptors (IL-4R) expressed on neurons but not myeloid cells in the healthy brain. To study the effect T cells are playing on cognition in depth, exploration of neurons participating in memory processing by single-nuclei RNAseq, provided insights into synaptic organization, plasticity-associated pathways and genes regulated by T cells and IL-4. IL-4Rα knockout in inhibitory neurons impaired contextual fear memory, suggesting participation of an IL-4-associated switch in regulating synaptic function and promoting contextual fear memory. These findings provide insights into immune dysfunction seen in neurological and psychiatric conditions. They also indicate that certain T cell subsets drive processing steps in the brain and potentially relay information to modulate mammalian behavior.

Disclosures: J. Herz: None. **Z. Fu:** None. **K. Kim:** None. **T. Dykstra:** None. **M. Wall:** None. **H. Li:** None. **A. Salvador:** None. **B. Zou:** None. **S. Blackburn:** None. **P. Andrews:** None. **D. Goldman:** None. **Z. Papadopoulos:** None. **I. Smirnov:** None. **X. Xie:** None. **J. Kipnis:** None.

Poster

P650. Mechanisms of Disordered Feeding

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P650.01

Topic: F.09. Food and Water Intake and Energy Balance

Title: Use of foods of varying palatability to induce binge-like eating behavior in male and female rats: Effects of lisdexamfetamine administration alone and in combination with dopamine antagonists with varying receptor selectivity profiles

Authors: *R. E. PRESBY[1], J. C. MASTHAY[1], M. SHEKAR[1], A. MEMON[1], M. BRAUN[1], R. A. ROTOLO[1], A. ECEVITOGLU[1], E. M. ZORDA[1], C. CARRATALÁ-ROS[2], E. ARIAS-SANDOVAL[2], N. M. MEKA[1], S. M. SRINATH[1], M. CORREA[2], J. D. SALAMONE[1];
[1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Psicobiologia. Univ. Jaume I, Castello, Spain

Abstract: Binge Eating Disorder (BED) is characterized by feelings of a lack of control in food consumption causing an individual to consume large amounts of food in a short period of time, leading directly to an array of physical and mental health sequelae. Animal models of binge-like eating behavior are essential for interrogating the brain systems underlying binge eating. Extensive work has demonstrated that intermittent and restricted access to highly palatable food in rats promotes an escalation of food intake. The only medication currently FDA approved for the treatment of BED, lisdexamfetamine (LDX; *Vyvanse*), acts as a d-amphetamine pro-drug (i.e., slow-release formulation) to facilitate dopamine (DA) transmission via inhibition of DA transport and stimulation of release. The focus of the present work is on the development of binge-like eating behavior in male and female rats involving food types with varying palatability, the manipulation of this behavior through administration of LDX, and the role

that DA receptors may be playing in the regulation of binge-like eating behavior through co-administration of various selective and non-selective DA receptor subtypes. Results indicate that the degree of induced binge-like eating behavior differed across food-type (chocolate > high-carbohydrate pellets > grain pellets) but LDX administration significantly reduced intake of all foods. A partial reversal of this LDX-induced reduction in binge-like eating of chocolate was seen after co-administration of selective antagonists for D1 and D2 DA receptors, as well as the non-selective DA antagonist flupenthixol. This indicates a role for both DA D1 and D2 receptor subtypes in the suppression of binge-like eating induced by LDX, but the partial nature of the reversal also leaves open the possibility of involvement from other neurotransmitters such as norepinephrine.

Disclosures: R.E. Presby: None. **J.C. Masthay:** None. **M. Shekar:** None. **A. Memon:** None. **M. Braun:** None. **R.A. Rotolo:** None. **A. Ecevitoglu:** None. **E.M. Zorda:** None. **C. Carratalá-Ros:** None. **E. Arias-Sandoval:** None. **N.M. Meka:** None. **S.M. Srinath:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

P650. Mechanisms of Disordered Feeding

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P650.02

Topic: F.09. Food and Water Intake and Energy Balance

Support: IBACS

Title: Characterization of the catecholamine uptake inhibitor bupropion and the opioid antagonist naltrexone on binge-like eating behavior

Authors: *J. C. MASTHAY[1], R. E. PRESBY[1], R. A. ROTOLO[1], A. ECEVITOGLU[1], E. M. ZORDA[1], C. CARRATALÁ-ROS[2], E. ARIAS-SANDOVAL[2], N. M. MEKA[1], S. M. SRINATH[1], M. CORREA[2], J. D. SALAMONE[1];
[1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Psicobiologia Univ. Jaume I, Castello, Spain

Abstract: The overconsumption of highly palatable foods, as seen in Binge Eating Disorder (BED), represents a substantial risk for both physical and mental health. Currently, the only medication FDA approved for the treatment of BED is lisdexamfetamine (LDX; *Vyvanse*) a d-amphetamine pro-drug (i.e., slow-release formulation) that acts to facilitate dopamine (DA) transmission. Development of novel therapies that will lead to more robust treatment options for patients diagnosed with BED is imperative, and animal models of binge-like eating behavior play an integral role in treatment development. An animal model of binge-like eating in which rats are given intermittent, short access to a highly palatable food (Cadbury's Milk Chocolate) was used in the present experiments. This research aimed to characterize the effects of two commonly prescribed drugs for weight-loss that have been suggested as novel treatment options for BED: the catecholamine uptake inhibitor bupropion (BUP; 10.0-40.0 mg/kg IP) and the opioid antagonist naltrexone (NTX; 0.1-3.0 mg/kg IP) on binge-like eating behavior in male and female rats. A significant reduction in binge-like eating was found at the highest dose of BUP and all doses of NTX in male rats. Female rats also showed suppression of chocolate intake after 40.0 mg/kg

BUP. These results are similar to what has been reported in humans, and give credence to the use of these drugs as treatment options for BED. Additional studies should examine the effects of bupropion administered in combination with naltrexone, which is an effective combined treatment for people with obesity. Furthermore, future research should determine the specific brain mechanisms through which these drugs act to suppress intake of palatable foods.

Disclosures: J.C. Masthay: None. **R.E. Presby:** None. **R.A. Rotolo:** None. **A. Ecevitoglu:** None. **E.M. Zorda:** None. **C. Carratalá-Ros:** None. **E. Arias-Sandoval:** None. **N.M. Meka:** None. **S.M. Srinath:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

P650. Mechanisms of Disordered Feeding

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P650.03

Topic: F.09. Food and Water Intake and Energy Balance

Support: Texas Woman's University Research Enhancement Program
Texas Woman's University Startup funds

Title: Knockout of MeCP2 in POMC neurons increases preference for high fat diet but does not alter motivation for food reward

Authors: P. FRAYRE[1], **A. BAIRD**[1], J. FRAYRE[1], K.-P. RUBIO[1], M. J. MORRIS[1], E. S. NA[2]; [1]Texas Woman's Univ., Denton, TX; [2]Texas Woman's Univerisity, Denton, TX

Abstract: The obesity epidemic has afflicted 42% of adults in the United States with obesity rates increasing at alarming rates worldwide. Monogenic causes of obesity are extremely rare thus there must other contributing factors to obesity. Disruptions in Methyl-CP-G binding Protein 2 (MeCP2) gene function have been associated with the etiology of Prader Willi Syndrome, a neurodevelopmental disorder characterized by hyperphagia and obesity. MeCP2 is a neuroepigenetic factor that activates or represses specific genes and when knocked out in mice produces obesity and hyperphagia. Given that MeCP2 knockout (KO) mice are hyperphagic, it is not clear if MeCP2 KO mice find food more rewarding or are more motivated to acquire food reward. Using transgenic mice in which MeCP2 is knocked out specifically in pro-opiomelanocortin neurons of the arcuate nucleus of the hypothalamus, POMC-MeCP2 KO mice were subjected to a conditioned place preference test and operant conditioning to assess food preference and motivation to acquire food reward. Body weight and high fat (HF) diet intakes were also recorded to examine the effects of POMC specific knockout of MeCP2 on body weight homeostasis after exposure to an obesogenic diet. Our current data suggest that POMC-MeCP2 KO mice have an increased preference for HF diet as demonstrated by increased time spent in the chamber paired with HF diet (conditioned place preference) but showed less motivation to work for food reward as evidenced by decreased breakpoint in a progressive ratio operant conditioning task. POMC-MeCP2 KO mice also displayed higher body weight relative to WT control mice. Taken together, these data indicate that POMC-specific MeCP2 disruption may cause KO mice to be more sensitive to obesogenic diets and increase preference for high fat food.

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Poster

P650. Mechanisms of Disordered Feeding

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P650.04

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH-NIDDK R01-DK114008

Title: Altered hedgehog signaling in adult neurons results in obesity

Authors: *S. E. ENGLE, P. J. ANTONELLIS, K. M. BREWER, R. BANSAL, N. F. BERBARI; IUPUI, Indianapolis, IN

Abstract: Primary cilia are important signaling centers found on nearly every cell type, including neurons throughout the brain. Their dysfunction leads to several different disease phenotypes including neurocognitive deficits. In ciliopathies such as Bardet-Biedl and Alström syndromes, patients present with hyperphagia associated obesity. Additionally, conditional cilia loss in adult mice leads to hyperphagia and obesity, yet how cilia dysfunction contributes to feeding behavior is complex and remains controversial and unclear. One well known pathway coordinated by cilia in mammals is the hedgehog pathway. While crucial for embryonic development, little is known about its role in terminally differentiated neurons. Here we show components of the hedgehog pathway are expressed in the feeding centers of the hypothalamus of adult mice. Furthermore, *in situ* hybridization has revealed hedgehog pathway expression in specific neuronal populations involved in feeding behavior. We also demonstrate by qPCR that hedgehog pathway activity appears responsive to nutritional status and is altered upon obesity. We next explored how body weight is impacted by altering the hedgehog pathway *in vivo.* Using a genetic approach, we constitutively activated hedgehog signaling specifically in adult melanin concentrating hormone receptor 1 (MCHR1) expressing neurons. MCHR1 is a ciliary GPCR with well-recognized roles in energy homeostasis. Hedgehog pathway activation in MCHR1 neurons in adult mice resulted in hyperphagia and obesity. These findings suggest a novel role for ciliary hedgehog signaling in the regulation of feeding behavior and adult energy homeostasis. Current studies are focused on understanding interactions between the hedgehog and MCH signaling pathways in adult neurons. Understanding how the hedgehog pathway influences ciliary GPCR signaling in terminally differentiated neurons could reveal molecular mechanisms associated with clinical features of ciliopathies, such as hyperphagia-associated obesity.

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Poster

P650. Mechanisms of Disordered Feeding

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Program #/Poster #: P650.05

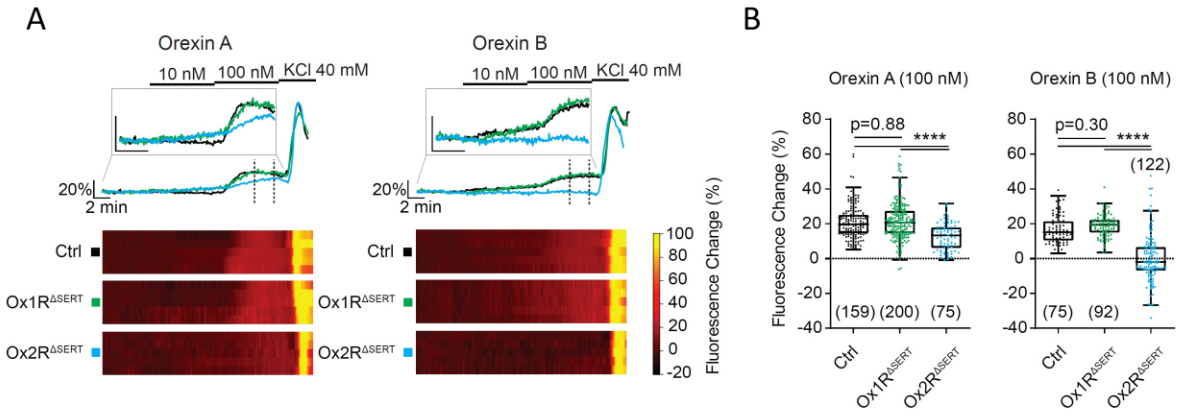
Topic: F.09. Food and Water Intake and Energy Balance

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Title: Orexin receptors 1 and 2 in serotonergic neurons differentially regulate peripheral glucose metabolism in obesity.

Authors: *G. YEGHIAZARYAN[1], X. XIAO[2], S. HESS[1], P. KLEMM[2], A. SIEBEN[2], A. KLEINRIDDERS[2], D. MORGAN[3], T. WUNDERLICH[2], K. RAHMOUNI[3], D. KONG[4], T. SCAMMELL[4], B. LOWELL[4], J. BRUENING[2], C. HAUSEN[2], P. KLOPPENBURG[1];
[1]Univ. of Cologne, Cologne, Germany; [2]Max Planck Inst. for Metabolism Res., Cologne, Germany; [3]Univ. of Iowa, Iowa City, IA; [4]Beth Israel Deaconess Med. Ctr. and Harvard Med. Sch., Boston, MA

Abstract: Orexins (hypocretins) are neuropeptides expressed by distinct neurons in the lateral hypothalamic area (LHA) and adjacent regions, including the perifornical area and dorsomedial and posterior hypothalamus in humans and rodents. The orexin system consists of the two distinct neuropeptides, orexin-A and orexin-B (hypocretin-1 and -2), which are both derived from a common precursor peptide, and they act on two G-protein coupled receptors, orexin receptor type 1 (Ox1R) and type 2 (Ox2R). The wake-active orexin system plays a key role in maintaining dynamic regulation and daily rhythm of peripheral glucose homeostasis. It has been described to have dual roles in regulating blood glucose, possibly through the autonomic nervous system. Here, we systematically investigated the expression and distribution of orexin receptors in serotonergic neurons in raphe nucleus, and the impact of optogenetic activation of orexin signaling and specific inactivation of Ox1R or Ox2R signaling in serotonin transporter (Sert)-expressing cells on glucose metabolism and energy homeostasis. We show that Ox1R and Ox2R are predominantly expressed in dorsal raphe nucleus-dorsal and -ventral, respectively. Serotonergic neurons in ventral median raphe nucleus and raphe pallidus selectively express Ox1R. Inactivation of Ox1R in serotonin transporter-expressing cells of mice reduced insulin sensitivity in diet-induced obesity, mainly by decreasing glucose utilization in brown adipose tissue and skeletal muscle. Selective inactivation of Ox2R improved glucose tolerance and insulin sensitivity in obese mice, mainly through a decrease in hepatic gluconeogenesis. Optogenetic activation of orexin neurons in the lateral hypothalamus or orexinergic fibers innervating the raphe pallidus impaired or improved glucose tolerance, respectively. Collectively, the present study assigns orexin signaling in serotonergic neurons critical yet differential orexin Ox1R- and Ox2R-dependent functions in the regulation of systemic glucose homeostasis.



Orexin A and orexin B effect on $[Ca^{2+}]_i$ of serotonergic neurons in DRV measured with GCaMP6. Recordings were performed in brain slices from control, Ox1R$^{\Delta SERT}$, and Ox2R$^{\Delta SERT}$ male mice, with GCaMP6 expression in serotonergic neurons. (A) Original recordings (top) and heat maps of 5 individual neurons for each set of experiments (bottom). The recordings show the responses to the orexins and high K^+ saline. Dashed lines indicate the range where the responses were quantified. (B) Calcium responses upon 100 nM orexin A and orexin B. Data are shown as the percentage of the maximal response to high K^+ saline.

Disclosures: G. Yeghiazaryan: None. **X. Xiao:** None. **S. Hess:** None. **P. Klemm:** None. **A. Sieben:** None. **A. Kleinridders:** None. **D. Morgan:** None. **T. Wunderlich:** None. **K. Rahmouni:** None. **D. Kong:** None. **T. Scammell:** None. **B. Lowell:** None. **J. Bruening:** None. **C. Hausen:** None. **P. Kloppenburg:** None.

Poster

P650. Mechanisms of Disordered Feeding

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Program #/Poster #: P650.06

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH K99DK120869
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CTSA/NIH-NCATS FP00002457

Title: Novel molecular profiling based pharmacological strategy leads to the identification of a preclinical compound for weight management.

Authors: *M. SCHNEEBERGER PANE[1], N. L. BRICE[2], K. PELLEGRINO[1], L. PAROLARI[1], J. SHAKED[1], T. TOLPIKO[3], K. PAGE[2], D. BARROWS[1], M. ORTUNO[4], T. CARROLL[1], N. RENIER[3], A. R. NECTOW[4], M. CARLTON[2], N. HEINTZ[5], J. FRIEDMAN[1];
[1]The Rockefeller Univ., New York, NY; [2]Cerevance, Cambridge, United Kingdom; [3]ICM, Paris, France; [4]Columbia Univ., New York, NY; [5]Lab. of Mol. Biol., Rockefeller Univ., New York, NY

Abstract: Distinct neural subpopulations in the Dorsal Raphe Nucleus (DRN) of the brainstem have recently been shown to acutely regulate food intake, energy expenditure and body weight[1,2]. Intriguingly, in the DRN, excitatory Vglut3- expressing glutamatergic neurons (DRN^{Vglut3}) induce satiety and increase locomotion. Thus, chronically activating DRN^{Vglut3} neurons could induce sustained feeding suppression and in principle be used to manage weight upon obesity.Here, we report that indeed chronic activation of DRN^{Vglut3} neurons using DREADDs stably reduces food intake and body weight in both genetic and diet induced obese (DIO) mice models, bypassing leptin resistance. Given those effects, we next designed a molecular profiling based pharmacological strategy to identify specific therapeutic targets in those neurons. By means of a three-tiered approach combining Translational Affinity Purification (TRAP) of DRN^{Vglut3} neurons with bioinformatic enrichment comparison to the Gene Expression Nervous System Atlas (GENSAT) database and Gene Ontology enrichment for signaling receptors in the plasma membrane, we narrowed down potential targets in DRN^{Vglut3} neurons to 3 highly selective and enriched targets for drug discovery: calcitonin receptor (Gs coupled), orexin 1 receptor (Gi coupled) and G-protein coupled receptor 4 (orphan). Importantly, we demonstrate through pre-clinical pharmacological studies that a new orally distributed and brain penetrant selective antagonist (CVN45502) of Orexin 1 receptor (Hcrt1) was capable of reducing food intake and ultimately body weight upon DIO[3].Together, these studies provide a general approach for the treatment of neuronally driven disorders by identifying drug targets in specific neuronal populations using a molecular profiling-based strategy. Such strategy is thus proven effective for preclinical drug screening and targeting in central populations of neurons, avoiding unspecific bindings and effectively speeding lead molecule identification for clinical trials.[1]Nectow A.R.[*], **Schneeberger M**.[*], ([*]co-first author) et al. Identification of a brainstem circuit controlling feeding. Cell. 2017 27;170(3):429-442
[2]**Schneeberger M.**, et al. Regulation of energy expenditure by brainstem GABA neurons. Cell. 2019 25;178(3):672-685
[3]**Schneeberger M.**, et al. Novel Molecular Profiling Based Pharmacological Strategy Identifies Novel Preclinical Compound for Weight Management. 2021. In Revision

Disclosures: M. Schneeberger Pane: None. **N.L. Brice:** None. **K. Pellegrino:** None. **L. Parolari:** None. **J. Shaked:** None. **T. Tolpiko:** None. **K. Page:** None. **D. Barrows:** None. **M. Ortuno:** None. **T. Carroll:** None. **N. Renier:** None. **A.R. Nectow:** None. **M. Carlton:** None. **N. Heintz:** None. **J. Friedman:** None.

Poster

P650. Mechanisms of Disordered Feeding

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Topic: F.09. Food and Water Intake and Energy Balance

Support: Nancy Nossal Fellowship (NIH-NIDDK) to A.K.S
NIH DK075087-06 to M.J.K
NIH DK075088 to M.J.K.

Title: Agrp neurons coordinate the mitigation of activity-based anorexia

Authors: *A. K. SUTTON, S. C. DUANE, A. M. SHAMMA, A. SKILLINGS, M. J. KRASHES;
NIH, Bethesda, MD

Abstract: Anorexia nervosa (AN) is a debilitating and deadly disease characterized by low body mass index due to diminished food intake, and oftentimes concurrent hyperactivity. A high percentage of AN behavioral and metabolic phenotypes can be replicated in rodents given access to a voluntary running wheel and subject to food restriction, termed activity-based anorexia (ABA). Despite the well-documented body weight loss observed in AN human patients and ABA rodents, much less is understood regarding the neurobiological underpinnings of these maladaptive behaviors. Here, feeding microstructure analysis revealed ABA mice decreased food intake due to increased interpellet interval retrieval and diminished meal number. Longitudinal activity recordings of hypothalamic agouti-related peptide (AgRP) neurons in ABA animals revealed a maladaptive inhibitory response to food. We then demonstrated that ABA development or progression can be mitigated by chemogenetic AgRP activation through the reprioritization of food intake (increased meal number) over hyperactivity. These results elucidate a potential neural target for the amelioration of behavioral maladaptations present in AN patients.

Disclosures: A.K. Sutton: None. **S.C. Duane:** None. **A.M. Shamma:** None. **A. Skillings:** None. **M.J. Krashes:** None.

Poster

P669. Neural Systems VI

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P669.01

Topic: G.02. Reward and Appetitive Learning and Memory

Support: RO1-DK111475
NIH Grant P30-DK020572

Title: Characterization of lateral hypothalamic area cells projecting to the dorsal vagal complex

Authors: *J. LEE[1], N. PENCE[1], L. RAYCRAFT[1], A. CALDWELL[1], A. JOHNSON[2];
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Abstract: The lateral hypothalamic area (LHA) is a large diencephalic structure that spans the entire rostral-caudal axis of the hypothalamus. The LHA houses a wide variety of molecularly distinct neuronal populations that play a critical role in a range of processes related to metabolic function and ingestive behavior. LHA descending projections to regions with parasympathetic innervation may serve a critical

role in mediating neuronal control of metabolism. Thus, in this study we used a dual-viral tracing approach to determine the nature of projections from the LHA to the dorsal vagal complex (DVC) a region implicated in integrating parasympathetic information to the periphery. Female Sprague Dawley rats received injections of retrograde AAV2 (rAAV2-Cre) containing Cre recombinase transgene into the DVC. When injected into axonal terminals, rAAV2-Cre is retrogradely transported to cell bodies and induces the expression of Cre-recombinase in these cells. In addition, a Cre-dependent virus expressing mCherry was then administered throughout the rostral-caudal axis of the LHA. This approach permits the identification and quantification of LHA cells that monosynaptically project to the DVC. Projections from the LHA to the DVC displayed a rostral-caudal gradient where cell bodies were seen more extensively in posterior sections of the LHA. Next, we examined overlap between LHA - DVC projecting cells and those expressing Melanin Concentrating Hormone (MCH)—an orexigenic neuropeptide implicated in glucoregulation and metabolism. Only a sparse number of LHA MCH expressing cells were found to project to the DVC. Overall, these findings provide insight into the location and properties of LHA projections to the DVC, laying the foundation to explore the function of this circuitry for feeding behavior and metabolism.

Disclosures: J. Lee: None. **N. Pence:** None. **L. Raycraft:** None. **A. Caldwell:** None. **A. Johnson:** None.

Poster

P669. Neural Systems VI

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P669.02

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01-DK111475
Internal funds to CS and KK

Title: Characterizing D1 and D2 receptor-mediated changes in palatable food intake in binge eating prone female rats.

Authors: *M. REES[1], N. FOWLER[2], N. PENCE[2], A. PATARO[3], J. LEE[2], K. KLUMP[2], C. SISK[2], A. JOHNSON[2];
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Abstract: Binge eating is a pathological eating behavior that can manifest in several eating disorders in humans. The dopamine system contributes to the regulation of eating behavior, therefore in this study we examined whether differential palatable food (PF) consumption was associated with stimulation and blockade of dopamine receptors in an animal model of individual differences in binge eating behavior. Sixty adult female Sprague Dawley rats were given intermittent access to PF 3x/week for 2 weeks to identify binge eating prone (BEP; consistently high levels of PF intake) and non-BEP rats (all other rats). Next, all rats received intraperitoneal injections of either vehicle, low, or high doses of the dopamine D1R agonist SKF 38393, D1R antagonist SCH 23390, D2R agonist quinpirole, and the D2R antagonist raclopride followed by PF and chow intake tests. Stimulation of D1R had minimal effect over PF or chow

intake in BEP or non-BEP rats, whereas relative to vehicle, high-dose blockade of the D1R led to a reduction in PF intake in BEP and non-BEP rats, with no effect on chow intake. BEP's were also more responsive to the hypophagic effect of D2R stimulation, and the hyperphagic effect of D2R blockade for PF but not chow intake. To examine whether this enhanced responsivity to pharmacological manipulations of dopamine receptors reflected individual differences in receptor expression, D1R and D2R mRNA in the nucleus accumbens was quantified in a subset of BEP and non-BEP rats. Collectively, our findings suggest that alterations in dopaminergic reward circuitry may underlie increased PF intake in BEPs.

Disclosures: M. Rees: None. **N. Fowler:** None. **N. Pence:** None. **A. Pataro:** None. **J. Lee:** None. **K. Klump:** None. **C. Sisk:** None. **A. Johnson:** None.

Poster

P669. Neural Systems VI

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P669.03

Topic: G.02. Reward and Appetitive Learning and Memory

Support: RO1DK111475

Title: Chemogenetic excitation of melanin concentrating hormone neurons produces unique effects on interval timing and motivation depending on sex, estrous cycle stage, and neuron location

Authors: *L. M. RAYCRAFT[1], M. BUNNEY[2], A. NALLA[2], A. PATARO[2], D. A. KASHY[1], E. NOBLE[3], S. E. KANOSKI[4], A. W. JOHNSON[1];
[1]Dept. of Psychology, [2]Neurosci. Program, Michigan State Univ., East Lansing, MI; [3]Nutritional Sci., Univ. of Georgia, Athens, GA; [4]USC, Los Angeles, CA

Abstract: In terms of timing, feeding behaviors have typically been studied from a circadian perspective. However, multiple timescales exist that likely inform feeding behaviors. Interval timing is a unique form of timing that refers to the ability to tell time in the seconds-to-minutes range. Importantly, interval timing enables the temporal contiguity that supports learning and decision-making. Notably, no studies have yet examined whether feeding peptides important for food-related learning and decision making can also influence interval timing. In the present study, we examined whether chemogenetic excitation of cells expressing the orexigenic neuropeptide melanin concentrating hormone (MCH) would influence responding in the peak interval task. Male and female Sprague Dawley rats first learned to lever press for sucrose reinforcement, where delivery was contingent on the response occurring after a 20 s criterion duration. Subsequently, non-reinforced probe trials were intermixed, where the lever remained available for ≥ 60 s period. During these trials, responding forms a normal distribution which peaks around the criterion duration (i.e., 20 s). Using a custom AAV to drive excitatory hM3Dq expression under the control of the MCH gene promoter, pMCH, we selectively excited MCH neurons throughout the rostrocaudal extent of the lateral hypothalamic area (LHA) during the peak interval task. Following MCH neuron excitation, we observed significant differences in peak interval responding during probe trials that depended on (1) the location of MCH neuronal excitation within the LHA, (2) sex, and (3) estrous cycle

stage. Furthermore, we used multi-level modeling to confirm effects of MCH neuronal excitation. Altogether, these results indicate that subpopulations of MCH neurons uniquely modulate interval timing and food-seeking depending on sex and estrous cycle stage. Moreover, these findings are the first to identify an influence of orexigenic neuropeptides on interval timing.

Disclosures: L.M. Raycraft: None. **M. Bunney:** None. **A. Nalla:** None. **A. Pataro:** None. **D.A. Kashy:** None. **E. Noble:** None. **S.E. Kanoski:** None. **A.W. Johnson:** None.

Poster

P669. Neural Systems VI

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Program #/Poster #: P669.04

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01DK111475

Title: Circuit-specific inhibition of dopaminergic signaling associated with phantom gustatory sensations in Disrupted-in-Schizophrenia-1 mice

Authors: *B. R. FRY[1], V. FEX[2], F. SOTOMAYORREINAT[2], M. NIWA[4], A. SAWA[5], A. W. JOHNSON[3];
[1]Psychology, [2]Natural Sci., [3]Neurosci. Program, Michigan State Univ., Lansing, MI; [4]Psychiatry and Behavioral Neurobio., Univ. of Alabama At Birmingham SOM, Birmingham, AL; [5]Dept. of Psychiatry, Johns Hopkins Univ., Baltimore, MD

Abstract: Disrupted-in-Schizophrenia-1 (DISC-1) is a gene which encodes a protein involved in a number of intracellular processes, particularly those critical for early neural development. In mice, perturbations of the DISC-1 genetic locus lead to a syndrome which mimics many of the core endophenotypes associated with schizophrenia. These mice have been shown to display impaired reality testing as revealed by heightened perceptual processing of an absent sucrose solution in the presence of an auditory conditioned stimulus (CS). These impairments were dopamine-dependent and associated with elevated insular cortex (IC) activity. In the current study, we examined whether these effects required activity of ventral tegmental area (VTA) dopamine cells projecting to the IC. To achieve this we bred DISC-1 mice to mice selectively expressing Cre-recombinase within cells expressing the dopamine transporter (DAT-Cre). These DISC-1 x DAT-Cre mice received bilateral infusions of a retrograde Cre-dependent Flp-O recombinase virus in IC, followed by bilateral VTA injections of a Flp-dependent hM4Di inhibitory DREADD virus. Through this approach, intraperitoneal (IP) injections of clozapine-N-oxide (CNO) allows for circuit-specific inhibition of dopamine cells projecting to IC. Following surgery, mice underwent Pavlovian conditioning in order to learn an association between a white-noise CS and delivery of sucrose solution. Subsequently, mice received IP injections of vehicle or CNO on separate test days, at which point the capacity of the CS to transfer sensory responses typically evoked by the sucrose was examined by presenting the CS alone with water. Our findings will offer insight into the genetic and neurobiological mechanisms underlying dopamine-mediated reality testing.

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Poster

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P669.05

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01DK111475

Title: Chemogenetic stimulation of telencephalic and mesencephalic GHSR-expressing cells differentially affects feeding behavior and stimulus palatability.

Authors: *A. KONDILIS[1], A. W. JOHNSON[2];
[1]Cell and Mol. Biol., [2]Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: The gastric hunger signal, ghrelin, influences feeding behavior via activation of the growth hormone secretagogue receptor (GHSR). GHSR's are expressed in multiple brain regions including the basolateral amygdala (BLA), ventral hippocampus (VHPC) and ventral tegmental area (VTA). These regions play a critical role in integrating motivational and reward signals to influence feeding behavior. In this study, we used a GHSR-IRES-Cre mouse line that expresses Cre directed by the GHSR promoter. Mice received Cre-dependent excitatory DREADD into either the BLA, VHPC, or VTA to examine whether chemogenetic stimulation of GHSR-expressing cells within these regions would influence consumption of lab chow or a palatable high fat diet (HFD). On test days, mice were injected with clozapine-N-oxide (CNO) or vehicle solution prior to the onset of the dark cycle and given portioned access to either lab chow or HFD. CNO-evoked DREADD stimulation of BLA or VHPC GHSR-expressing cells significantly enhanced lab chow but not HFD intake. Conversely, stimulation in the VTA attenuated lab chow consumption. To examine intake of specific macronutrients and the nature of any changes in ingestive behavior, we separately investigated fluid intake of lipid (45% corn oil), sugar (20% sucrose), and starch (20% maltodextrin) through an analysis of licking microstructure. This quantitative approach is capable of dissociating overall intake into individual components of pre-ingestive (e.g., orosensory, palatability; via burst size) and post-ingestive (e.g., negative feedback; via burst number) variables that regulate meal intake. The chemogenetic manipulations mainly influenced short-term solution intake in VHPC mice, such that excitation of GHSR-expressing cells in this region surprisingly inhibited sucrose intake through a decrease in burst number. Conversely, DREADD activation of these cells increased the palatability of corn oil. These data provide insight into the differential role of central nervous system GHSR-expressing cells on ingestive behavior that is in part dependent on the neuronal loci in which they are expressed and the nature of the tastant being consumed.

Disclosures: A. Kondilis: None. **A.W. Johnson:** None.

Poster

P669. Neural Systems VI

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: ERC grant PSY345

Title: Central Amygdala Htr2a neurons are required for ghrelin-induced hedonic feeding

Authors: *C. PETERS, H. LIM, R. KLEIN;
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Abstract: Ghrelin, a gastric-derived small peptide, influences the activities of hypothalamic circuits to promote homeostatic feeding and extra-hypothalamic areas to regulate hedonic feeding. The latter behavior may involve the amygdala, a highly conserved brain region important for the expression of defensive and appetitive behaviors, including feeding. Previous work from our lab showed that the activation of Htr2a+ neurons in central amygdala (CeA) increases food intake through a positive valence signal (Douglass et al, 2017). We hypothesized that part of the rewarding mechanism induced by ghrelin to increase appetite occurs through CeA^{Htr2a} neurons. Our results show that ghrelin increases c-Fos staining and excitatory neurotransmission in CeA^{Htr2a} , but not $CeA^{PKC\delta}$ neurons, a major anorexigenic subpopulation. Chemogenetic inhibition of CeA^{Htr2a} neurons completely blocked the effects of systemic application of ghrelin. Importantly, direct infusion of ghrelin into the CeA increased food consumption of satiated mice, an effect that was dependent on ghrelin (GHSR) and opioid receptors. Our findings also indicate that the neurons activated by ghrelin in CeA project to the parabrachial nucleus (PBN), inhibiting PBN neurons and thereby promoting feeding. This conclusion is consistent with our previous observations that at least part of the orexigenic activities of CeA^{Htr2a} neurons are mediated by projections to the PBN. These findings suggest that ghrelin activates a specific CeA-to-PBN circuit to induce hedonic feeding.

Disclosures: C. Peters: None. **H. Lim:** None. **R. Klein:** None.

Poster

P669. Neural Systems VI

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: DAMD W81XWH-19-1-0428
5 R01 DK109934

Title: The cholinergic basal forebrain and its imapct on the basolateral amygdala and feeding behavior

Authors: *J. ORTIZ-GUZMAN[1], J. SWANSON[1], M. KUCHOKOV[1], E. HANSON[1], K. UNG[1], E. TANTRY[1], A. ADDISON[1], S. DOOLING[1], Q. TONG[3], B. ARENKIEL[2];
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Abstract: Body weight homeostasis is regulated by balancing energy expenditure with caloric intake. Obesity, a major public health concern, is often the result of excessive caloric intake without reciprocal caloric expenditure. The hypothalamus is considered the master regulator of energy homeostasis and has garnered significant attention towards understanding the neural circuits that govern feeding behavior and body weight homeostasis. However, the hypothalamus does not act independently; extra-hypothalamic circuits throughout the brain perceive, anticipate, and adapt to the availability of food. We recently discovered a population of basal forebrain cholinergic neurons that govern aspects of appetite suppression. Through viral tracing methods, we found that basal forebrain cholinergic neurons densely innervate the basolateral amygdala (BLA). The BLA has known connections to the hypothalamus and reward centers, and is implicated in affecting appetitive behavior. However, the circuit mechanisms that govern BLA-driven feeding behaviors remain largely unknown. Here, using Channelrhodopsin-assisted circuit mapping, we identified muscarinic and nicotinic responses in BLA excitatory principal neurons following cholinergic basal forebrain terminal axon stimulation. Additionally, we found that BLA neurons signal to the nucleus accumbens via differential muscarinic or nicotinic responses. Through in vivo optogenetic manipulations, we show that increased cholinergic signaling from the basal forebrain to the BLA results in reduced food intake in fasted animals with no major effects on stress and/or anxiety. Together, these data support a model in which cholinergic signaling from the basal forebrain onto projection-defined neurons within the basolateral amygdala leads to appetite suppression.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: National Science Foundation Graduate Research Fellowship
NIH Grant DA035443

Title: Dopamine projections to the basolateral amygdala mediate the encoding of outcome-specific reward memories

Authors: *A. SIAS[1], K. WASSUM[1,2];
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Abstract: Adaptive decision making requires one to accurately anticipate specific rewarding events. When not readily observable, environmental stimuli enable us to mentally simulate the likelihood of particular rewarding outcomes and choose accordingly. Dopamine is known to be critical for reward learning and more recently has been implicated in learning the associative structure between cues and the specific rewards they predict, i.e., model-based learning. But the projections through which dopamine facilitates detailed stimulus-reward learning is unknown. One likely candidate is the basolateral amygdala (BLA). The basolateral amygdala is a hub for emotional learning, and we recently demonstrated it to be critical for encoding detailed, sensory-specific stimulus-reward memories. To investigate whether dopaminergic inputs support the BLA in forming these sensory-specific, appetitive associations, we combined optogenetics with a translationally-relevant behavioral task that assesses the use of unique stimulus-reward memories to inform decision making. Using optical inhibition, we found dopamine projections from the ventral tegmental area (VTA) to the BLA are necessary for encoding detailed stimulus-reward memories. Inhibiting dopaminergic VTA-->BLA projections upon reward experience during Pavlovian stimulus-reward conditioning did not disrupt acquisition or expression of a Pavlovian conditional goal-approach response but did prevent encoding of the sensory-specific stimulus-reward relationships, as evidenced by an inability to subsequently use this information to guide selective choice in a Pavlovian-to-instrumental transfer test. These data reveal that midbrain dopamine projections to the BLA are not needed to develop a Pavlovian response policy but are essential for encoding rich associative memories that link stimuli to the unique rewards they predict.

Disclosures: A. Sias: None. **K. Wassum:** None.

Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NRSA MH117931
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UW ADAI

Title: Cell type characterization of the lateral septum during morphine dependence and withdrawal

Authors: *R. SIMON[1], A. D. SANDERS[2], M. A. ROSSI[3], G. D. STUBER[1];
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Abstract: Neuropsychiatric disorders such as addiction and anxiety stem from dysregulation of neural substrates that govern motivated behaviors. Developing therapeutic strategies for individuals suffering from these conditions therefore requires further study of brain areas underlying reward- and anxiety-related behaviors. The lateral septum (LS) has been recognized as both a site of reinforcement and as a regulator of fear expression. Its connectivity with key brain structures in reward learning and in fear and anxiety gives rise to the LS's involvement in diverse behaviors, including locomotion, feeding, mating,

avoidance, and even addiction. Although the LS has genetically defined neuronal subtypes, it is unclear how various populations within the LS respond to positive and negative-valent stimuli. To evaluate how discrete LS cell types respond to divergent stimuli, we used a morphine administration and withdrawal model in which male and female mice received an escalating dose of morphine to cause drug dependence. A separate group of mice received naloxone (NAL) to facilitate withdrawal, an aversive state during which we predict LS cell types to be selectively activated. Mice were then sacrificed for their septal tissue, which next underwent single-nucleus RNA sequencing. This approach allowed us to profile LS cell types and their responsivity to both positive (morphine) and negative (withdrawal) experiences. To ensure rigor and reproducibility of our results, we used litter- and age-matched male and female mice (8 weeks old WT C57/b6) were combined into 3 samples (saline control, morphine dependence and NAL withdrawal). We identified at least 19 septal neuron clusters, including 2 GLUergic and 17 GABAergic types. Our data captured canonical LS types, such as neurotensin+ (*Nts*) and somatostatin+ (*Sst*) cells, and revealed previously unidentified neuron types. Immediate early gene expression not only varied across cell types, but they also highlighted cells that respond differentially to morphine dependence and NAL precipitated withdrawal. Further, morphine substantially altered gene expression across most LS cell types, but we have also identified cell clusters that are preferentially perturbed by drug dependence. For example, neurons co-expressing *Nts* and *Sst* appear especially sensitive to both morphine action and drug withdrawal. While *Nts* and *Sst* cells have been implicated in fear and avoidance behaviors, there is currently little known about their role in drug dependence and withdrawal. These data will provide an atlas for septal gene expression and supply insight into LS cell types that are involved in opioid dependence and affective behaviors.

Disclosures: R. Simon: None. **A.D. Sanders:** None. **M.A. Rossi:** None. **G.D. Stuber:** None.

Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIMH R01MH106500
NIDA R01DA038613

Title: Rhoa overexpression in nucleus accumbens-to-ventra tegmental area projection neurons suppresses motivation for sucrose reward

Authors: *S. COLE, D. FRANCO, M. E. FOX, R. CHANDRA, D. MARTIN, N. E. ZLEBNIK, D. J. CALU, J. F. CHEER, M. LOBO;
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Abstract: RhoA is a GTPase involved in the regulation cytoskeletal, neuronal morphology, and dendritic arborization. Previous research from our lab has demonstrated that enhanced RhoA in nucleus accumbens (NAc) D1-dopamine receptor expressing medium spiny neurons (D1-MSNs) leads to enhanced dendritic atrophy in promotes depressive-like behaviors. However, whether RhoA impairs or enhances natural

reward seeking behavior has been left unexplored. Here, we infused a retrograde transsynaptic vector expressing Cre recombinase into the ventral tegmental area (VTA) and Cre-dependent viral vectors to overexpress RhoA or control EYFP in NAc-to-VTA projection neurons, and examined whether RhoA regulation affects impacts affects reward learning or motivation in operant tasks for sucrose. *Ad lib* fed mice were able to choose between 1) a nose poke port producing a light cue or 2) a second nose poke port producing a light cue and delivering sucrose into an adjacent food cup. Both RhoA and EYFP control mice showed similar acquisition in our sucrose operant task. However, we found RhoA overexpression decreased operant responding and breakpoint during progressive ratio testing. Interestingly, in sucrose seeking tests, where operant responding produces light cues but no sucrose delivery, RhoA overexpression decreased persistent seeking for sucrose reward relative to EYFP controls. Collectively, our data demonstrate that the overexpression of RhoA in NAc-VTA (putative D1-MSNs) impairs motivation for sucrose.

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Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

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Program #/Poster #: P672.03

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSF IOS 1655365

Title: The neuronal glutamate transporter EAAC1 controls reward-based behaviors

Authors: *B. BENNINK, A. SCIMEMI;
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Abstract: Genetic association studies in humans identify the Slc1a1 gene, encoding the neuronal glutamate transporter EAAT3 (EAAC1 in mice), as a candidate gene for Obsessive Compulsive Disorder (OCD). Patients affected by OCD display structural and functional connectivity changes in cortico-striatal circuits, but the relationship between disrupted basal ganglia activity and OCD remains incompletely understood. Mice represent valuable species for studying the molecular mechanisms underlying complex behaviors in the context of neuropsychiatric disease. In mice, EAAC1 is expressed at relatively high concentrations in the basal ganglia nucleus of the striatum, where it serves to limit the activation of metabotropic glutamate receptors. Here we use a battery of behavioral tests to determine how loss of glutamate uptake via EAAC1 alters the execution of striatal-dependent behaviors. We assessed the acquisition of a simple continuous reinforcement (FR1), operant conditioning task, where a reward was delivered in response to individual lever presses, in C57BL/6J (wild type, WT) and EAAC1$^{-/-}$ mice. Active responses and reward consumption were reduced in EAAC1$^{-/-}$ compared to WT mice, suggesting that EAAC1 enhances the ability to perform instrumental learning tasks. When we switched to a different reinforcement regime (FR8), however, EAAC1$^{-/-}$ mice outperformed WT mice by collecting more rewards, due to their ability to perform the sequence lever presses faster and more frequently than WT

mice. This behavior, which was indicative of increased impulsivity, was associated with changes in immediate early gene expression not only in the striatum but mostly in cortical areas. Similar findings were obtained when constraining the timing of the sequence lever presses. Together, these findings suggest that EAAC1 specifically controls the timing for repeated execution of reward-based behaviors, and point to a novel understanding of how this transporter may contribute to the execution of behaviors implicated with OCD.

Disclosures: B. Bennink: None. **A. Scimemi:** None.

Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

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Burroughs Wellcome Fund PDEP Fellowship

Title: Dopamine release and behavior are patterned by the action potential

Authors: *B. JUAREZ[1], M.-S. KONG[1], Y. JO[2], J. ELUM[1], J. X. YEE[1], S. EVANS[1], M. M. CLINE[1], A. C. HUNKER[4], M. A. BAIRD[5], M. A. QUINLAN[1], A. MENDEZ[6], N. L. GOODWIN[1], M. E. SODEN[1], L. S. ZWEIFEL[3];
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Abstract: Reinforcement learning is an essential process by which an organism links environmental stimuli and actions with desired outcomes. Dopamine producing neurons within the ventral tegmental area (VTA) modulate information processing in the forebrain, most notably in the nucleus accumbens (NAc) region of the striatum, to facilitate reinforcement learning and to promote goal-oriented behavior. Precise shifts in patterns of dopamine activity in the VTA and dopamine release in the NAc have been associated with distinct phases of reinforcement learning including learning acquisition, invigoration during goal oriented responses, and extinction. However, whether regulators of intrinsic firing properties of dopamine neurons influence patterned dopamine release and reinforcement learning has not been fully established. Here, we used cell-type specific, viral mediated CRISPR/Cas9 gene editing technology to interrogate how two potassium channel subunits that mediate distinct parts of the action potential contribute to dopamine release during reinforcement learning. We found that genetic disruption of Kv4.3 (Kv4.3 LOF) subunits in VTA dopamine neurons caused an increase in the action potential width, an increase in spontaneous activity and increase in intrinsic excitability. Genetic disruption of BKCa1.1

(BKCa1.1 LOF) subunits, however, induced a more depolarized afterhyperpolarization and increased dopamine neuron burst activity. To determine if these distinct effects on the action potential shape, intrinsic excitability and spontaneous activity effected reinforcement learning, we combined a fixed ratio 1 (FR1) operant reinforcement learning task for sucrose with fiber photometry of dopamine release in the NAc using the dopamine sensor dLight1.3b. We found that BKCa1.1 LOF in VTA dopamine neurons, and not Kv4.3 LOF, caused an increase in learning acquisition on the first day of the task and increased phasic-like dopamine release events in the NAc. Interestingly, after learning of the reinforced task had been acquired, mice with Kv4.3 LOF, and not BKCa1.1 KOF mice, displayed robust performance of the task and had an associated increased ramp of dopamine activity during the performance of the goal-oriented lever press response. During extinction training, we found that Kv4.3 LOF mice learned to extinguish their behaviors faster on the first day while BKCa1.1 LOF mice had slower extinction learning. These results demonstrate that potassium channels that contribute to the generation of the action potential regulate the patterns of dopamine release to influence reinforcement learning, performance, and extinction.

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Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P672.05

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Open University research funds
King's College London research funds

Title: Variation in cue-evoked motivation and dendritic spine dynamics in the nucleus accumbens

Authors: *M. COLOM[1], I. KRAEV[1], A. K. STRAMEK[1], I. B. LOZA[1], C. L. ROSTRON[1], C. J. HEATH[1], E. J. DOMMETT[2], B. F. SINGER[3];
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Abstract: *Introduction*
Environmental stimuli associated with rewards can acquire motivational properties and influence behaviour. There is considerable variation in their ability to do so, and some individuals are particularly prone to attribute incentive salience to discrete Pavlovian cues. Much research has focused on pre-synaptic characteristics underlying this phenotype, revealing that differences in motivation are related to dopamine neurotransmission in areas involved in reward learning, including in the nucleus accumbens (NAc). However, post-synaptic characteristics, although crucial for learning and plasticity, have not yet been explored. Here, we assessed whether individual variation in motivation in male and female rats is associated with specific spine properties in the NAc core.

Materials and Methods
A first group (n = 45) of male and female Lister Hooded rats was trained on a Pavlovian conditioning procedure. For 5 consecutive days, a lever was repeatedly paired with the delivery of food pellets. Animals were re-exposed to the lever-cue in the absence of reward during a final test session. A 'no learning' control group (n = 12) underwent a similar procedure during which the lever and the reward were temporally dissociated to prevent the lever from becoming a predictive cue. A third cohort (n = 36) was tested under the same paired conditions than the first group, however during the test session rats were subjected to the reward as well. Brains were removed 6h after the final session and prepared for neuroanatomical analysis (Golgi-impregnation technique). Stained NAc dendrites were reconstructed with Neurolucida and dendritic spine density, length and size were examined.
Results
Conditioned animals were found to have lower spine density than control rats in the NAc core. Within this paired group, individuals who approached the lever faster - and therefore attributed more incentive salience to the reward cue - had greater density of spines and longer spines in the NAc core. We did not observe differences in spine properties between males and females.
Conclusion
The lower density of spines found in trained rats might be explained by the omission of the reward on test day, which could have caused a 'negative prediction error' characterised by a decrease in dopamine signalling. The analysis of the third group will allow to explore this hypothesis. Changes in spine length linked to the attribution of incentive value to the cue may be related to the growth of spines and, thus, density measurements. This study offers the possibility of further understanding individual variation in spine dynamics and relate these novel neurobiological findings to prediction errors.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA P50 DA037844

Title: Genome-wide association study in 3,228 outbred heterogeneous stock rats identifies convergent loci for pavlovian conditioned approach and conditioned reinforcement

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Abstract: Addiction vulnerability is associated with non-drug traits such as the tendency to attribute incentive salience to reward cues and is influenced by environmental and genetic factors. To characterize the genomic regions associated with these behaviors, we performed a genome-wide association study (GWAS) in two cohorts of phenotypically and genetically diverse N/NIH Heterogeneous Stock (HS) rats at two institutions. We first tested HS rats in a Pavlovian Conditioned Approach task, in which we characterized the individual responses to food-associated stimuli ("cues"), and report two general categories of Pavlovian conditioned responses: cue-directed "sign-tracking" behavior, and food-cup directed "goal-tracking" behavior. We then used the conditioned reinforcement procedure to examine whether rats would perform a novel operant response for presentations of the food cue alone, and demonstrate that sign-tracking was associated with heightened cue-directed responding. Finally, we identified genetic loci associated with multiple measures across both tasks in HS rats at each institution. We identified several loci across a number of measures during Pavlovian conditioned approach, with each measure associated with 1-8 loci. Many loci associated with sign-tracking reflected measures that showed the largest heritability values (h^2 = .189-.215) and were identified on chromosome 1. Interval sizes of loci varied, although some of the strongest associations for sign-tracking contained few genes (e.g. *Tenm4*, *Mir708*). During conditioned reinforcement, we also detected multiple loci on chromosome 1, many containing genes identified for the Pavlovian conditioned approach phenotype. We demonstrate that HS rats are useful for investigating the genetic variants underlying complex behavior and may be useful for identifying candidate genes for future testing.

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Poster

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Title: Molecular characterization of cocaine-relapse ensemble neurons in the infralimbic cortex using single nuclei RNA sequencing in Fos-mRFP transgenic rats

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Abstract: Learned associations are thought to be encoded by sparse populations of strongly activated neurons called neuronal ensembles, commonly identified using the immediate early gene *Fos*. Our lab and others previously identified unique transcriptional changes within ensemble neurons following drug-related behaviors. However, these studies used pooled samples (Fos-positive vs Fos-negative) and measured a panel of candidate genes from brain areas of interest. Therefore, the complete transcriptional signature and corresponding cell types within these regions is currently unknown.
Here we use single nuclei RNA sequencing (snRNAseq) and a Fos-based transgenic rat (Fos-mRFP rat) to characterize cocaine relapse ensemble neurons in the infralimbic cortex (IL). We trained rats to self-administer cocaine during twice daily 3 h sessions. Following training and 21 days of abstinence, we tested rats for cocaine-seeking (30 min, extinction conditions) and collected brains 3 h after test (peak Fos driven mRFP expression). We used fluorescence activated cell sorting (FACS) to isolate mRFP-positive (ensemble) and mRFP-negative (non-ensemble) nuclei from IL and will perform snRNA-seq analyses on these isolated nuclei.
Using this unbiased approach, we will determine cell types that comprise cocaine-memory ensemble neurons and identify ensemble-specific differentially expressed genes within specific cell types. In future experiments, we will use CRISPR-based transcriptional modulators to assess causal roles for these cocaine memory-specific genes in relapse. This work was supported by NIDA/NIH.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSERC-Discovery Grant
NSERC-PGSD

Title: Long-lasting changes in corticolimbic structures following exposure to intermittent physical stress in mid-adolescence.

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Abstract: Exposure to stress during mid-adolescence increases rats' risk-taking behaviour in adulthood, as indexed by their greater willingness to explore the normally avoided open arms of the elevated plus maze. While this outcome is consistent across several studies in our lab and others, the potential underlying neural mechanisms for this behavioural change remain largely unknown. We aimed to extend our behavioural findings by examining the lasting impact of intermittent physical stress (IPS) in mid-adolescence on neuronal arborization and dendritic spine density in three corticolimbic regions of interest: the medial prefrontal cortex (mPFC), the hippocampus, and the basolateral amygdala (BLA). Male and

female Long-Evans rats were exposed to our IPS protocol (i.e., foot-shock, water immersion, and elevated platform; two times each, randomly across mid-adolescence; postnatal day [PD] 35-46). In adulthood (PD 73), rats were tested in the elevated plus maze and 48-72hrs after behavioural testing, their whole-brain tissue was harvested. As expected, exposure to IPS in mid-adolescence increased open-arm exploration. This treatment produced regionally specific changes in neuronal architecture. There was no evidence of stress-induced changes in dendritic arborization or synaptic spine density in the mPFC. Within the hippocampus, exposure to IPS in mid-adolescence reduced dendritic arborization of pyramidal neurons in male rats but produced modest increases in arborization in female rats. The most pronounced stress-induced changes, however, occurred in the BLA as IPS in mid-adolescence produced long-lasting reductions in the complexity of dendritic arborization and spine density within this region. It is possible that the IPS-induced changes in open-arm exploration are due, at least in part, to these structural changes in the BLA, which, in turn, could promote reward-centric, as opposed to security-centric, behaviour.

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Poster

P672. Reward Memory: Cellular and Molecular Mechanisms

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Program #/Poster #: P672.09

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Dysregulation of a hypothalamically controlled brain aversion network drives addiction-like eating in obesity

Authors: *R. M. O'CONNOR[1], V. MATHIS[5], M. V. MICIONI DI BONAVENTURA[6], K. DEVARAKONDA[2], S. CALIGIURI[7], A. W. SMITH[3], V. E. LEHMANN[8], M. ISHIKAWA[4], P. J. KENNY[9];
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Abstract: Obesity is characterized by a dysregulation to range of motivated behaviors, including homeostatic and hedonic feeding patterns, ultimately leading to caloric intake that far supersedes energy demands. Furthermore, successful body weight management is confounded by the fact that individuals will continue to overeat despite the well-known negative health and social consequences. Thus, in obesity chronic hyperphagia is accompanied by consummatory patterns that becomes compulsive in nature, failing to respond to internal and external stimuli that typically result in suppression of food intake. We know little about the obesity induced remodeling of brain function that precipitates the emergence of such inflexible feeding patterns. We hypothesized that obesity is accompanied by changes to a complex neuronal network leading to obesity associated behavioral abnormalities that drive compulsive addiction-like eating. Single cell sequencing of RNA transcripts from mouse revealed excitatory neurons in the lateral hypothalamus (LH) show marked obesity-associated alterations in gene expression. Specifically,

transcripts from genes associated with glutamatergic neurotransmission were significantly lower in tissue harvested from obese mice. Using electrophysiology and whole brain clearing with automated quantification of synaptic contacts, we found this transcriptional plasticity accompanied the emergence of LH glutamatergic hypofunction and a profound restructuring of hypothalamic output to a range of brain loci including the lateral habenula, periaqueductal gray and dorsal raphe nucleus. Finally, using transgenic mice and viral manipulation of neuronal function in vivo we linked this LH glutamatergic hypofunction in individual circuits led to the emergence of discrete obesity associated behaviors such as hyperphagia, rejection of less palatable food items and compulsive feeding. Our data indicated obesity induced remodeling of LH activity leads to a wide-ranging functional reorganization of a broad network of brain sites controlled by LH glutamatergic neurons. The consequences of which are the emergence of discrete complex shifts to food motivated behaviors which together amount to an obesity associated behavioral syndrome primed to maintain excessive levels of energy harvesting in our modern food environment. Our research posits rescuing excitatory hypothalamic output as a novel therapeutic strategy for reversing the hyperphagia and motivational shifts associated with obesity and thus correcting caloric intake to match energy expenditure.

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Poster

P711. The Effects of Psychedelics on Brain and Behavior

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Topic: G.05. Mood Disorders

Support: Research and Development Grant UW Madison Department of Anesthesiology
R01MH122742

Title: Increased synaptic excitability in mouse hippocampus and prefrontal cortex following psychedelic administration

Authors: *Z. ZAHID[1], Z. SULTAN[2], S. M. GRADY[2], C. J. WENTHUR[3], R. A. PEARCE[2], M. I. BANKS[2];
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Abstract: Introduction: Classical psychedelics (i.e. psychoactive agonists at 5-HT2A receptors) and ketamine demonstrate rapid and long-lasting efficacy in the treatment of psychiatric disorders, yet the underlying mechanisms remain unknown. The pro-neuroplastic effects of psychedelics likely play a role in their therapeutic effects, but it is unclear whether psychedelics acutely induce plasticity, or whether they do so post-acutely. Using *in vivo* and *in vitro* electrophysiology in mice, we explored the effects of psychedelic and ketamine administration on synaptic excitability and plasticity in hippocampus and along the ventral hippocampus - medial prefrontal cortex (mPFC) pathway, areas which are dysregulated in

psychiatric illness. **Methods:** Experiments were conducted on male and female C57BL/6J mice (3-5 mo). For *in vivo* experiments, a stimulating electrode was placed in CA1 of ipsilateral ventral hippocampus (vCA1), and recording electrodes in mPFC and contralateral vCA1. Recordings of evoked responses were obtained at baseline, 4hr, 1, 3, and 7d after IP injection of DOI (1 mg/kg) or 4-AcO-DMT (1 mg/kg). Long term potentiation and depression (LTP/D) were induced using standard protocols. For *in vitro* experiments, transverse hippocampal slices were obtained 1 day after injection of DOI (1 mg/kg; n=21 slices), ketamine (10 mg/kg; n=20), or saline (n=20). After obtaining baseline stimulus-response curves, field EPSPs were recorded from *s. radiatum* of CA1 for 30 min before and 60 min following LTP induction. One-way ANOVA with Tukey post-hoc tests were conducted to compare effects of drug treatment on LTP and sigmoidal stimulus-response model fit coefficients, with $p<0.05$. **Results:** Increased maximal evoked responses were observed 24h after psychedelic administration *in vivo* in ipsilateral mPFC. Fractional change for DOI was 0.50 +/- 0.33 (mn +/- SD, n=3) and for 4-AcO-DMT was 0.37 +/- 0.15 (n=3). In slices, DOI, but not ketamine, enhanced excitability, as measured by increased slope coefficients of stimulus-response curves (DOI: 0.019 +/- 0.012; ketamine: 0.013 +/- 0.002; saline: 0.013 +/- 0.004) and large but variable increases in maximal evoked responses (DOI: 3.24 mV +/- 1.48; ketamine: 2.52 mV +/- 0.67; saline: 2.47 mV +/- 1.04). LTP and LTD were unaffected *in vivo*, and there was no significant effect of drug on LTP *in vitro* ($p = 0.39$). **Conclusions:** We observed evidence for increased excitability but not synaptic plasticity in CA1 and mPFC synapses during an acute window after psychedelic administration. This increase in excitability in limbic regions may underlie the observed therapeutic benefit shown in clinical trials.

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Poster

P711. The Effects of Psychedelics on Brain and Behavior

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Support: NINDS Grant T32NS105602
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NIGMS Grant T32GM008688
Internal Funding from UW-Madison School of Pharmacy/Medicine and Public Health

Title: Ketamine and psilocybin on fear acquisition and extinction in mice

Authors: *J. A. RAZIDLO[1], J. R. NERAD[2], N. T. JONES[3], M. I. BANKS[4], C. J. WENTHUR[5]; [1]Neurosci. Training Program, [2]Sch. of Pharm., [3]Mol. and Cell. Pharmacol. Program, Univ. of Wisconsin - Madison, Madison, WI; [4]Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; [5]Pharm., Univ. of Wisconsin Madison, Madison, WI

Abstract: Major depressive disorder (MDD) has become an increasingly prevalent issue and is compounded by the limited efficacy of current treatment options. To combat this disorder, researchers

have focused their attention on novel therapeutic approaches. Two promising treatments are the N-methyl-D-aspartate receptor (NMDAR) antagonist, ketamine, and the serotonergic $5HT_{2A}$ agonist and classical psychedelic, psilocybin. These compounds have been shown to exert rapid antidepressant effects through mechanisms that have yet to be fully understood. Both of these rapidly-acting antidepressants have been observed to induce an acute stress response, as measured by elevated glucocorticoid release after administration. We propose that the therapeutic effects of these drugs are due to a transient enhancement of neural plasticity in the ventral hippocampal medial-prefrontal-cortex (HPC-mPFC) pathway and subsequent memory formation produced by this acute stress. Impaired plasticity in the HPC-mPFC pathway is observed in patients with MDD, and individuals have reported decreased depressive symptoms after taking either psilocybin or ketamine. These improvements have been reported to last hours or even weeks, with psilocybin typically having longer lasting increases in mood. Despite this, there are no studies to date that assess the duration of this critical window. To study this window of plasticity at the behavioral level, we used C57BL/6J (male and female) mice and the associative learning task of fear conditioning. Mice were administered a single intraperitoneal (IP) injection of saline, ketamine (10-30 mg/kg), or psilocybin (3 mg/kg) at 4 or 24h prior to fear conditioning. Here we found that mice that received ketamine (30 mg/kg) 4h prior to initial testing showed enhanced fear acquisition compared to those that received ketamine 24h prior, psilocybin, or saline ($p<0.05$). This effect was even more pronounced in animals that received a lower dose of ketamine (10 mg/kg, $p<0.05$). Interestingly, psilocybin did not alter fear acquisition from saline controls when administered at either time point. Animals that received ketamine or psilocybin also displayed enhanced fear extinction, although these trends were non-significant. Our results suggest ketamine's enhancement of fear acquisition is negatively correlated with both dose and latency to initial testing after administration. Psilocybin's ability to modulate fear acquisition may be blunted by the acute stress induced by the foot shocks during the fear conditioning trials. Our future studies will continue to evaluate the effects these compounds have on fear memory and their possible interaction with stress.

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Poster

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Topic: G.05. Mood Disorders

Support: R01MH122742
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T32NS105602

Title: Role of HPA axis activation in psilocybin's effects in rodent models of anxious behaviors

Authors: *N. JONES[1], Z. ZAHID[2], J. RAZIDLO[2], C. WENTHUR[3];
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Abstract: Research into classical psychedelics as potential therapeutics has increased after demonstrating therapeutic efficacy in small-scale clinical studies. Among these compounds, psilocybin, a serotonin receptor (5-HT_{2A}) agonist, has shown positive results when administered to individuals with major depressive disorder (MDD) or end-of-life anxiety. Despite these long-term anxiolytic effects, psychedelics induce an acute stress response. This leads to an increase in glucocorticoid levels, particularly that of corticosterone (CORT). Clinical protocols for administering psilocybin-assisted therapy have noted a correlation between anxious responding and therapeutic outcomes for patients with MDD. Despite this, few studies have directly assessed the role that these drug-induced changes in CORT release have in altering psilocybin's anxiolytic effects. To determine the effect of psilocybin (3 mg/kg) on CORT release, we injected male C57BL/6J mice and collected retro-orbital blood samples at 15 min, 4 h, and 7 d post-injection. When measured, psilocybin induced significantly higher levels of plasma CORT than saline at 15 min but had returned to baseline at 4 h. We then tested an acute and chronic oral CORT protocol to suppress the hypothalamic-pituitary-adrenal-axis (HPA-axis), which controls CORT release. In our preliminary data, as validation for the model, mice that were exposed to oral CORT (80 μg/mL) for 21 d spent significantly less time in the center of an open field apparatus than vehicle-treated mice. We used the novelty suppressed feeding test (NSF) to test the post-acute (4 h) anxiolytic effects, we used the novelty suppressed feeding test (NSF). We found psilocybin significantly reduced the latency to feed, however, this effect was lost following exposure to chronic CORT. When tested in the open field test (OFT) 7 d following administration, mice that received [vehicle + psilocybin] spent significantly more time in the center than those that received [psilocybin + CORT]. To further investigate this interaction, we then administered the glucocorticoid antagonist, mifepristone (10 mg/kg), and saw psilocybin's effects were blunted in both the NSF and OFT. These results suggest that suppression of the HPA-axis via exposure to chronic exogenous CORT not only critically impacts psilocybin's efficacy, but that the acute stress response may have an important role in the mechanism of action. An important goal moving forward is to identify the method by which increased CORT levels alter psilocybin's behavioral effects, which will contribute to the application and development of this breakthrough treatment.

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Poster

P711. The Effects of Psychedelics on Brain and Behavior

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Topic: G.05. Mood Disorders

Support: Research and Development Seed Grant, Department of Anesthesiology UW Madison
R01MH122742

Title: Time course of acute behavioral, endocrinological, and electrophysiological changes in response to administration of classical psychedelics and DMT analogues

Authors: *A. J. ZEIMET[1], M. A. KUPPE[1], J. L. ZHENG[1], S. M. GRADY[1], Z. ZAHID[2], N. T. JONES[3], M. I. BANKS[5], C. J. WENTHUR[4], Z. W. SULTAN[1];
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Abstract: Introduction: Classical psychedelics (i.e., psychoactive agonists at 5-HT2A receptors) produce rapid and long-lasting therapeutic benefit for diverse psychological disorders. These agents induce a constellation of acute behavioral, physiological, and biochemical effects, but the intersection of these effects and psychedelics' post-acute effects and therapeutic mechanisms remains unclear. The acute stress response induced by psychedelics has been postulated to play a role in these agents' pro-neuroplastic effects, which likely contribute to their therapeutic effects. We characterized the magnitude and duration of the acute behavioral, biochemical, and neural effects of these drugs in mice **Methods:** Three sets of experiments were conducted on male and female C57BL/6J mice (3-5 mo). Behavioral effects were assayed using induced head twitch responses (HTRs) quantified via magnetometry pre/post intraperitoneal (IP) injection of DOI and various DMT analogues (1 mg/kg), and psilocybin (3 mg/kg), with saline and ketamine (30 mg/kg) for comparison. Endocrinological effects were assayed by measuring plasma corticosterone (CORT) concentrations at various time points (t = 5 min, 15 min, 30 min, 60 min, 4 hr, 24 hr) after IP injection of DOI or saline, and at 15 min & 4 hr after psilocybin and ketamine. Neural effects were assayed by measuring changes in delta and alpha band power via skull screw electroencephalographic (EEG) recordings pre/post injection of psilocybin. **Results:** Administration of DOI, psilocybin, and some analogs, but not ketamine or saline, elevated HTRs by 0.4-0.7/min, with variable duration: DOI, >4 hrs; 4-AcO-DMT, 28 min; 5-MeO-MiPT, 19 min; psilocybin, 17 min. Smaller and shorter effects were observed for 5,6-DiMeO-MiPT (0.21/min, 14 min) and 5-MeO-pyrT (0.37/min, 23 min). No change in HTRs was observed for Pyr-T, 5-MeO-DET and 6-F-DET. CORT was elevated 5 - 60 mins following administration of DOI, with return to baseline at 4 hours. Both psilocybin and ketamine caused an increase of CORT at 15 min with a return to baseline at 4 hours. Finally, psilocybin induced changes in posterior EEG delta and alpha band power that lasted >180 mins and >65 mins, respectively. **Conclusions:** The acute stress response to DOI and psilocybin tracks the duration of behavioral effects, and thus may be causally related. Neural effects of psilocybin in mice are similar to those reported in human subjects and appear to outlast both the acute stress response and behavioral effects. Taken together, these data provide evidence for a role of stress glucocorticoids in changes in neural activity and behavior affected by psychedelic administration.

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Poster

P711. The Effects of Psychedelics on Brain and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P711.05

Topic: G.05. Mood Disorders

Title: Psilocybin selectively suppresses REM sleep in the Wistar Kyoto rat model of treatment-resistant depression

Authors: *S. KANTOR, L. GIGGINS, N. UPTON, M. DUXON;
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Abstract: Introduction: Wistar–Kyoto (WKY) rats show depression-like neurochemical and behavioural characteristics and have been suggested to serve as a model for treatment-resistant depression (TRD). Compared to other rat strains, WKY rats have increased baseline REM sleep amounts that is less sensitive to the suppression by conventional monoamine-based antidepressants. We have shown previously that WKY rats are also more susceptible to the modulation of cortical activity by ketamine, a novel rapid-acting antidepressant with high efficacy in TRD patients. Although the psychedelic drug psilocybin has been shown to be effective in TRD, but its effect on REM sleep in TRD has not been studied yet. The aim of this study was to determine whether psilocybin has differential effects on sleep-wake behaviour and EEG in WKY rats in comparison with an outbred rat strain. **Methods**: 8 Sprague-Dawley (SD) and 8 WKY adult (200-250 g) male rats were surgically implanted with telemetry transmitters (HD-S02; DSI, USA) for EEG, EMG and locomotor activity recordings. Following post-surgical recovery, we treated the rats with different (1, 3 and 10 mg/kg i.p.) doses of psilocybin or its vehicle and monitored the changes in their sleep-wake behaviour for 22h. Vigilance states were automatically scored using a customized algorithm (SleepSign, Kissei Comtec, Japan). EEG power spectra were computed for 2 s epochs (FFT routine, Hanning window) between 0.5-100 Hz per each vigilance state. **Results**: Psilocybin supressed REM sleep in both SD and WKY rats in a dose-dependent manner, but it had no significant effect on the amount of NREM sleep or wakefulness. The differential effect of psilocybin on REM sleep was further evident by a dose-dependent decrease in the REM/NREM sleep ratio seen in both strains. Furthermore, psilocybin also suppressed high-frequency gamma oscillations in the EEG. **Conclusions**: Since early suppression of REM sleep by antidepressants is one of the most consistent findings in patients with depression, suppression of REM sleep after psilocybin treatment could potentially indicate antidepressant-like properties of the drug in WKY rats. Thus suppression of REM sleep in WKY rats may serve as a key translational tool in an effort to discover novel therapeutics against TRD.

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Poster

P711. The Effects of Psychedelics on Brain and Behavior

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Program #/Poster #: P711.06

Topic: G.05. Mood Disorders

Title: Naltrexone blocks the acute and sustained antidepressant-like effects of ketamine, but not it's locomotor effects in mice

Authors: F. ZHANG[1], P. M. ANDERSON[2], P. O. KOPPENHAVER[2], T. N. KEGEN[2], S. G. MANIKA[1], J. T. LANE[1], E. POTTANAT[1], M. VAN FOSSEN[1], E. CELIK[1], R. RICE[1], T. M. HILLHOUSE[2], ***J. H. PORTER**[1];
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Abstract: Ketamine has acute and sustained antidepressant effects in both depressed and treatment-resistant depressed patients. However, the neuropharmacological mechanisms responsible for ketamine's antidepressant effects remain unclear as other NMDA antagonists have failed to produce similar effects in the clinical population. As more patients turn to ketamine for treatment, it is important to understand the mechanisms underlying its therapeutic effects. Recent clinical studies have reported that pretreatment with the nonselective opioid antagonist naltrexone attenuated both the rapid antidepressant and antisuicidal effects of ketamine (but not its dissociative effects), suggesting that activation of the opioid system may be involved in ketamine's antidepressant effects. The current study investigated the opioid system's role in ketamine's antidepressant-like effects by testing ketamine with the nonselective opioid antagonist naltrexone in the tail suspension test (TST) and differential-reinforcement-of-low-rate responding (DRL) 72 s task. In addition, open field locomotor activity also was measured. Ketamine at 10 mg/kg produced acute and sustained antidepressant-like effects in TST, which were blocked by pretreatment of 2 mg/kg naltrexone. Ketamine at 32 mg/kg produced an acute antidepressant-like effect in the DRL 72 sec task that was blocked by pretreatment of 2 mg/kg naltrexone (no sustained ketamine effects of ketamine were found in DRL). Both 10 and 32 mg/kg ketamine produced significant increases in locomotor activity; however, pretreatment with 2 mg/kg naltrexone failed to block ketamine's hyperactivity effects. Results from the TST and the DRL 72 s task confirm recent clinical findings suggesting that ketamine's antidepressant effects involve activation of the opioid system. However, opioid systems do not appear to be involved in ketamine's motor effects, thus showing a separation forf the role of opioid systems in the antidepressant and side effects of ketamine.

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P724.01

Topic: G.09. Drugs of Abuse and Addiction

Support: ANR; contract ANR-17-EURE-0022, EURIDOL graduate school of pain

Title: Central metabolism as a potential origin of sex differences in morphine analgesia but not in the induction of analgesic tolerance in mice

Authors: *F. GABEL[1], V. HOVHANNISYAN[1], V. ANDRY[1,2], Y. GOUMON[1,2];
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Abstract: Sex differences in morphine analgesia and side effects, particularly in the analgesic tolerance to morphine, have been described in both humans and rodents. In mice, morphine is metabolized in the liver in morphine-3-glucuronide (M3G), reported to have pronociceptive effects. Therefore, the metabolic M3G/morphine ratio found in the periphery and in the brain, especially in brain regions related to pain,

might modulate morphine analgesia. We have studied whether the metabolism of morphine is impacted during analgesic tolerance in male and female mice. The tail-immersion test was used to determine the analgesic effect of morphine and LC-MS/MS was used to quantify morphine and M3G in the blood and pain-related brain regions. First, we have observed that morphine has a weaker analgesic effect in females compared to males. In addition, in female mice, we have found higher levels of M3G in the periphery as well as lower amounts of morphine and higher levels of M3G in several pain-related brain regions. These last differences were related to sex differences in central metabolism of morphine. Secondly, we have determined that females become tolerant to the analgesic effect of morphine earlier than males. Moreover, we have found less morphine in the blood and several pain-related brain regions of tolerant mice than control mice. However, central metabolism did not seem to be implicated in these differences. In conclusion, the sex differences observed in the central metabolism of morphine are consistent with the lower potency of morphine in female than in male mice. However, morphine metabolism does not seem to be involved in the induction of morphine analgesic tolerance. **ACKNOWLEDGMENTS AND GRANT SPONSOR -** This work was funded by CNRS, University of Strasbourg (Unistra), French Ministère Délégué à la Recherche et à l'Enseignement Supérieur and FHU Neurogenycs, French National Research Agency (ANR; contract ANR-17-EURE-0022, EURIDOL graduate school of pain).

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P724.02

Topic: G.09. Drugs of Abuse and Addiction

Title: Use of stable isotope-labelled morphine to investigate in vivo morphine metabolism and brain transport in tolerant mice

Authors: *Y. GOUMON[1,2], I. WEINSANTO[1], A. LAUX-BIEHLMANN[1], J. MOUHEICHE[1], T. MADUNA[1], V. ANDRY[1,2], F. GABEL[1];
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Abstract: ***Context*-** In mice, morphine is mainly metabolized in morphine-3-glucuronide (M3G) in the liver. However, the metabolism of morphine in the brain is poorly characterized. Chronic morphine treatments induce analgesic tolerance, resulting in a decrease in analgesia. No data is available on the potential implication of central metabolism of morphine on analgesic tolerance and the impact on blood-brain barrier (BBB) permeability. Thus, we have characterized *in vivo* the morphine metabolism at central and peripheral levels and its BBB permeability after chronic treatment. ***Methods*-** morphine or NaCl solutions were injected into male mice for eight days to induce analgesic tolerance. On the last day, both groups were injected with a solution of 85% (w/w) of morphine and 15% of d3-morphine (morphine bearing three 2H) to get rid of the remaining morphine and M3G. 90min after the injection, mice were killed, and blood, urine, brain and liver samples were recovered. The levels of morphine, M3G and their d3-labelled counterparts were quantified by LC-MS/MS. ***Results & conclusions*-** We didn’t observe a

significant change in morphine metabolism within the central nervous system (CNS) and BBB permeability between control and tolerant mice [1]. However, we observed that d3-morphine metabolism was reduced by one third compared to morphine without any interference with our study. Thus, our results indicate that analgesic tolerance seems not linked to increased morphine metabolism or a modification of the BBB permeability. Nevertheless, as we have used the whole brain for our analysis and only a 90min time point, it can not be ruled out that either local CNS alterations or a difference in morphine metabolism and uptake occur ([2] and the poster by Gabel et al.). Additional studies at different time points and focusing on discrete brain areas (*e.g.* PAG) are needed to clarify if M3G is involved in morphine analgesic tolerance [2]. [1] Weinsanto I et al. (2018) Br J Pharmacol ;175(19):3844-3856 [2] Gabel F et al (2021)) Br J Pharmacol ; under review.

Disclosures: Y. Goumon: None. **I. Weinsanto:** None. **A. Laux-Biehlmann:** None. **J. Mouheiche:** None. **T. Maduna:** None. **V. Andry:** None. **F. Gabel:** None.

Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P724.03

Topic: G.09. Drugs of Abuse and Addiction

Title: Rescue and prolonged protection from fentanyl overdose with novel bioorthogonal covalent mu opioid receptor antagonists

Authors: *J. P. MCLAUGHLIN[1], S. O. EANS[1], J. THOMAS[2], S. A. ZAIDI[2], T. CHE[4], B. L. ROTH[5], J. REICH[6], S. MAJUMDAR[4], V. V. FOKIN[2], V. KATRITCH[3];
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Abstract: Respiratory depression mediated by mu-opioid receptor (MOR) agonists is life-threatening, with overdose from synthetic opioids such as fentanyl responsible for 36,359 deaths in the U.S. in 2019. While naloxone can reverse these effects, its short duration of MOR antagonist activity limits therapeutic efficacy, particularly against high doses of fentanyl. To generate a longer-lasting treatment against MOR agonist overdose, we synthesized and characterized a series of 12 novel covalent MOR antagonists capable of highly selective irreversible binding to MOR via a recently developed bioorthogonal proximity-guided Sulfur (VI) Fluoride Exchange (SuFEx) reaction. Computational design guided the synthesis of a series of naloxone derivatives functionalized with a weak electrophilic SuFEx “warhead”, SO_2F, that by itself is not reactive in human cells. However, when selectively guided into the MOR pocket by naloxone, and properly oriented in close proximity to nucleophilic tyrosine-150 of the MOR, the SO_2F moiety covalently attaches to the receptor via a SuFEx reaction. In radioligand competition binding experiments, the initial racemic compound TJ-345 displayed high affinity (K_i=5 nM) and selectivity for the MOR with only trace partial agonism (<10% E_{max}) in G-protein or arrestin recruitment assays. Moreover, TJ-345 demonstrated irreversible binding and potent antagonism at MOR, with a wash-

resistant inhibition of binding >48 h after initial incubation. In mice tested with the 55ºC warm-water tail-withdrawal assay *in vivo*, TJ-345 produced brief antinociception (<40 min), but dose-dependently antagonized morphine antinociception after i.c.v. (>3 nmol) or s.c. pretreatment (3-60 mg/kg). TJ-345 (3 nmol, i.c.v.) significantly antagonized morphine up to 48 h, but showed only partial blockade of morphine at 24 h after a 30 mg/kg s.c. treatment. In contrast, the stereoisomer TJ-171 showed no antinociception on its own, and fully antagonized morphine for 24 h after a 30 mg/kg s.c. treatment, consistent with the reported turnover time of the MOR in mice. Prophylactic administration of TJ-345 or TJ-171 (30 mg/kg, s.c., each) to mice further protected against fentanyl-induced respiratory depression and hyperlocomotion in the CLAMS assay, lasting up to 48 h with TJ-171. Moreover, acute administration of TJ-171 to mice 21 minutes after exposure to fentanyl dose-dependently and swiftly reversed MOR agonist-induced respiratory depression and hyperlocomotion, maintaining that protection against additional doses of fentanyl 12 hours later. These results validate the development of selective bio-orthogonal covalent MOR antagonists against fentanyl overdose.

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P724.04

Topic: G.09. Drugs of Abuse and Addiction

Title: Discriminative stimulus effects of gabapentin in rats

Authors: *A. PRUS, A. N. IANNUCCI, J. N. PRETE, C. E. CLIFTON, B. E. BEAVERS, T. S. BOHINSKI;
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Abstract: Gabapentin is a blocker for Ca2+ channels that contain an $\alpha_2\delta$-1 or $\alpha_2\delta$-2 subunit and is prescribed for neuropathic pain, anxiety, fibromyalgia, and epilepsy. There are increasing reports of abuse with gabapentin, along with its analog pregabalin, suggesting that gabapentin may elicit positive subjective effects. Further, concomitant use occurs with opioids and other substances of abuse. In order to examine the subjective effects of gabapentin, the present study utilized a drug discrimination procedure in 12 male adult Sprague Dawley rats trained to discriminate a 30.0 mg/kg dose of gabapentin versus saline in a two choice operant task for food reinforcement. All 12 of the rats met the training criteria, consisting of 5 out 6 consecutive sessions of at least 80% condition-appropriate responding. Gabapentin (3.75 - 240 mg/kg) produced full-substitution (>80% gabapentin-lever responding; ED_{50}=7.2 mg/kg, 95% confidence interval [CI] = 5.3 to 9.7 mg/kg), with full substitution occurring for all doses at 15.0 mg/kg and higher. Pregabalin (3.75 to 15.0 mg/kg) also produced full substitution (ED_{50}=7.1 mg/kg, 95% CI=4.9 to 10.2 mg/kg), which occurred for a 15.0 mg/kg dose. Partial substitution (> 20% gabapentin-lever responding) was observed for the opioid agonist fentanyl, with the highest percentage of gabapentin lever responding (58.3%) found for a 0.04 mg/kg dose. The present findings indicate that gabapentin elicits subjective effects that can be readily established as a discriminative cue. Further, full substitution by pregabalin

indicates that this compound also produces subjective effects and that these effects are likely mediated by similar pharmacological actions. Similarly, partial substitution observed with fentanyl also suggests some degree of similarity across the subjective effects of these compounds, potentially generated through a shared pharmacological mechanism of action. Overall, the demonstration that gabapentin produces discriminative stimulus effects in rats, which carry a degree of similarity to fentanyl, implies that positive subjective effects may account for increasing trends of gabapentin abuse.

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Enantioselective drug-binding kinetics shape the psychostimulant effect of dopamine transporter inhibitors

Authors: *M. NIELLO[1], S. SIDEROMENOS[2], R. GRADISCH[2], R. O'SHEA[4], J. SCHWAZER[2], W. SANDTNER[2], J. MAIER[2], K. JÄNTSCH[2], C. R. LUPICA[5], A. F. HOFFMAN[6], A. F. HOFFMAN[6], T. STOCKNER[2], D. D. POLLAK[3], M. H. BAUMANN[7], H. H. SITTE[8];
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Abstract: The pharmacology of different compounds is normally assessed under thermodynamic equilibrium, however, in the human body, the drug-target interaction is influenced by the constant flux of fluids and a variety of physiological processes. Hence, the in vivo properties of a drug differ from the in vitro thermodynamic equilibrium. α-Pyrrolidinovalerophenone (αPVP) is a psychostimulant and drug of abuse associated with severe intoxications in humans. αPVP exerts long-lasting psychostimulant effects, when compared to the classical dopamine transporter (DAT) inhibitor cocaine. We used radiotracer assays, computational approaches, transporter electrophysiology and behavioural assays in mice to investigate the role of binding kinetics in the psychostimulant effect elicited by αPVP enantiomers. We found that αPVP enantiomers substantially differ from the DAT-inhibitor cocaine in their binding kinetics. The two enantiomers differ from each other in their association rates, but they show similar slow dissociation rates leading to pseudo-irreversible binding kinetics at DAT. The pseudo-irreversible binding kinetics of αPVP is responsible for the observed non-competitive pharmacology, correlates with persistent

psychostimulant effects in mice and differ from the fast-acting DAT-inhibitor cocaine. Our work shows that drug binding kinetics at DAT can have a significant impact on the psychostimulant effects of drugs in vivo. Given this information, a more detailed assessment of drug-binding kinetics for DAT inhibitors might provide insights for the design of novel DAT inhibitors with improved clinical utility. Furthermore, it shows how psychopharmacological research on illicit drugs may help to reach a better understanding of physiological and toxicological processes.

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Circadian Effects on Opioid Use Disorder Transcriptome

Authors: *S. V. MOVVA[1], E. F. MENDEZ[2], K. NAJERA[2], L. STERTZ[2], G. R. FRIES[2], T. D. MEYER[2], H. WEI[3], J. WU[3], C. WALSS-BASS[2];
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Abstract: Opioid use disorder has been identified as a public health crisis, affecting over 1.7 million people per year in the US. Therefore, understanding the molecular effects of OUD is essential in this opioid use epidemic. Opioids and opioid withdrawal can also disrupt the circadian rhythm, a 24-hour oscillatory cycle that regulates certain gene networks. Previous studies identified 394 differentially expressed (DE) coding and long non-coding (lnc) RNAs in post-mortem human brains of opioid users. In this study, we aimed to test the hypothesis that some of these differentially expressed genes are correlated with time of death in postmortem brains of opioid users and controls, and are therefore affected by circadian rhythm. We calculated Zeitgeber time of death (zTOD) for each postmortem subject. After correcting for human tissue covariates, we performed sine regression analysis to determine the influence of the time of day on gene expression. We found that 3 canonical genes involved in circadian rhythm (CRY1, NPAS2, PER3) were significantly correlated with zTOD in the postmortem subject. We also found 8 DE coding RNAs and 3 DE lncRNAs that were influenced by the zTOD. In the future, we will compare the genes' zTOD effect in the OUD subjects versus controls, and validate these results in a cell model.

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Poster

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Title: Methamphetamine-induced cellular stress response in primary human brain vascular pericytes

Authors: *N. FATTAKHOV, S. TORICES, M. PARK, M. TOBOREK;
Dept. of Biochem. and Mol. Biol., Univ. of Miami, Miami, FL

Abstract: Methamphetamine (METH) is a powerful, highly addictive psychostimulant that has a pronounced effect on the central nervous system. Recent studies in animal models have indicated that METH can induce impairment of the blood-brain barrier (BBB), suggesting that some of the neurotoxic effects resulting from METH abuse could be the outcome of BBB disruption. The BBB operates within the neurovascular unit, which includes clusters of neurons, endothelial cells, pericytes and glial cells. Pericytes regulate BBB permeability, angiogenesis, clearance, cerebral blood flow, neuroinflammation and stem cell activity. The present study aimed to investigate cellular stress response in METH-treated primary human brain vascular pericytes (pHBVP), particularly the production of mitochondrial reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress markers. Mitochondrial superoxide levels, as detected by MitoSOX Red staining, were increased in pHBVPs in response to the acute treatment (24 hours) with the higher concentrations (10, 25 and 50 µmol) but not the lower concentrations (1 and 5 µmol) of METH in a dose-dependent manner. Western blot analysis showed that the expression of the main ER stress marker, activating transcription factor 6 (ATF6), was significantly higher in pHBVPs treated for 24 hours with 10 µmol METH compared to the vehicle control. No differences in expression of SIRT3, the major deacetylase in mitochondria, were detected between METH-treated and control groups. The data from gene expression analysis and immunofluorescence staining for Toll-like receptor (TLR)2 and TLR4 showed no evidence of their involvement in mediating cellular cytotoxic responses during acute METH treatment in pHBVPs. Overall, our preliminary study suggests that METH-induced mitochondrial oxidative stress can disrupt the protein folding mechanism and enhance the production of misfolded proteins, causing further ER stress in pHBVPs and potential BBB damage. A deeper understanding of how oxidative stress damages the BBB may open up more effective therapy options for the treatment of METH-induced neurotoxicity.

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Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01DA044859
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Title: Molecular Signatures of Drug Induced Neurotoxicity in Human Brain Models

Authors: *E. F. MENDEZ[1], H. WEI[2], R. HU[3], L. STERTZ[1], G. FRIES[1], X. WU[2], K. NAJERA[1], M. MONTEREY[4], C. LINCOLN[5], S. V. MOVVA[7], J.-W. KIM[5,6], K. MORIEL[1], T. D. MEYER[1], S. SELVARAJ[1], A. L. TEIXEIRA[1], Z. ZHAO[3], J. XU[5,6], J. WU[2], C. WALSS-BASS[1];
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Abstract: Opioid use disorder (OUD) is a public health crisis in the U.S. that causes over 50 thousand deaths annually due to overdose. Using next-generation RNA sequencing and proteomics techniques, we identified 394 differentially expressed (DE) coding and long noncoding (lnc) RNAs as well as 213 DE proteins in Brodmann Area 9 of OUD subjects. The RNA and protein changes converged on pro-angiogenic gene networks and cytokine signaling pathways. Four genes (LGALS3, SLC2A1, PCLD1, VAMP1) were dysregulated in both RNA and protein. We found cell-type specific effects in these OUD gene networks with enrichment in astrocyte, endothelial, and microglia correlated genes. Furthermore, using *ex vivo* magnetic resonance imaging, we identified increased vascularization in postmortem brains from a subset of subjects with OUD. This is the first study integrating dysregulation of angiogenic gene networks in OUD with qualitative imaging evidence of hypervascularization in postmortem brain. Future studies include exploring and validating these cell-specific gene expression signatures using single nuclei RNA sequencing of postmortem brain and investigating gene expression in an *in vitro* neuron model of morphine exposure derived from postmortem human fibroblasts.

Disclosures: E.F. Mendez: None. **H. Wei:** None. **R. Hu:** None. **L. Stertz:** None. **G. Fries:** None. **X. Wu:** None. **K. Najera:** None. **M. Monterey:** None. **C. Lincoln:** None. **S.V. Movva:** None. **J. Kim:** None. **K. Moriel:** None. **T.D. Meyer:** None. **S. Selvaraj:** None. **A.L. Teixeira:** None. **Z. Zhao:** None. **J. Xu:** None. **J. Wu:** None. **C. Walss-Bass:** None.

Poster

P724. Tolerance, Dependence, and Toxicity of Addictive Drugs

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P724.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA-IRP Grant ZIADA000566

Title: Effects of alcohol on brain oxygenation and brain hypoxia induced by intravenous heroin

Authors: *E. KIYATKIN, S. A. THOMAS, C. M. CURAY;
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Abstract: Alcohol is the most commonly used psychoactive drug, often taken in conjunction with opioid drugs. Since both alcohol and opioids can induce CNS depression, it is often assumed that alcohol potentiates the known hypoxic effects of opioid drugs, thus contributing to coma and death during opioid overdose. To address this supposition, we used oxygen sensors to examine the effects of alcohol on brain oxygenation and hypoxic responses induced by intravenous heroin in awake, freely moving rats. To eliminate robust sensory effects of alcohol following its oral or intraperitoneal delivery, alcohol was administered directly into the stomach via chronically implanted intragastric catheters at human relevant doses. Alcohol delivered at a 0.5 g/kg dose did not affect brain oxygen levels, except for a weak transient increase during drug delivery. This phasic oxygen increase was stronger at a 2.0 g/kg alcohol dose and followed by a weaker tonic increase. Since alcohol absorption from intragastric delivery is much slower and more prolonged than with intraperitoneal or intravenous injections, the rapid rise of brain oxygen levels suggests direct action of alcohol on sensory afferents in the stomach well before the drug physically reaches brain tissue via circulation. Despite slow tonic increases in brain oxygen, alcohol at the 2.0 g/kg dose strongly potentiates heroin-induced oxygen responses, increasing both the magnitude and duration of oxygen decrease. Therefore, under the influence of alcohol, the use of opioid drugs becomes much more dangerous, increasing brain hypoxia and enhancing the probability of serious health complications, including coma and death. Supported by the NIDA-IRP (NIDA-IRP Grant ZIADA000566).

Disclosures: E. Kiyatkin: None. **S.A. Thomas:** None. **C.M. Curay:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P760.01

Topic: G.09. Drugs of Abuse and Addiction

Support: BBSRC DTP/Shionogi & Co. RG73357
MRC Programme Grant MR/N02530X/1

Title: The behavioural effects of heroin depend on the recruitment of the peripherally-generated effects by the central mechanisms of heroin.

Authors: *D. D. JOSHI[1], M. PUAUD[1], L. MARTI-PRATS[1], M. FUJITA[2], D. BELIN[1];
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Abstract: The behavioural effects of heroin have long been considered to be mediated by its actions on μ-opioid receptors (μ-ORs) in the brain. However, heroin, like all drugs of abuse, also produces interoceptive states suggested to depend on the integration by the insular cortex of the peripheral effects of heroin. Our recent demonstration that the anterior insular cortex (AIC) exerts an inhibitory effect on the loss of control of heroin intake and the subsequent propensity to relapse after forced abstinence, suggests a role for interoceptive mechanisms in the development of addictive behaviour. However, whether the functional engagement of the AIC and its associated circuitry underlying the control over behaviour by interoceptive mechanisms results from direct peripheral actions of heroin, central mechanisms downstream to the activation of μ-ORs in the brain or their interplay has not been established. Here we tested the hypothesis that the behavioural effects of heroin, such as its locomotor activating properties, depend on an interplay between its central and peripheral mechanisms. In a between-subject study, we compared in male Sprague Dawley rats (n=102) the effect of systemic administrations of several doses of the selective peripheral μ-OR antagonist *9g* on the locomotor activating effects of heroin to that of μ-OR antagonism by naloxone. As compared to saline (n=12), intraperitoneal (IP) administration of heroin (2mg/kg, n=8) resulted in a delayed but sustained increase in locomotor activity over a 45-minute session. This locomotor effect was equally blocked by the IP administration of 9g (0.01, 0.03 and 0.1 mg/kg, n=7-8 per dose) and naloxone (0.14 mg/kg, n=7), suggesting a role of peripheral μ-ORs in the behavioural effects of heroin. To further probe this effect, we investigated the locomotor effect of the selective peripheral μ-OR agonist loperamide. In contrast to heroin, loperamide across multiple doses (vehicle, 1, 2.5, 5 and 7.5 mg/kg, n=7-8 per group), showed no stimulatory locomotor effects like heroin. This suggests that the activation of peripheral μ-ORs alone is not sufficient to support the locomotor activating effects of heroin.Together, the results of this study indicate that the locomotor activating effects of heroin depend on a centrally-mediated integration of the peripherally-generated interoceptive effects of the drug, thereby providing further evidence for a role of brain-body interactions in the regulation of the behavioural responses to addictive drugs.

Disclosures: D.D. Joshi: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Cambridge. **M. Puaud:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Cambridge. **M. Fujita:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **D. Belin:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Cambridge.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P760.02

Topic: G.09. Drugs of Abuse and Addiction

Support: Rutgers' Brain Health Institute
Dorothy and David Cooper Endowment
Aresty Research Center

Title: A quantitative and morphological analysis of microglia in dopamine target regions following chronic fentanyl self-administration in rats

Authors: *A. N. DAO, A. MONTEMARANO, V. MAYR, A. W. KUSNECOV, M. O. WEST;
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Abstract: Opioid addiction is associated with increased prevalence of bacterial and viral infections, reflecting known immunomodulatory effects of opioids in both immune and CNS compartments. Microglial cells, the resident immune cells of the CNS, function as macrophages and assume various activational states in response to neural injury, systemic inflammation, and psychological stress. They also generate and secrete pro-inflammatory cytokines that may regulate neuronal functions and mediate local inflammatory responses. Microglia also express opioid receptors and toll-like receptors, which may allow for direct immunomodulation by opioids resulting in altered microglial activation and morphological states, as well as apoptosis and suppression of proliferation. While there is significant evidence citing the immunomodulatory effects of opioids, there is an absence of research on how neuroinflammatory events involving microglial activation are affected by chronic fentanyl self-administration (SA) or persist after cessation of drug. To test this, the current project employed a rat model of voluntary chronic, long-access fentanyl SA to examine the microglial response to chronic fentanyl abuse after a period of abstinence from drug. Male Sprague-Dawley rats self-administered fentanyl (Fent/SA) for 30 consecutive days before being assigned an abstinence period of either 1 week (N=5) or 1 month (N=5). Control animals (Sal/SA) similarly received access to SA saline and subsequent abstinence periods (N=9). On the last day of abstinence all animals received an injection of lipopolysaccharide (LPS; 1.5 mg/kg, i.p.), an endotoxin that produces a vigorous systemic inflammatory response, followed by perfusion and brain collection. All brains were assayed by IHC for the microglial marker Iba1 to quantitate microglial cell numbers and morphological states. Preliminary analyses have indicated a large effect size for the interactions of SA treatment x Abstinence Period for both IL-1ß concentrations (partial eta^2=0.277) and TNF-α concentrations (partial eta^2=0.445) indicating that these cytokines were initially suppressed after 7 days of abstinence but returned to control levels after 30 days of abstinence. It is expected that ongoing analyses will similarly show microglial suppression in Fent/SA animals after 1 week of abstinence compared to Sal/SA animals, but not after 30 days abstinence. The results of this study will show for the first time whether recovery from systemic and central immunosuppression is possible after an extended period of abstinence from chronic fentanyl abuse.

Disclosures: A.N. Dao: None. **A. Montemarano:** None. **V. Mayr:** None. **A.W. Kusnecov:** None. **M.O. West:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P760.03

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA T32 DA007621

Title: Pain effects dopaminergic inputs from ventral tegmental area to nucleus accumbens during fentanyl self-administration in a sex dependent manner

Authors: *J. G. ABT[1], J. A. HIGGINBOTHAM[2], J. A. MORON-CONCEPCION[2];
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Abstract: Up to 50 million people in the US suffer from chronic pain. Opioids are commonly prescribed for pain symptoms but are highly prone to misuse. Clinical evidence suggests that the influence of pain on opioid misuse is sex dependent, but preclinical support for this phenomenon is lacking. Here, we used a model of persistent inflammatory pain and cue-induced relapse to test the hypothesis that pain influences opioid use and mesolimbic dopamine circuit function in a sex-dependent manner. To do this, male and female TH-Cre rats (2-3 months old) were injected with Cre-dependent GCaMP7s in the ventral tegmental area (VTA) to selectively target VTA dopamine neurons. An optic fiber was implanted in the shell of the nucleus accumbens (NAc) to detect calcium transients from GCaMP-expressing VTA terminals in the NAc. Rats were implanted with an IV catheter and subjected to pain (hind paw injection of Complete Freuds Adjuvant) or no pain (saline) prior to undergoing fentanyl self-administration. Correct lever presses during daily 2-hour sessions were reinforced with illumination of a cue light and a fentanyl infusion of 5µg/kg (IV) for the first five days and 2µg/kg for the next ten days. Then rats underwent extinction training (seven days) where fentanyl and drug-paired cues were withheld. Cue-induced reinstatement was assessed the next day by reintroducing drug-paired cues in the absence of fentanyl. Rats were then tested during a final self-administration session in the absence of cues to dissociate effects of drug reinforcement. Wireless *in vivo* fiber photometry recordings were made at least every five days throughout training and signals were aligned with correct lever responses. Each day, mechanical sensitivity was assessed using Von Frey and vaginal smears were collected to track estrus cycling. We found that males in pain escalated their intake of fentanyl over time while males without pain and females in both groups did not show significant changes in fentanyl intake. Moreover, males in pain were less likely to exhibit changes in GCaMP fluorescence at VTA to NAc terminals in response to fentanyl than any other group, suggesting that pain disrupted mesolimbic circuit function, particularly in males. Finally, lever responses during extinction, cue-induced reinstatement, and fentanyl infusions in the absence of cues distinctively impacted VTA to NAc GCaMP fluorescence, suggesting this circuit encodes discrete components of reinforcement. Together, these findings demonstrate a sex-specific influence of pain on opioid use and mesolimbic dopamine function in a circuit- and cell-type-specific manner.

Disclosures: J.G. Abt: None. **J.A. Higginbotham:** None. **J.A. Moron-Concepcion:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P760.04

Topic: G.09. Drugs of Abuse and Addiction

Support: 5R01DA041781-05

Title: Study of inflammatory pain impact on alcohol-drinking and seeking behavior: implication of sex differences

Authors: *Y. CAMPOS-JURADO[1], J. D. LORENTE[2], L. HIPOLITO[2], J. MORON-CONCEPCION[1]; [1]Anesthesiol., Washington Univ. In St Louis, St Louis, MO; [2]Pharm. and Pharmaceut. Technol. and Parasitology, Univ. of Valencia, Valencia, Spain

Abstract: During the last years, multiple clinical and epidemiological studies have revealed that the presence of chronic pain is closely related to Alcohol Use Disorder (AUD). In fact, previous preclinical studies have shown that inflammatory pain induces relapse-like behavior in female rats whereas only male mice under inflammatory pain increase their alcohol intake during an acquisition phase. However, there is only a few number of studies approchig this problematic and therefore the global effect of pain on AUD remains not fully discern. In this study we aimed to deeply explore wether the development of an inflammatory pain condition induced by the intraplantar injection of the Complete Freud Adjuvant (CFA) could impact alcohol related behaviors depending on the onset of the pain condition. For that, we use a non-operant intermittent alcohol consumption paradigm in rodents with an Arduino controlled two-bottle choice apparatus that allows us to obtain real-time licking measurements. Moreover, we corralate our behavioral data with the study of neural activation of different regions in the mesocorticolimbic system measured by fluorescence immunohistochemistry of delta-Fos B. First, we observed that females and males show differences in their total alcohol intake levels. Interestingly, our preliminary results also show that inflammatory pain differentially affects total alcohol intake and seeking behavioral patterns among different phases of the addiction cycle. These findings may contribute to the better understanding of the intersection between pain and AUD and to the development of more individualized treatments for chronic pain patients with a history of alcohol abuse.

Disclosures: Y. Campos-Jurado: None. **J.D. Lorente:** None. **L. Hipolito:** None. **J. Moron-Concepcion:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

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Program #/Poster #: P760.05

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA T32 DA007621
WM Keck Fellowship
NIH NIDA R01 DA041781

Title: Wireless in vivo fiber photometry to detect sex-specific effects of pain on ventral tegmental area function during IV fentanyl self-administration in freely behaving rats

Authors: *J. A. HIGGINBOTHAM[1], J. G. ABT[2], J. MORON-CONCEPCION[3]; [1]Anesthesiol., Washington Univ., Saint Louis, MO; [2]Washington Univ. Sch. of Med., st. louis, MO; [3]Anesthesiol., Washington Univ. In St Louis, St Louis, MO

Abstract: Chronic pain effects up to one-third of US adults. Opioids are frequently used to treat pain symptoms but are highly prone to abuse. Clinical evidence suggests males are vulnerable to negative outcomes associated with opioid use and preclinical evidence indicates that pain reduces dopaminergic

signaling in the ventral tegmental area (VTA). However, it remains unclear whether pain impacts the ability of VTA dopamine neurons to respond to opioid reinforcement in a sex-dependent manner. To investigate this possibility, GCaMP7s was expressed in a Cre-dependent manner in the VTA of male and female TH-Cre rats (2-3 m.o.) and an optic fiber was implanted. After 14 days, rats were implanted jugular catheters and received right hind-paw injections of saline (No Pain) or Complete Freund's Adjuvant (CFA; Pain). After 3 days, rats underwent self-administration during 15 daily 2-h sessions where correct lever presses were reinforced with an infusion of fentanyl (5 ug/kg or 2 ug/kg, iv) and illumination of a light cue (5 s). This was proceeded by extinction training for 7 days where drug and cue reinforcement were withheld. Next, rats underwent daily test sessions of cue-induced reinstatement, non-cued fentanyl relapse, and non-contingent drug exposure. Von Frey mechanical sensitivity and estrus cycle phase were determined each day. Every 1-5 days, a battery-powered transmitter head stage was secured to the optic fiber and GCaMP fluorescence was measured throughout the duration of the session (1-2 hr) and aligned to correct lever responses. There were no sex differences or effects of pain on the acquisition of fentanyl self-administration but over time, fentanyl intake in males was greater than females. Pain exacerbated these effects in males as indicated by higher escalation ratios than any other group. Interestingly, the ability of pain to facilitate fentanyl self-administration in males coincided with opposite effects on VTA dopamine neuron GCaMP responses to fentanyl, such that, ΔF/F signals time-locked to fentanyl-reinforced lever presses were reduced in amplitude and efficacy compared to all other groups. Moreover, GCaMP fluorescence elicited by lever presses varied as a function of reinforcement. Together, these findings provide evidence for a novel means of conducting fiber photometry in parallel to IV self-administration and suggest that sex-specific effects of pain on fentanyl consumption may be due to impairments in the ability of VTA dopamine cells to respond to opioid reinforcement.

Disclosures: J.A. Higginbotham: None. **J.G. Abt:** None. **J. Moron-Concepcion:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

Location: Virtual Only

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Program #/Poster #: P760.06

Topic: G.09. Drugs of Abuse and Addiction

Support: T32 DA007261
R01-DA041781
R01-DA042499
R33-DA041883

Title: Opioid-induced respiratory depression involves opioid receptors at both central and peripheral sites

Authors: *B. RUYLE, K. YOON, N. MASSALY, J. MORON-CONCEPCION;
Washington Univ. in St Louis, St Louis, MO

Abstract: Intravenous administration of fentanyl produces profound and sustained respiratory depression, and there is abundant evidence that this involves direct actions at mu opioid receptors in brainstem respiratory nuclei. Opioid receptors are also present in the periphery, but the contribution of these

receptors in the generation of opioid-induced respiratory depression (OIRD) is poorly understood. Male and female rats were administered fentanyl (2 and 20 ug/kg, intravenous delivery) and cardiorespiratory parameters (oxygen saturation, heart rate and respiratory rate) were measured using a wired collar oximeter. Intravenous fentanyl produced rapid decreases in all measured parameters, effects which were sustained for up to 20 minutes. To gain insight into the role of central vs peripheral opioid receptors in OIRD, subsets of male and female animals were intravenously pretreated with either the nonselective opioid receptor antagonist naloxone (NLX, 1 mg/kg), or the peripherally-restricted opioid receptor antagonist naloxone methiodide (NLXM, 1 mg/kg) prior to receiving intravenous fentanyl (20 ug/kg). As expected, NLX blocked all cardiorespiratory changes that were evoked by fentanyl. Surprisingly, NLXM pretreatment strongly attenuated fentanyl-induced respiratory depression, with only a small decrease in oxygen saturation observed. Immunohistochemical analysis was then performed for Fos (marker of neuronal activation) in the nTS, which is a critical site of cardiorespiratory integration. Fentanyl induced a dose-dependent activation of nTS neurons. Pretreatment with NLX limited Fos-IR in the nTS. Interestingly, NLXM pretreatment still produced a similar degree of activation that was observed after fentanyl alone. This strong activation occurred even in the absence of respiratory depression. Taken together, these data suggest that fentanyl induces activation in nTS neurons. Furthermore, peripheral opioid receptors may play a larger role in driving fentanyl-induced respiratory depression than previously thought.

Disclosures: B. Ruyle: None. **K. Yoon:** None. **N. Massaly:** None. **J. Moron-Concepcion:** None.

Poster

P760. Circuitry and Neurophysiology of Opioid Addiction

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P760.07

Topic: G.09. Drugs of Abuse and Addiction

Support: UG3 DA048353 01
R01 DA047855 01

Title: Comparison of Central Mu-Opioid Receptor Activity Following Oral Administration of Mitragynine, 7-Hydroxymitragyine, and Mitragynine Pseudoindoxyl

Authors: *S. OBENG[1], A. PATEL[1], N. P. HO[1], L. R. GAMEZ JIMENEZ[1], V. L. C. PALLARES[1], M. MOTTINELLI[2], F. LEON[2], C. R. MCCURDY[2], L. R. MCMAHON[1], T. HIRANITA[1];
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Abstract: Mitragynine (MG) is the most abundant alkaloid contained in kratom (*Mitragyna speciosa*), which is widely used to self-treat pain, mood disorders, and opioid use disorder. MG has active metabolites: our group has demonstrated that MG is metabolized *in vivo* into 7-hydroxymitragynine (7-OH-MG), which is in turn converted into MG pseudoindoxyl (MG-P). MG and the two metabolites might contribute to the *in vivo* μ-opioid receptor (MOR) activity of kratom; however, the relative *in vivo* activity of MG and these metabolites has not been established. Here we compared their MOR pharmacology *in vitro* and *in vivo*. *In vitro* displacement of [^{3}H]DAMGO at human MOR yielded the rank order affinity

(Ki in nM) of MG-P (1.5) > morphine (4.0) > 7-OH-MG (78) > MG (709). Stimulation of [^{35}S]GTPγS binding yielded the rank order efficacy (% stimulation normalized to DAMGO) of morphine (92) > 7-OH-MG (46) > MG-P (32) > MG (4.0). Thermal antinocicpetive effects were measured in mice using a hotplate assay (52°C). 100% maximum possible effects were produced by oral administration of MG and 7-OH-MG whereas MG-P produced significant increases in hotplate response latency with a plateau at approximately 50% maximum possible effects at 17.8-320 mg/kg. The increases in hotplate response latency were obtained without concomitant decreases in locomotor activity relative to oral administration of vehicle. Robust increases in activity counts were obtained with 7-OH-MG and MG-P. The rank order antinociceptive potency (ED_{50}s in μmol/kg, p.o.) was 7-OH-MG (151) > MG-P (161) > MG (568). The antinociceptive effects of MG, 7-OH-MG, and MG-P were reversed to the vehicle levels with the opioid antagonist naltrexone (1 mg/kg). The same dose of naltrexone also fully antagonized the activity-increasing effects of 7-OH-MG and MG-P. In contrast, none of the antinociceptive or activity-increasing effects was antagonized by a 3.2-fold higher dose (3.7 mg/kg) of methylnaltrexone, an analogue of naltrexone that has less capacity to penetrate the blood brain barrier. These results suggest that MG and its metabolites tested are MOR agonists *in vivo*, with the intrinsic activity and potency of 7-OH-MG being greater than both MG and MG-P. Despite MG-P exhibiting the highest MOR binding affinity and intrinsic activity *in vitro* among the compounds tested, these results suggest that MG-P has relatively low bioavailability as compared with MG and 7-OH-MG, and that 7-OH-MG is the most orally bioactive MOR agonist of the compounds tested.

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Poster

P857. Invertebrates: Learning and Memory II

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P857.01

Topic: H.08. Learning and Memory

Support: NIH grants NS019895
NIH grants NS102490

Title: Quantitative description of the interactions among kinase cascades underlying long-term plasticity of Aplysia sensory neurons

Authors: Y. ZHANG, P. SMOLEN, L. CLEARY, J. BYRNE;
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Abstract: It is generally acknowledged that kinases and growth factors play critical roles in synaptic and neuronal changes involved in the formation of memory. However, significant gaps exist in understanding the dynamics, cross talk and feedback interactions among these cascades. These processes will contribute to the mechanistically distinct temporal domains of memory ranging from short-term memory lasting minutes to long-term memory lasting days to lifetimes. Activation of protein kinase A (PKA) and

mitogen-activated protein kinase (MAPK) - ribosomal S6 kinase (RSK) pathways are critical for long-term enhancement of neuronal excitability and long-term synaptic facilitation, essential processes in memory formation. We have combined empirical and computational methods to develop new insights into how these pathways contribute to the distinct temporal domains of memory. Empirical studies of *Aplysia* sensory neurons delineated two new pathways: PKA-dependent, but MAPK-independent, regulation of RSK, and RSK-dependent activation of p38 MAPK. The first pathway suggests the existence of a positive feedforward loop regulating RSK, whereas the second supports a negative feedback loop within a MAPK cascade. A computational model incorporated these findings and others from the literature (e.g., Kopec et al., 2015; Zhang et al., 2017; Jin et al., 2018). It simulated dynamics of kinase activity, and neurotrophin and transforming growth factor-beta feedback loops, produced by different stimulus protocols. A prediction of the critical roles of kinase interactions in the dynamics of these pathways was validated by subsequent empirical studies. These findings may provide insights into the ways in which kinases contribute to aberrant synaptic plasticity observed in disorders such as RASopathies and Coffin-Lowry syndrome.

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Poster

P857. Invertebrates: Learning and Memory II

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Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P857.02

Topic: H.08. Learning and Memory

Support: NIH Grant R01 NS101356

Title: Operant conditioning engage synergistic in excitability and chemical and electrical synaptic transmission

Authors: *Y. MOMOHARA[1], C. NEVEU[1], H.-M. CHEN[2], D. A. BAXTER[3], J. H. BYRNE[1];
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Abstract: Operant conditioning (OC) is a ubiquitous form of learning in which animals learn the consequences of behavior. The neural circuit that mediates feeding behaviors in *Aplysia* provides a tractable model system for analyzing neuronal mechanisms that underlie OC. Previous studies found that OC increases the intrinsic excitability and electrical coupling among some neurons involved in the initiation and selection of the reinforced feeding behavior. It is not known, however, whether changes in chemical synaptic transmission and/or whether reduced cellular excitability also contributes to OC. Here, isolated buccal ganglia, which contain key elements of the feeding circuitry, were subjected to an in vitro analog of OC. Contingent reinforcement reduced the excitability of the inhibitory neuron B4. Similar changes in excitability were obtained using a single-cell analog of operant conditioning. In addition, contingent reinforcement reduced the B4-to-B51 inhibitory postsynaptic potential (IPSP) but not the B4-to-B8 IPSP. These results indicated that OC was mediated by both non-synaptic and synaptic changes and that a single neuron manifests target-specific changes in synaptic efficacy. Finally, a conductance-based

model of the circuit was used to investigate the ways in which diverse and distributed forms of neuronal plasticity act synergistically to modify behavior.

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Poster

P857. Invertebrates: Learning and Memory II

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Program #/Poster #: P857.03

Topic: H.08. Learning and Memory

Support: NIH Grant NS019895

Title: Deficient synaptic plasticity in model of Coffin-Lowry Syndrome is rescued by combining pharmacological activation of PKA and ERK

Authors: *R.-Y. LIU, L. J. CLEARY, J. H. BYRNE;
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Abstract: Developing treatment strategies to improve cognitive functions in both healthy individuals and people with memory deficits is an important goal of neuroscience research. Recent studies suggest that multiple kinases converge on the transcription factor cAMP response element-binding protein (CREB) to enhance the expression of proteins essential for long-term synaptic plasticity and memory. p90 ribosomal S6 kinase (RSK) is one such kinase. Our previous investigation (Liu et al., 2020) demonstrated that RSK is required in long-term synaptic facilitation (LTF), a cellular correlate of long-term memory (LTM). Inhibition of RSK impairs LTF, suggesting that this may be a useful cellular system to study aspects of deficient synaptic plasticity observed in Coffin-Lowry Syndrome (CLS), a cognitive disorder caused by mutations in *rsk2*. The present study focused on pharmacological approaches to rescue defective LTF. Activation of multiple biochemical signaling cascades, such as the protein kinase A (PKA) and extracellular signal-regulated kinase (ERK) pathways, is necessary to induce LTF. Previously, combining an ERK activator, NSC, and a PKA activator, rolipram, enhanced LTF to a greater extent than did either drug alone (Liu, et al., 2017). The present study exploited the technical advantages of the *Aplysia* sensorimotor culture system to examine whether dual drugs can restore the deficit in LTF induced by inhibition of RSK activity. We found that the impairments in LTF in the cellular analogue of CLS can be rescued by the NSC - rolipram combination, targeting PKA and ERK signaling pathways. The drug combination also enhanced RSK activation, which may contribute to LTF. Therefore, our data further supports the hypothesis that RSK is a site of convergence for training-induced PKA activation and ERK activation, upstream of CREB1. Combined pharmacological activation of PKA and ERK may be a potential approach to rescue synaptic plasticity impairments in disorders that affect neuronal signaling pathways.

Disclosures: R. Liu: None. **L.J. Cleary:** None. **J.H. Byrne:** None.

Poster

P857. Invertebrates: Learning and Memory II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P857.04

Topic: H.08. Learning and Memory

Support: NSERC Discovery Grant GR002982
NSERC PGSD Fellowship

Title: Different peptidergic signaling pathways underlying sensitization and dishabituation in C. elegans

Authors: *A. YU, C. RANKIN;
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Abstract: Non-associative learning is categorized as the simplest form of learning that helps animals selectively allocate attention or neural resources to promote survival. Sensitization and dishabituation are two forms of non-associative plasticity that facilitate the likelihood and/or magnitude of responses. The dual-process theory, the prevailing theory regarding non-associative learning originally hypothesized that sensitization is an organism-wide facilitatory phenomenon, and viewed dishabituation as a specific case of sensitization, that is exhibited on a habituation background. However, later studies suggest that the two forms of behavioral plasticity are dissociable. Work from Aplysia showed that although both sensitization and dishabituation both require the neuromodulator serotonin, but they can be differentiated by the developmental stages they emerge, the electrophysiological profiles, and the downstream second messengers recruited etc.In this work, we demonstrated that sensitization and dishabituation are mediated by different neuropeptide signaling pathways in *Caenorhabditis elegans*. Using our previously established paradigms to produce mechanosensory-induced facilitation of a nociceptive response, we identified a peptidergic signaling pathway underlying the sensitization of the response; surprisingly, this peptidergic signaling pathway is not involved in the dishabituation of the same response. Further, we found that sensitization of response duration and response speed, two components of nociceptive response, are differentially regulated by additional peptidergic signaling components. We have found that dishabituation is mediated by yet unknown neuropeptides- we are currently performing a screen to identify the molecules and their molecular and cellular signaling pathways.Taken together, these data show that sensitization and dishabituation can be mediated by completely different underlying molecular mechanisms, and that sensitization may not be a global, organism-wide, phenomenon, rather, sensitization of different aspects of behavior can be differentially regulated by multiple neuromodulatory pathways.

Disclosures: A. Yu: None. **C. Rankin:** None.

Poster

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Program #/Poster #: P857.05

Topic: H.08. Learning and Memory

Support: Texas Comprehensive Research Fund

Title: Cellular effects of serotonin on the memory impairments caused by prolonged food deprivation in Aplysia

Authors: *X. DENG, R. MOZZACHIODI;
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Abstract: Malnutrition causes brain dysfunctions including memory deficits. The ability of the mollusk *Aplysia* to sustain up to fourteen days of food deprivation (14DFD) without health deterioration or behavioral alterations (Kupfermann, 1974; Mac Leod et al., 2018) is difficult to achieve in more complex animals, thus making this organism a suitable model to study memory deficits raised from prolonged food deprivation. In this study, an elementary form of learned fear known as sensitization was utilized to investigate the detrimental effects of prolonged food deprivation on memory formation. In *Aplysia* fed every two days (2DFD), one trial of electrical shocks to the body wall induces short-term sensitization (STS) of the tail-induced siphon withdrawal reflex (TSWR) for at least 15 min (Kandel, 2001). In a reduced ganglionic preparation containing the TSWR neural circuit, cellular correlates of STS, including increased excitability of tail sensory neurons (IE), can be induced *in vitro* by electrical stimulation of afferent nerves (Weisz et al.,2017). Serotonin (5-HT) mediates sensitization and IE in *Aplysia* (e.g., Kandel, 2001). Sensitizing stimuli lead to 5-HT release in the neuropil (Marinesco and Carew, 2002) and hemolymph (Levenson et al., 1999). *In vitro* 5-HT application induces IE for at least 15 min (Walters et al., 1983). Recent work revealed that STS was not observed in 14DFD animals (MacLeod et al., 2018). In addition, 14DFD prevented short-term IE and reduced 5-HT levels in the hemolymph. This project aimed to investigate the role of 5-HT in the absence of short-term IE following 14DFD. We hypothesized that 5-HT application may elicit IE under 14DFD. Four groups of 10 preparations each, dissected from adult *Aplysia* (100-200 g), were utilized: 2DFD preparations treated with 5-HT or artificial seawater (ASW, vehicle), 14DFD preparations treated with 5-HT or ASW. Excitability was measured prior to (pre-tests), 5 min and 15 min after 5-min treatment with either ASW or 50 µM 5-HT (post-tests). 5-min post-test was used to evaluate whether 5-HT induced shorter IE. Percentages of IE in each group were calculated as [(post-pre)/pre]x100% and were analyzed with the Kruskall-Wallis test followed by Student-Newman-Keuls *post-hoc* comparisons. In both 5-min and 15-min post-tests, 5-HT significantly induced IE in 2DFD and 14DFD preparations. Notably, the amount of IE under 14DFD did not significantly differ from that under 2DFD, indicating that 5-HT alone was able to induce the maximal amount of IE in 14DFD animals. The ability of 5-HT to induce normal IE under14DFD suggests that reduced 5-HT may be responsible, at least in part, for the lack of short-term IE and STS in 14DFD *Aplysia*.

Disclosures: X. Deng: None. **R. Mozzachiodi:** None.

Poster

P857. Invertebrates: Learning and Memory II

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Program #/Poster #: P857.06

Topic: H.08. Learning and Memory

Support: U.S. - Israel Binational Science Foundation Grant No. 2017624
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Title: Learning that food is inedible in Aplysia affects connectivity from buccal ganglia mechanoafferents to motor neurons

Authors: *A. J. SUSSWEIN[1], S. TAM[1], I. HURWITZ[1], H. J. CHIEL[2];
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Abstract: Memory after learning that food is inedible in *Aplysia* is expressed in part as a bias to reject an object in the mouth, rather than to ingest it. This change has been partially explained by changes in connectivity from a population of buccal ganglia mechanoafferents to motor neurons with different functions. During rejection, protraction is the power phase, and retraction is the return phase. After training, both monosynaptic excitation to a protraction motor neuron (B61/B62), and monosynaptic inhibition to a retraction motor neuron (B3) were enhanced. In addition, excitation to a neuron whose activity biases patterns toward rejection (B4/B5) was increased. After training, both excitation and inhibition increased in a motor neuron closing the radula (B8); radula closing occurs during retraction in ingestion but during protraction in rejection. No changes in connectivity were observed after training to a neuron that contributes to the decision to initiate responses (B31/B32), whether the response is ingestion or rejection. Rather than examining the response to a single spike in the mechanoafferent neurons, we have now delivered 3 trains of 5 spikes to the S1 population of mechanoafferents before or after training. In addition, data were examined separately for 4 anatomically distinct regions of the S1 mechanoafferents, allowing us to determine whether changes in connectivity were localized to specific populations. Spike trains cause changes in amplitude of the fast PSPs, and also reveal the presence of slow PSPs. Patterns of synaptic change were qualitatively similar to those previously found in response to single spikes in mechanoafferents. Training caused increased inhibition of both fast and slow PSPs to the B3 retraction motor neuron, and increased fast excitation to the B61/B62 protraction motor neurons, as well as increased fast and slow excitation to B4/B5, which bias movement to rejection. Training caused mixed effects onto the B8 radula closing neurons, producing decreases in excitation in the most medial and posterior areas of the S1 cluster, but not in the other areas. No effects of training were found in connectivity to B31/B32, which initiates both ingestion and rejection. Additional evidence for localization to sub-populations of the S1 mechanoafferents was present, in that changes in connectivity to B3 and B61/B62 were seen in only 3 of the 4 regions of the S1 cluster. Variability in changes in connectivity as a result of training suggests variability in function of the different areas of the mechanoafferent clusters. Ongoing experiments are examining such functional differences.

Disclosures: A.J. Susswein: None. **S. Tam:** None. **I. Hurwitz:** None. **H.J. Chiel:** None.

Poster

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Program #/Poster #: P857.07

Topic: H.08. Learning and Memory

Support: DFG BR 1892/17-1

Title: Developmental expression of dFoxP is required in motorneurons for operant self-learning in Drosophila

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Abstract: Out of the four FOXP genes in humans the FOXP2 transcription factor was shown to have an unique role in speech learning and articulation. This function is highly conserved as homologous motor learning functions were identified in songbirds, rodents or fruit flies. While *Drosophila* is not a vocal learner, the process of torque learning in tethered flies is an analogous motor learning process to vocal learning. An initially very variable behaviour (e.g. sub-song in finches or torque in flies) is being modulated via an operant feedback (auditory or temperature) loop to shape the variable actions to the desired output (crystalized song, avoidance of heat). Accordingly, the fly orthologue of the FOXP2 gene, *dFoxP* is also involved in this operant self-learning task. Due to the broad expression, it remains unknown which brain regions or gene targets are important for this learning process. We performed different spatial or temporal knockouts of *dFoxP* using CRISPR/Cas9. Knocking out *dFoxP* in individual brain regions did not lead to any learning defects. A knockout of dFoxP in all neurons of adult flies showed no immediate effect, but 14 days old flies were impaired in learning. Knocking out *dFoxP* in motorneurons results in an impairment to fly. As protein kinase C (PKC) is required in motorneurons for torque learning, we expressed PKCi, an inhibitor of PKC in *dFoxP* isoform B (*FoxPiB*)-positive neurons and found a learning impairment. Knocking out only the atypical PKC (aPKC) in motor neurons or *dFoxPiB*-positive neurons via CRISPR/Cas9 also leads to learning defects, suggesting that aPKC is the gene responsible for operant self-learning in *Drosophila*.

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Poster

P947. Cellular Models II

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Program #/Poster #: P947.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01NS110079

Title: Mechanisms of Dominant Electrophysiological Features of Four Subtypes of Layer 1 Interneurons

Authors: *J. MENG[1], B. SCHUMAN[2], B. RUDY[3], X.-J. WANG[1];
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Abstract: Neocortical Layer 1 (L1) receives extensive "top-down" information conveyed by long-range inputs from many sources. The integration of these inputs into local processing is thought to be mediated by a population of GABAergic inhibitory interneurons (INs) residing in L1 and INs in deeper layers with dendrites or axons in L1. In a previous study, we identified four unique populations of INs in L1, each with a distinct molecular profile, morphology, and electrophysiology. These four types were Canopy cells, Neurogliaform cells (NGFCs), cells with strong somatic expression of the α7 nicotinic receptor (α7 cells), and vasoactive intestinal peptide (VIP) expressing cells. However, a modeling study at the single-cell level of these subtypes had not been established, which hinders studying the functions of L1 interneurons in a circuit model. In this study, we discovered different dominant electrophysiological features for each IN subtype. Canopy cells showed an irregular firing pattern near rheobase, NGFCs were late-spiking and their firing rate ramped up during positive current injections, α7 cells displayed initial bursting, and VIP cells' most salient features were high input resistance, strong adaptation and irregular firing. Next, we built generic models for each IN subtype. We first showed that an exponential integrate-and-fire (EIF) model with a slow potassium (SK) channel could reproduce the irregular firing observed in Canopy cells through the mechanism of square-wave bursting. Second, by increasing the timescale of the inactivation gating variable of the SK channel, we reproduced the late-spiking and ramping of NGFCs. Third, the initial bursting of α7 cells was reproduced by including a T-type calcium channel. VIP cells in L1 had heterogeneous firing patterns, such as strongly adapting, irregular firing, initial bursting, and high threshold fluctuation. We first reproduced all these features in a generic VIP cell model that included an SK channel, a T-type calcium channel, and a calcium-dependent potassium channel that reproduced a strong adaptation. Further, we showed that heterogeneous firing patterns could be reproduced by choosing different parameters in the generic model. Last, we explained that irregular firing was more frequently observed in VIP cells due to the interaction between strong adaptation and the SK channel. To summarize, the dominant electrophysiological features of the L1 IN subtypes were reproduced in the models, and their mechanisms were explained. This work was an essential initial step to study the function of L1 INs in circuit models. Also, the analysis we used in this study could contribute to the classification of cell types.

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Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Synergetic effects of ionic currents on electrical features of biophysically detailed models

Authors: *M. REVA, A. ARNAUDON, M. ZBILI, W. VAN GEIT, H. MARKRAM;
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Abstract: Neuronal membrane potential is sculptured by a large amount of ionic currents present in the cell. Different values of neuronal electrical features (spike duration, interspike interval, afterhyperpolarization amplitude, etc.) can be observed from the combination of various numbers of ionic current densities. While electrophysiological experiments provide us with a general understanding of the contribution of currents to certain electrical features, we lack a systematic exploration of the interplay of ionic currents. However, detailed biophysical models allow us to tackle this issue in greater detail by unravelling the inner mechanisms of the interactions between currents. In this study, we explore the synergetic effect of ionic currents and their role in shaping neuronal electrical features using statistical methods and information theory. Using Monte Carlo Markov Chain methods on a detailed model of juvenile rat layer 5 pyramidal cell (L5PC) with 33 parameters (representing maximum conductances of ionic channels and calcium dynamics) and 61 electrophysiological features, we generated thousands of non-identical electrical models with biologically plausible features. We leveraged this large amount of data, with several measures from information theory to detect correlations between model parameters and features at all orders, beyond pairwise correlations. In particular, we use multivariate generalisation of mutual information, such as the total correlation (Watanabe, 1960) or O-information (FE Rosas et al, 2019) to show that most features depend on the synergetic or redundant combinations of several parameters. Only a small fraction of the features were influenced by two to three ionic currents while most were correlated with more than 5 model parameters. In our L5PC model, we were able to map the landscape of synergies and redundancies between ionic currents and showcase the complexity of the relations between electrophysiological properties and ion channel dynamics. Further studies could be undertaken to analyse other cell types, more detailed models or even their dependency on morphological properties.

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Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Extracellular stimulation in pyramidal cell models with full axonal arbor

Authors: *J. THARAYIL[1], M. ZBILI[1], A. ARNAUDON[1], W. VAN GEIT[1], E. NEUFELD[2], M. REIMANN[1], F. SCHÜRMANN[1], H. MARKRAM[1];
[1]Blue Brian Project, École Polytechnique Fédérale de Lausanne Campus Biotech, Geneva, Switzerland; [2]Computat. Life Sci., IT'IS Fndn., Zuerich, Switzerland

Abstract: Joseph Tharayil and Mickael Zbili contributed equally to this work
Extracellular electrical stimulation with small electrodes, also known as intracortical microstimulation (ICMS), can be used to perturb neurons and neuronal circuits. It is believed that ICMS primarily affects axons, but it is unclear how this effect depends on axonal properties. In silico experiments with realistic axon models may therefore provide insight into the mechanisms of ICMS. It is also known that a significant proportion of neural activity triggered by ICMS can be attributed to synaptic effects rather than direct recruitment by electrical stimulation. In this study, we analyze synaptic activation triggered by extracellular stimulation.
In this work, we present an extension of the juvenile rat pyramidal cell models of Markram et al. 2015, by adding a full axon model comprising axon initial segment (AIS), myelinated internodes, nodes of Ranvier and unmyelinated collaterals; with an axon-specific pool of ion channels and optimized ion channel densities. We show that this model reproduces the main axonal electrical features (axonal action potential (AP) waveform, preferential AP initiation at the AIS, propagation of high frequency AP trains throughout the axonal arbor), and that the modelling approach generalizes to a wide range of reconstructed pyramidal morphologies.
To study ICMS of a population of cells, we instantiate a population of pyramidal cells. We simulate ICMS of this population, with the electrode location scanned systematically throughout the entire space, and calculate recruitment curves for the population. We find that ICMS triggers action potentials largely in the middle of axonal sections, with threshold currents that depend on the reciprocal of the cubed distance between the neurite and the electrode, and on pulse width. Moreover, stimulus locations near the AIS tends to have lower threshold currents.
For certain stimuli, action potentials are triggered in part of the axonal arbor, but do not propagate throughout the entire arbor. It may be possible to take advantage of this effect to trigger selective activation of postsynaptic targets. We identify synaptic terminals of the simulated neurons that are activated by electrical stimulation-triggered activity. We then identify the postsynaptic cells that receive stimulation-triggered synaptic activity. We find that the properties of the postsynaptic targets, including cell type and location, vary with stimulus parameters. Our model may therefore help in clarifying the mechanisms of ICMS stimulation and in optimizing stimulation parameters.

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Poster

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Program #/Poster #: P947.04

Topic: I.06. Computation, Modeling, and Simulation

Title: Utilizing deep neural networks to infer ionic conductances of mutli-compartmental models.

Authors: *R. BEN-SHALOM[1], J. BALEWSKI[2], V. BARATHAM[3], S. SHOREWALA[3], Y. SHUE[3], K. J. BENDER[4], K. E. BOUCHARD[5];
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Abstract: A major focus of cellular and systems neuroscience has been to determine how ionic conductances are distributed within a neuron's morphology to support neuronal excitability. Unfortunately, careful empirical dissection of the complement and distribution of conductances across a given neuronal class' morphology is experimentally laborious, and have been performed on relatively few neuronal classes. Ideally, one could infer the values of microscopic variables, including ion channel classes and their distribution, from the membrane potential alone, which is a macroscopic variable that is experimentally accessible *ex vivo* and *in vivo***.** However, we currently lack methods to accurately infer ionic conductances from membrane potentials in real neurons. Here, we present a novel approach to solve this problem using deep neural networks.

Deep learning and convolutional neural networks (CNNs) techniques are potentially well suited to address the inverse problem by learning how each conductance contributes to the membrane potential. We trained CNNs to predict ionic conductances (output) from membrane potentials (inputs) using simulated data, where the ground truth correspondence between the input-output is known. Using 169 different neuronal compartmental models (12 excitatory and 157 inhibitory) from the Blue Brain Project portal we tested if CNNs can predict their ionic conductaces only from the voltage responses at different recording locations (67 probes) along the membrane. Using this data, we studied the correlation between the conductacnes prediction error and number of recording electrodes. We found that measuring membrane potentials from 3-4 locations is sufficient to accurately recover the vast majority of the conductances of the model. We trained and optimized CNNs under two different conditions. The first was tailored to each neuron type and can predict most of the conductances with very low error. The second CNN is a general network that predicts conductances for all different inhibitory models without prior knowledge of the neuron's type. This second CNN has slightly higher error but can recover the same conductances as the per-neuron CNN.

These results shows that CNNs are an efficient tool to infer ionic conductances from membrane potentials. Utilizing this approach to infer the ionic conductances of experimentally recorded neurons would aid understanding etiology of diverse human illnesses that affect the integrative properties of neurons, including many forms of neurodevelopmental and neuropsychiatric disorders.

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Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: PAPIIT-DGAPA UNAM IN 102420
Conacyt CB A1-S-10610

Title: Frequency-dependent modulation of neural reliability

Authors: *P. PUIGVERT[1], A. FRANCI[2];
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Abstract: Neurons are not always reliable in the transmission of action potentials. In other words, the same neuron can respond to the same stimulus in different ways. Reliability can be quantified by spike timing of neurons in a network (Mainen *et al.*, 1995). Furthermore, the reliability spike timing depends on the stimulus temporal properties. It was observed that a stimulus with constant or rapidly fluctuating applied current could cause unequal or more accurate and reliable spike times, respectively. On the other hand, the reliability with which a neuron transmits information, changes with the mental state of the animal studied (Goard, 2009). In particular, the level of reliability of neurons increases in the attentive state. Modulation of neural electrical activity is the basis for many long-lasting changes in animal behavior (Levitan *et al*, 1996), including alterations of the attention state of the animal.
In this work we use computational modeling to analyze how neuromodulation shapes neural reliability as a function of the input frequency content. In particular, we use a modification of the McCormick-Huguenard model for thalamo-cortical neurons and analyse the reliability of its response to an incoming Poissonian train of synaptics pulses. Reliability is quantified as a function of exogenous (average frequency of the incoming spike train), synaptic (synaptic maximal conductance and activation time constant), and endogenous (neural polarization level, modulation of intrinsic conductances) parameters. The resulting reliability parameter chart reveals that neuromodulation can have opposite effects on neuronal reliability depending on the frequency content of the input, as determined by the average frequency of the incoming spike train and by the synaptic activation time constant.
Our results show that neuromodulation can effectively change the timescale of salient stimuli, with rapidly (reps. slowly) changing stimuli reliably transmitted in one neuromodulatory state and unreliably transmitted in another.

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Poster

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Program #/Poster #: P947.06

Topic: I.06. Computation, Modeling, and Simulation

Title: An ISI study of a stochastic ML bursting neuron

Authors: *P. ROWAT[1], P. GREENWOOD[2];
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Abstract: In Chapter 9 of his book, "Dynamical systems in neuroscience", Izhikevich describes the deterministic dynamics of various types of neurons which emit a number of rapid spikes with quiet intervals between these bursts.

In this study we explore the stochastic pattern of bursts which results from including in the model the random noise which plays a part in the behaviour of any active neuron. The inter-spike interval histogram, which uses long simulation runs of the process and plots the number of occurrences of times between bursts as a function of time, is an estimator of the probability distribution of times between bursts, and is a useful characteristic of such a model. Here we extend an earlier study of the sample path behaviour of the stochastic Morris Lecar process to the case of a Morris Lecar family of bursters.

Disclosures: P. Rowat: None. **P. Greenwood:** None.

Poster

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Topic: I.06. Computation, Modeling, and Simulation

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Title: Automated tool for modeling single neurons

Authors: P. CANFIELD[1], D. DOPP[1], M. STROUD[2], *S. S. NAIR[2];
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Abstract: Neurons receive input from excitatory and inhibitory neuronal cells and integrate the information causing the cell to fire. The dynamics involves a complex set of intrinsic conductances that seemingly work in coordinated groups although prevalent single cell modeling techniques do not consider such potential interactions. A recent paper suggesting possible grouping of currents into distinct modules associated with specific neurocomputational properties suggests that the process of selection of model parameters could be simplified (Alturki et al., 2016). That insight led to the development of design methodology that simplified the biophysical conductance-based cell design process by allowing the designer to focus on specific attributes of the cell one at a time: starting with passive properties, moving to base-line firing dynamics, then adding features such as burst firing and low- and high-threshold oscillations. By separating the cell design process into these stages, parameter selection can be simplified due to decreased interaction between extraneous conductance groups. The present work extends the study by incorporating a Bayesian based machine learning approach to automate this design process. Preliminary results using biological data related to passive and constant current injection responses at three levels for one of our example cases, a hippocampal neuron, was replicated well by the automation scheme. This specific neuron showed burst firing followed by tonic spiking, and the parameters tuned by the scheme were the maximal conductances for the following channels: NaT, Kdr, Km, and Nap, and the

time constant for the Km current. Usage of the segregation approach thus permitted rapid optimization of parameters over a large 5-dimensional space in this case. Leveraging the segregation approach, we are finalizing a pipeline which automates the biophysical neuronal model design process of cells exhibiting complex dynamics starting from biological data supplied by the neuroscientist. This software pipeline will be made available for public download on our site cyneuro.org.

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Poster

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Topic: I.06. Computation, Modeling, and Simulation

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Title: Experimental analysis of serotonergic fibers utilizing a von Mises-Fisher model

Authors: *K. C. MAYS[1], J. H. HAIMAN[1], M. MILLWATER[1], S. JANUSONIS[2];
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Abstract: All neural processes in the brain take place in a dense matrix of axons (fibers) that release serotonin (5-HT), a neurotransmitter with powerful effects on brain cells. This matrix is present in all vertebrates and appears to represent an ancestral state of neural tissue. In humans, it modulates global brain states and, in particular, supports waking consciousness and perception. Many mental disorders have been associated with perturbations of serotonin signaling (Major Depressive Disorder, Autism Spectrum Disorder, Obsessive Compulsive Disorder, and others). We have recently shown that serotonergic fibers can be modeled as paths of spatial stochastic processes. Here, we focus on experimental analyses using a step-wise model based on the directional von Mises-Fisher (vMF) distribution. We have previously shown in simulations that the value of the vMF concentration parameter (κ) can determine the resultant density of serotonergic fibers in a given brain region. Therefore, this model can bridge the behavior of individual fibers and the regional densities of the serotonergic matrix. In addition, it can provide quantitative data about the heterogeneity of serotonergic fibers.In the present study, we visualized the continuous trajectories of individual serotonergic fibers in a transgenic mouse model (a Tph2-iCre line crossed with a Cre-reporter line (tdTomato/EGFP)). The signal was further enhanced with immunohistochemistry and high-resolution confocal images were obtained in a set of brain regions. Fiber trajectories were automatically traced in 3D using an algorithm developed in our laboratory and the regional estimates of κ were obtained (e.g., $\kappa \approx 20$ in the inferior colliculus, with the 1.5 μm step). In order to achieve reliable separation of individual serotonergic trajectories in dense regions, fibers were visualized with a random combination using Brainbow AAVs stereotaxically injected into the dorsal raphe nucleus of Tph2-iCre mice. This approach also allows us to differentiate fibers and determine how extensively unique serotonergic fibers intermingle in a small brain region.

Disclosures: K.C. Mays: None. **J.H. Haiman:** None. **M. Millwater:** None. **S. Janusonis:** None.

Poster

P947. Cellular Models II

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P947.09

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CRCNS (#1822517)
NIMH (#MH117488)
California NanoSystems Institute

Title: Spatiotemporal dynamics of single serotonergic axons in ex vivo systems

Authors: *M. T. HINGORANI[1], A. M. VIVIANI[1], J. C. CHIU[2], A. M. VARGAS[1], R. STOWERS[3], C. M. BATES[4], S. JANUSONIS[1];
[1]Psychological and Brain Sci., [2]Biol., [3]Bioengineering, [4]Materials, Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Previous work in our group has shown that the self-organization of the serotonergic matrix depends in part on the decisions made by individual fibers. Evidence suggests that the trajectories of serotonergic fibers are strongly stochastic and can be well described by step-wise random walks or fractional Brownian motion (a time-continuous process). The success of these modeling efforts crucially depends on experimental data which are necessary to validate the general structure of a model and to constrain the values of its parameters. In particular, further progress crucially depends on the experimental capability to track individual serotonergic axons in *time* and *space*. However, visualizing this dynamic behavior *in vivo* is currently extremely challenging. In this study, we cultured primary mouse brainstem neurons in several *in vitro* and *ex vivo* systems. Using a combination of methods such as confocal microscopy, digital holotomography, false fluorescent neurotransmitters, and novel 3D hydrogel systems, we investigated serotonergic neurons and their axons with unprecedented spatiotemporal precision. The dynamics of axon growth cones, branching events, and other key processes were analyzed with respect to the properties of the tunable extracellular environment and to the refractive index-sensitive intracellular movements. These experimental data include the first holotomographic images of serotonergic axons and provide essential information for the predictive modeling of the serotonergic matrix. In addition to the importance of these findings for fundamental neuroscience, they may also support future efforts in the restoration of brain tissue (serotonergic fibers are almost unique in the mammalian brain in their ability to robustly regenerate). Some of the novel approaches developed in this study may be applicable to other axons in the ascending reticular activating system.

Disclosures: M.T. Hingorani: None. **A.M. Viviani:** None. **J.C. Chiu:** None. **A.M. Vargas:** None. **R. Stowers:** None. **C.M. Bates:** None. **S. Janusonis:** None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.01

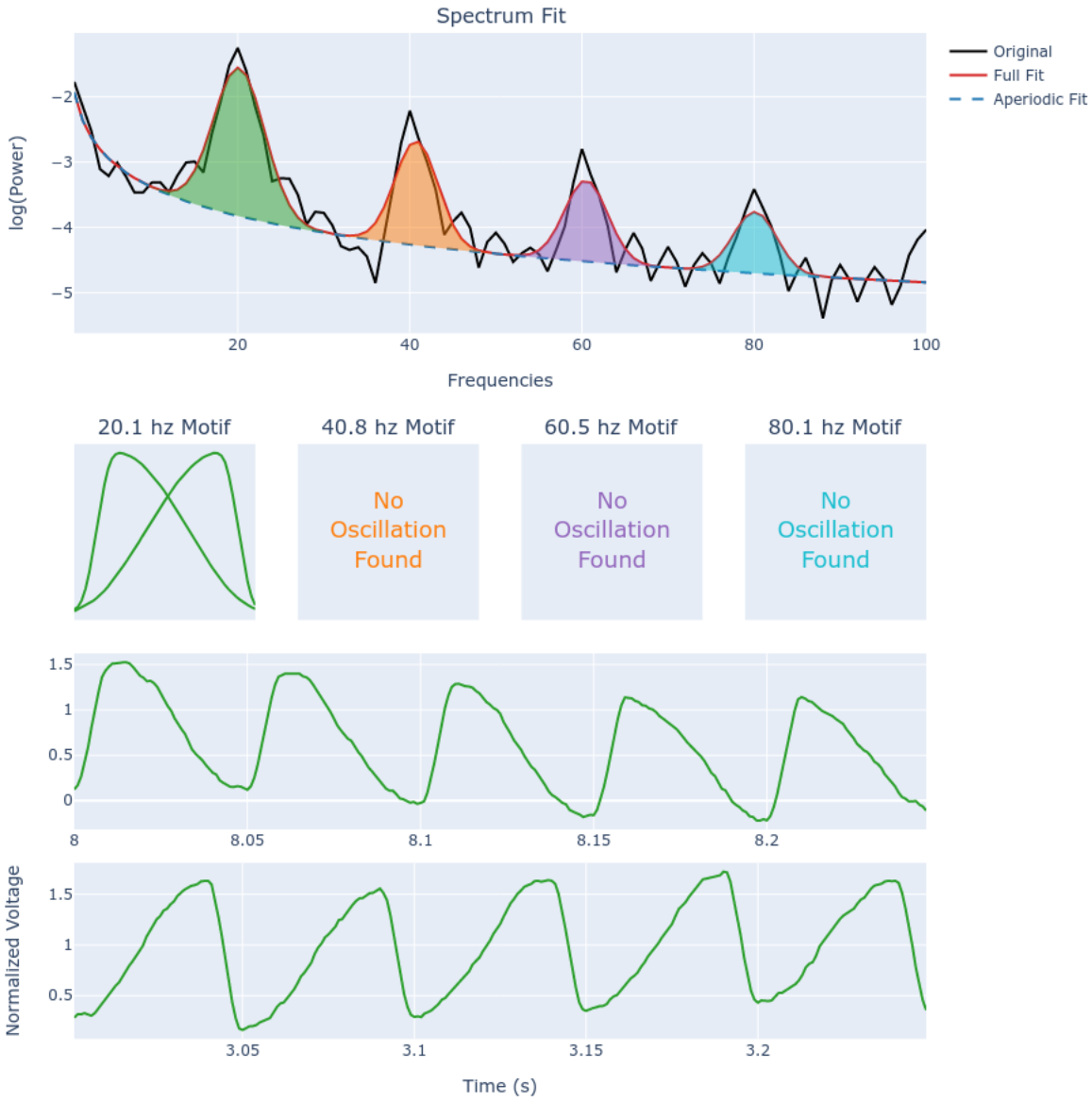
Topic: I.07. Data Analysis and Statistics

Support: R01 GM134363-03

Title: A combined time- and frequency- domain processing pipeline for parameterizing neural periodic and aperiodic activity.

Authors: *R. HAMMONDS[1], T. DONOGHUE[2], B. VOYTEK[1];
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Abstract: Analysis of neural oscillations are typically performed using either time or frequency domain approaches. Fourier based methods reduce the dimensionality of neural signals by decomposing it into a set of sinusoids, facilitating simpler interpretations and comparisons. Time domain methods allow the exploration of non-sinusoidal features. While both of these approaches are powerful, and have provided many insights into the physiology and function of neural oscillations, they are each also limited in their own ways. For example, without careful consideration, Fourier based approaches can conflate oscillations with aperiodic activity, and the harmonics that arise from nonsinusoidal rhythms can look like multiple oscillations. Similarly, traditional time-frequency analyses fail to associate high spectral power with nonsinusoidal rhythms. Time domain approaches suffer from high dimensionality and the difficulty in identifying oscillatory cycles in noise. Analyses of spectral peaks and waveform shape are typically performed independently and rely heavily on parameter optimization, such as spectral peak width and height ranges or frequency ranges of interest when examining waveforms. Here we provide a signal processing pipeline that combines frequency and time domain approaches to help address these shortcomings. Rather than having two independent processing pipelines for time and frequency domains, this approach identifies spectral peaks in the frequency domain to uncover nonsinusoidal oscillatory motifs in the time domain. We demonstrate this approach using both simulated and real data. This pipeline allows spectral and waveform parameterization to inform one another. The proposed pipeline is not limited to neural signals and may be broadly applied to any time series that contains spectral peaks.



Disclosures: R. Hammonds: None. **T. Donoghue:** None. **B. Voytek:** None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.02

Topic: I.07. Data Analysis and Statistics

Support: P50MH109429

R01MH111439

Title: Seecog: an interactive browser-based visualization tool for intracranial electrodes and multi-modal data

Authors: *N. B. MARKOWITZ[1], A. D. MEHTA[2], S. BICKEL[3];
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Abstract: Objective: SEECOG: An interactive browser-based visualization tool for intracranial electrodes and multi-modal data
Rationale: Data acquired from a participant undergoing intracranial electroencephalography (iEEG) is multi-modal in nature. Simultaneously visualizing this multi-modal data is difficult and becomes even more so when looking at data acquired across multiple patients. Viewing and interacting with such data is challenging and can take multiple softwares that specialize in visualizing each unique modality. To overcome this, we developed an easy to use and intuitive browser-based program for visualizing this multi-modal data for single and multiple subjects.
Methods: The application is developed using a combination of html, css and javascript files that can be run online or locally and on any operating system. The application directly integrates with a variety of file formats such as BIDS, NWB, nifti and Freesurfer meshes. Volumes, surfaces and individual electrodes are rendered in an interactive 3D environment. An accompanying electrode table allows further labeling and annotating of individual and groups of electrodes. These applied labels can then be reflected in how the electrode appears in the 3D environment.
Results: An interactive application that allows the visualization and manipulation of multi-modal data across many subjects. Channel locations can be visualized in a single subject's native space or in one of the commonly used standard spaces (such as fsaverage). Using the accompanying table, channel properties can be changed at will to mark channels of specific interest such as those that display significant activity in an analysis. These properties can then be reflected by the channels appearance to differ special or significant channels from others. Multiple channels can be queried based on custom properties, names and general location. The annotated table can be downloaded for use in other softwares.
Conclusion: Visualizing multi-modal data that is inherent to iEEG cases is necessary and invaluable. However, no such program has yet been created that provides an easy interface for all users and allows working with multiple subjects. SEECOG allows iEEG labs to more easily aggregate and examine their data collected from multiple subjects and different modalities to better understand, interpret, and present their work. The easy interface also lets the data become more accessible to those without technical knowledge or familiarity with other complex softwares. The viewing and querying of this large and varied amount of data is invaluable to researchers working with iEEG data.

Disclosures: N.B. Markowitz: None. **A.D. Mehta:** None. **S. Bickel:** None.

Poster

P975. Software Tools V

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Program #/Poster #: P975.03

Topic: I.07. Data Analysis and Statistics

Support: Gitcoin Grant Round 10
Gitcoin Grant Round 9
Gitcoin Grant Round 8

Title: Reimagining value in academia through the blockchain: Ants-Review, a decentralised platform for incentivising peer-reviews

Authors: *B. TROVÒ[1,2];
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Abstract: Peer review is a necessary and essential quality control step for scientific publications but lacks proper incentives for being not only very costly in terms of time and intellectual investment, but also not remunerated by the journals and not openly recognized by the academic community as a relevant scientific output for a researcher. In addition to that, the number of manuscripts submitted to journals and preprints keeps increasing every year. Therefore, scientific dissemination is affected in timeliness, quality, and fairness. This problem is particularly evident in the biomedical field like in neuroscience in which the peer review process can take up to years. Some solutions to incentivize and reward peer review services have been proposed but without much success. This is because traditional systems do not manage to capture the scientific value of the peer review into an actual impact factor measure or fail to see in it a commodity that can be fungible. A conceptually similar system to peer review is the peer-to-peer validation process in a blockchain, in which blocks must be first verified in order to be added to the network. Blockchains, though, act as 'incentive machines' by programming rewards that push to work for the honest nodes. Here, leveraging this analogy, we propose to solve this issue through a blockchain-based incentive platform that rewards scientists for peer-reviewing other scientists' work and that builds up trust and reputation. We designed a privacy-oriented protocol of smart contracts called Ants-Review that allows authors to issue a bounty for open access, double-blind peer reviews on the Ethereum blockchain. If requirements are met, peer reviews will be accepted and paid by an approver proportionally to their assessed quality. To promote ethical behavior and inclusiveness and reduce biases the platform will implement a gamified mechanism and cryptographic tools that allow the whole community to anonymously evaluate the peer reviews and vote for the best ones while remaining accountable. The platform is currently at the MVP stage on the Kovan Testnet. Future research (such as large-scale surveys and computational modeling) will be needed to study the effect of reward mechanisms on human agents in such a complex scenario and evaluate the advantages of mechanism design on accelerating biomedical publications.

Disclosures: B. Trovò: None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.04

Topic: I.07. Data Analysis and Statistics

Support: MITACS Elevate Scholarship

Title: Umit: an open-source toolbox for management of large-scale widefield cortical imaging datasets.

Authors: *B. DE SOUZA[1,2], S. BELANGER[2], S. TISSIER[1], M. ABRAN[2], M. VANNI[1];
[1]Univ. of Montreal, Montreal, QC, Canada; [2]Labeo Technologies, Montreal, QC, Canada

Abstract: *In vivo* widefield optical imaging techniques have been used for decades to investigate the brain function. Recent advances in genetic tools, such as fast-responding calcium indicators (e.g., GCaMP6f) as well as the increasingly accessible high-speed, high-resolution and high throughput longitudinal recording systems allowed the acquisition of faster and more detailed images at mesoscale level for months on large cohorts of animals. This generates large amounts of data that need to be stored, pre-processed and analysed in a timely manner. This can be a limiting factor as experiments become larger and more complex. In order to address this issue, we have built a high-throughput toolbox named *umIT* (*u*niversal *m*esoscale *I*maging *T*oolbox) that provides a set of tools to manage and automate critical steps of processing large-scale imaging datasets.
The toolbox was created in MATLAB. It consists of four main modules that manages the experiment metadata (i.e., information about experimental subjects and recordings), creates pipelines to import and pre-process data, provides data visualization tools and basic group comparison and statistical analysis. The toolbox was developed using datasets from a longitudinal mesoscale cortical imaging experiment with a cohort of GCaMP-expressing mice (n = 30) that were recorded several times for 60 days. It managed a large amount of data (>16TB) consisting of distinct protocols (e.g., resting state, retinotopy of visual cortex, event-triggered average response) which provided an opportunity to test the adaptability and extensibility of the toolbox in a real-world setting.
The use of the toolbox during the cortical imaging experiment provided a structured framework that organized the experiments data (raw and processed) as well as metadata. In addition, the automated processing pipelines and visualization tools greatly improved the efficiency of the data processing and analysis. Although, as of today, the toolbox covers most of the needs of a typical imaging experiment, it was designed to be as adaptable and extensible as possible with the option for the user to create custom functions that can be fully integrated in the processing pipeline. Thus, these features make *umIT* a valuable tool for large-scale imaging experiments.

Disclosures: B. de Souza: Other; Scholarship partially supported by Labeo Technologies. **S. Belanger:** A. Employment/Salary (full or part-time):; Labeo Technologies. **S. Tissier:** None. **M. Abran:** A. Employment/Salary (full or part-time):; Labeo Technologies. **M. Vanni:** None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.05

Topic: I.07. Data Analysis and Statistics

Support: NINDS U24NS109043

Title: The Open Ephys GUI: a collaboratively developed platform for high-channel-count electrophysiology data acquisition

Authors: *J. SIEGLE[1], A. DOSHI[1], P. KULIK[1], A. CUEVAS LOPEZ[2], J. VOIGTS[3];
[1]Allen Inst., Seattle, WA; [2]Ctr. for biomaterials and Tissue engineering, Univ. Politècnica De València, Valencia, Spain; [3]Brain and Cog. Sci., MIT, Cambridge, MA

Abstract: The Open Ephys GUI (https://open-ephys.org/gui) is an open-source, cross-platform application for acquiring data from multichannel implanted electrodes, a technique that has fostered countless discoveries in systems neuroscience. The GUI is compatible with a variety of data sources, including the Open Ephys acquisition board, Intan data acquisition systems, and Neuropixels probes. Unlike most other software in this domain, the GUI was designed from the ground up with collaborative development in mind. Modules for real-time analysis and visualization are encapsulated within plugins that adhere to a standardized interface, providing a straightforward way for users to write their own extensions without needing to understand the entire code base. To facilitate plugin dissemination, we have created a centralized repository for pre-compiled plugin binaries, which can be downloaded and installed via a single click. Support from a BRAIN Initiative U24 award has allowed us to collect, polish, and document additional community-developed plugins in order to expand the capabilities of the GUI. Providing free, user-friendly, and performant software for recording spiking activity makes extracellular electrophysiology experiments more accessible to labs around the globe.

Disclosures: J. Siegle: None. **A. Doshi:** None. **P. Kulik:** None. **A. Cuevas Lopez:** None. **J. Voigts:** None.

Poster

P975. Software Tools V

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Program #/Poster #: P975.06

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1K08NS105929-01A1
NIH Grant 1R21NS122011-01
CURE Epilepsy Award

Title: Deep Learning Classifier for the Combined Scoring of Sleep-Wake and Seizures in Mice

Authors: *B. HARVEY[1], V. OLÁH[1], L. AIANI[1], L. ROSENBERG[1], M. ROWAN[1], N. P. PEDERSEN[2];
[2]Neurol., [1]Emory Univ., Atlanta, GA

Abstract: The relationship between sleep and seizure is complex and bidirectional, including seizure-frequency-associated sleep fragmentation as well as sleep-deprivation-induced increases in seizures. In order to provide better throughput for sleep studies in Intra-Amygdalar Kainic Acid (IAKA) Temporal Lobe Epilepsy (TLE) model mice, we have designed a data processing pipeline and Keras-based deep learning classifier for sleep staging and seizure scoring. While sleep-wake classifiers and seizure detection algorithms abound, the combination is difficult given the abnormal EEG background in mice

with epilepsy. We obtained electrocorticogram (ECoG), electromyogram (EMG), video and bilateral hippocampal depth electrode data from mice implanted using a customized 3D-printed headplate designed in our lab. Our dataset included 972 12-hour recordings (11,664 hours of data), from a group of 47 mice (including 23 mice that developed spontaneous seizures and 10 control mice), that included 642 seizures. We used 80% of the data for training and 20% for testing. The classifier was trained on previously manually scored 20-second epochs from existing downsampled recordings (from 2kHz to 200Hz), using Fourier bins of alpha, beta, delta, gamma, and theta frequency bands in downsampled recordings from this montage. With a sequential model in Keras using TensorFlow, the classifier has achieved >90% scoring accuracy in most categories for our epileptic mice, with a categorical accuracy of 93% for Wake, 91% for Non-REM sleep, 86% for REM, and 95% for seizure states. This reliable classification will allow for rapid combined sleep-wake and seizure scoring in our IAKA sleep-wake paradigm. Using this classifier to improve our throughput, we hope to improve the mechanistic and symptomatic understanding of sleep disruption in epilepsy, leading to improved patient treatment and outcomes.

Disclosures: B. Harvey: None. **V. Oláh:** None. **L. Aiani:** None. **L. Rosenberg:** None. **M. Rowan:** None. **N.P. Pedersen:** None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.07

Topic: I.07. Data Analysis and Statistics

Support: Mitacs Elevate
Fonds de recherche du Québec Postdoctoral Fellowship[

Title: Detecting artifacts in brain MRI with a deep-learning algorithm: implementation in large databases

Authors: *R. PIZARRO[1], H.-E. ASSEMLAL[2], S. K. B. JEGATHAMBAL[1], T. JUBAULT[2], S. ANTEL[2], D. ARNOLD[1], A. SHMUEL[1];
[1]McGill Univ., Montreal, QC, Canada; [2]NeuroRx Res., Montreal, QC, Canada

Abstract: MRI is increasingly being used to delineate morphological and organizational changes underlying neurological disorders. Successfully detecting these changes depends on the MRI data quality. Image artifacts frequently compromise the utility of MRI and cause irreproducible results. Therefore, it is critical to screen MRI data for artifacts prior the analysis. Currently, quality assessment requires visual inspection by experts. This process is time-consuming and impractical for ‘big-data’ analysis. Automating the quality rating of MRI could improve the efficiency of the process, in particular when dealing with a large database.
We analyzed a database constructed through a software pipeline to process over 10^5 MRI datasets. MRI artifacts were identified by visual inspection and the results used as the ground truth. We developed a deep-learning (DL) algorithm based on convolutional neural networks (CNNs) to automatically detect MRI artifacts. In the testing phase, we incorporated dropout layers to generate *N* Monte Carlo (MC) inferences summarized with a prediction probability, *p*, and three uncertainty metrics: sample variance

(σ;^{2}), entropy (H), and mutual information (MI). We normalized the uncertainty metrics and compared the baseline (no threshold) to setting a threshold: η; < [0.5, 0.1, 0.01, 0.001]. For each η;, we set a classification threshold on p to generate ROC plots to evaluate the DL algorithm performance. For each ROC curve, we computed J, the operating point that maximized Youden's index.

We illustrate the results by using η; on σ;^{2} in Figure 1. As η; is lowered, the number of the retained datasets decreased, but the AUC increased, and J moved closer to the top left. For each J, we computed the corresponding statistics as η; was lowered, summarized in Table 1. We developed a DL algorithm to detect artifacts in brain MRI automatically. The algorithm has been successfully implemented into the processing pipeline. The tool we developed has saved database management teams valuable resources, including hours spent by technicians for identifying artifacts in the MRI volume.

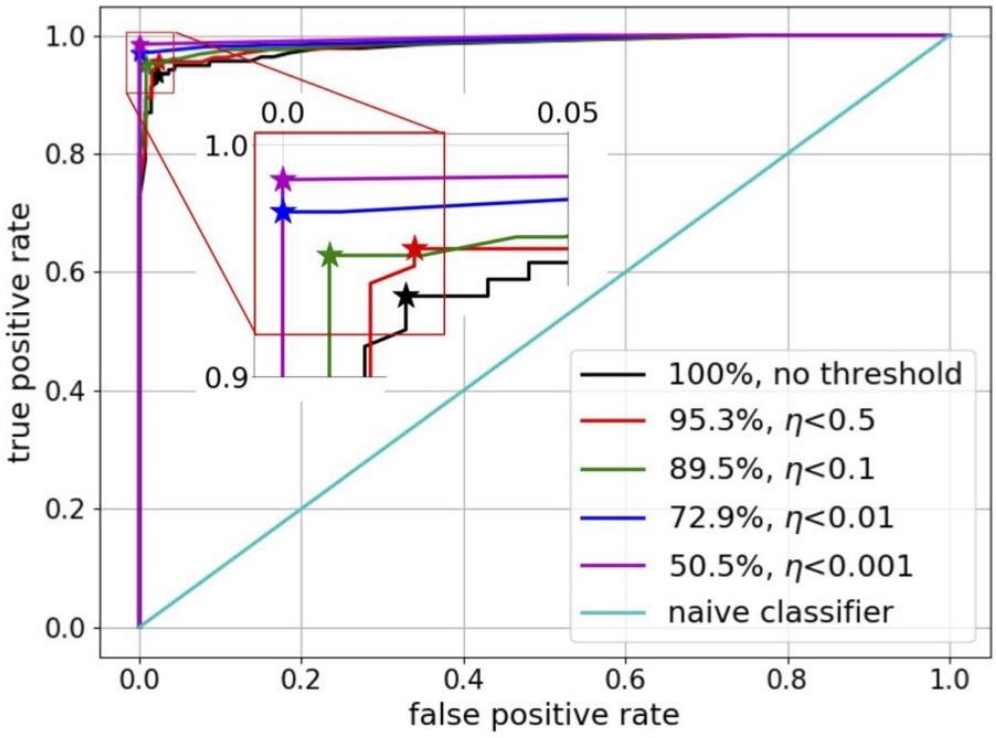


Figure 1 - ROC plots generated by computing 100 Monte Carlo (MC) inferences on the test set. We used the MC inferences to compute the prediction probability p and the sample variance σ^2. We set an uncertainty threshold η on the normalized σ^2 to screen volumes classified with low confidence, i.e., high σ^2. The legend specifies the η value used along with the resulting percent retained. Youden's index is denoted with a color-coded star for each curve. The inset is a zoomed-in version over the red square to highlight how Youden's index move as η is lowered.

Table 1. Summary statistics computed from each ROC curve and corresponding Youden's index (***J***) as the uncertainty threshold η on the sample variance is lowered. We color-coded the rows to correspond to the same colors used in Figure *1*.

η	% retained	AUC	Youden	accuracy	specificity	tn	fp	sensitivity	fn	tp
N/A	100.0	0.987	0.69	0.957	0.935	129	9	0.978	3	136
0.5	95.3	0.990	0.72	0.966	0.955	128	6	0.977	3	127
10^{-1}	89.5	0.993	0.91	0.972	0.952	120	6	0.992	1	121
10^{-2}	72.9	0.998	0.97	0.985	0.971	101	3	1.000	0	98
10^{-3}	50.5	1.000	0.99	0.993	0.985	66	1	1.000	0	73

Disclosures: R. Pizarro: None. **H. Assemlal:** None. **S.K.B. Jegathambal:** None. **T. Jubault:** None. **S. Antel:** None. **D. Arnold:** None. **A. Shmuel:** None.

Poster

P975. Software Tools V

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Topic: I.07. Data Analysis and Statistics

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NIH Grant MH105330
NIH Grant DA052209
NIH Grant DA026306 (P5) to M.K.

Title: Training and Validating an Accessible Automatic Cell Counting Methodology Using Precision and Recall

Authors: *T. KATARAS[1], J. KOURY[2], H. SINGH[2], M. KAUL[2];
[1]Genetics, Genomics and Bioinformatics, [2]Biomed. Sci., Univ. of California, Riverside, Riverside, CA

Abstract: Trainable Weka Segmentation (TWS) provides user-friendly access to machine learning tools for cell quantification. However, analyzing whole datasets requires further development of methods for training, validation and processing. We present here the advancement in our automatic cell counting methodology, which leverages iterative use of the TWS plugin within ImageJ with cell-level accuracy validation. Cell counting remains one of the primary methods of assessing disease progression in neuroscience. However, this analysis is commonly time-intensive even for trained observers, and is difficult to standardize between different observers. We compared our automatic counts to hand counts of immunofluorescence stained microglia in mouse cerebral cortex. The analysis included microglia of wild-type (Resting) and a transgenic mouse model for HIV-induced brain injury (HIVgp120tg, Activated microglia). HIVgp120 mice showed behavioral deficits, and an increase in microglia numbers presumably driven by chronic exposure to the gp120 protein. For the analysis, images were collected from sagittal brain sections of 11-14 month-old mice at 10X magnification. Manual counts obtained by two observers were compared to automated quantification of cells. The results demonstrate the accuracy achievable with TWS while addressing the challenges that come with imaging under experimental conditions which can induce morphological changes in cells of interest. A large advantage of this strategy is the much shorter time required to apply the automatic counting strategy compared to a manual count and the accessibility of the software in ImageJ. Using TWS took less than a fifth of time of the manual count, including time spent training the program. As with all ImageJ plugins, the TWS software is free to use and integrated with a host of other image analysis tools. Our study demonstrates the applicability of this technique to quickly explore large amounts of image data, leaving open the possibility to audit the results by manually counting a randomly selected subset of images.

Disclosures: T. Kataras: None. **J. Koury:** None. **H. Singh:** None. **M. Kaul:** None.

Poster

P975. Software Tools V

Location: Virtual Only

Time: Thursday, November 11, 2021, 10:45 AM - 11:45 AM

Program #/Poster #: P975.09

Topic: I.07. Data Analysis and Statistics

Title: Assessing Agreement of Measures of Heart Rate Variability Between Kubios and AcqKnowledge

Authors: *F. GILBERT, N. THOM;
Wheaton Col., Wheaton, IL

Abstract: Objective: Although heart rate variability (HRV) is a common measure of autonomic influence on the heart, the reliability of commonly-used software programs utilized to analyze HRV data remains untested. Therefore, the present study sought to compare Kubios and AcqKnowledge in order to evaluate the agreement between these programs. **Methods:** Electrocardiogram (ECG) recordings were collected from 14 college students at three different time points across a semester for a total of 34 recordings after data pre-processing. HRV parameters were then transformed by the natural log and input into MedCalc to calculate the 95% limits of agreement (LoA) between programs. Limits were deemed appropriate if they fell within the a priori limits calculated from normalized HRV ranges and showed minimal or no amount of bias. **Results:** Assessment of the LoA and means demonstrated poor agreement under paced breathing conditions for the measures of RMSSD (mean = 0.026, [LoA = 0.121, -0.069]), VLF (mean = -1.325, [LoA = -0.599, -2.052]), and LF (mean = -0.040, [LoA = 0.260, -0.341]), but good agreement for HF (mean = -0.008, [LoA = 0.152, -0.169]). A large constant bias was present for the measure of VLF (mean bias = -1.325), while the measures of HF (R^2 = 0.122, F = 4.445, b-value = -0.033, p = 0.043) and RMSSD (R^2 = 0.355, F = 17.624, b-value = -0.062, p = 0.000) demonstrated proportional bias between programs. **Conclusions:** These results suggest that while some metrics of HRV may be comparable between these software programs, they do not all meet standards of comparability. Future studies should consider the differences in program accessibility and data output when choosing an HRV software program, and explicitly state which program was utilized and what analysis settings were used to preserve accuracy and transparency of data reporting.

Disclosures: F. Gilbert: None. **N. Thom:** None.

Poster

P975. Software Tools V

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Program #/Poster #: P975.10

Topic: I.07. Data Analysis and Statistics

Support: FJC was supported by a Peruilh doctoral fellowship
HGR was supported by an MRC CiC grant

Title: Online spike sorting and rapid data analysis to identify selective neuronal responses

Authors: F. J. CHAURE[1], S. A. SHETH[2], ***H. G. REY**[2,3];
[1]Inst. of Biomed. Engin., Univ. of Buenos Aires, Buenos Aires, Argentina; [2]Neurosurg., Baylor Col. of Med., Houston, TX; [3]Neuroscience, Psychology and Behavior, Univ. of Leicester, Leicester, United Kingdom

Abstract: When extracellular electrodes are implanted in the brain, one important methodological issue is identifying the relevant stimuli that will elicit a neural response from the neurons that are close to the recording tip. This is particularly important when the electrodes cannot be moved to focus on different neurons (as it is the case of single cell recordings in the human brain) and instead we have to rely on showing a large number of stimuli. However, this task can be very time consuming, not just for the data acquisition but also for its analysis. Although the proposed framework is very general, we focus here on the screening procedure to find “concept cells” in the human medial temporal lobe. This typically involves showing ~100 pictures, 6 trials each, which takes ~25 minutes of data acquisition.The main features of the proposed method include: 1) Use of APIs from electrophysiology acquisition systems to acquire the data online as the task is being performed (we developed our method for Blackrock Microsystems and Ripple Neuromed). 2) Use of parallel processing so that some cores can focus on presenting the stimuli during the task while others perform spike extraction and clustering (the latter being done with the iso-split algorithm to improve the computing time). 3) Develop a statistical criterion so that neural responses can be ranked, with stimuli ranking poorly being replaced with new ones.In terms of performance, the online and fully automatic spike sorting algorithm led to very similar results to those from other offline methods. The ranking criterion was also robust and effective. First, it did not exclude any of the responses that would have been obtained with the standard screening procedure followed by a scoring from an expert. In ~30 minutes, recording from 32 microwires and using an 8-core desktop, we were able to screen 330 pictures, with the candidate stimuli eliciting neural responses being presented at least 15 times each. This way, the number of false positive responses was largely reduced in comparison to the standard screening procedure. Finally, when the number of active channels is large, the processing time can be compensated by using more cores in parallel. Overall, the proposed method not only increases the number of response-eliciting stimuli that can be obtained during a given screening session, but also reduces dramatically the processing time to analyze the data and start a follow up experiment with the response-eliciting stimuli . This is essentially the time to plot the rasters and instantaneous firing rate for the candidate neural responses on each microwire, which is only in the order of a few tens of seconds.

Disclosures: F.J. Chaure: None. **S.A. Sheth:** None. **H.G. Rey:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.01

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R01 NS113516
NIH Grant R21 AG66496

Title: Modeling SARS-CoV-2 infection of the developing brain using human cortical organoids

Authors: *C. L. MCMAHON[1], H. STAPLES[2], M. GAZI[2], R. CARRION[2], J. HSIEH[3];
[1]Biology/Neurobiology, Univ. of Texas At San Antonio, San Antonio, TX; [2]Texas Biomed. Res. Inst., San Antonio, TX; [3]Biol., The Univ. of Texas At San Antonio, San Antonio, TX

Abstract: The prevalence of neuropsychiatric disorders is increasing, and a major cause of these disorders is aberrant fetal brain development. There is growing evidence implicating prenatal exposures as a driving factor. A common exposure that has undergone an exponential increase in incidence during recent years is that of viral infections, due in part to the novel coronavirus disease 2019 (COVID-19) pandemic. Up to 30% of COVID-19 patients have manifested neurological complications, and SARS-CoV-2 RNA has been found in brain biopsies from fatal cases. Furthermore, increasing rates of pre-term birth, miscarriages, and other defects have been seen following a maternal infection. The neurotropism of SARS-CoV-2 and the implications of neuroinflammation on the adult and developing brain are still poorly understood, therefore, it is imperative to gain insight into the mechanism(s) responsible for these complications. We hypothesize that SARS-CoV-2 infection and neuroinflammation trigger neurodevelopmental changes leading to a disruption of neural structure and circuit function in the developing cortex. Due to the inaccessibility of brain tissue from COVID-19 patients, we will address these questions using human stem cell-derived cortical organoids. To elucidate the cellular effects of SARS-CoV-2 infection on the development of the fetal brain, we first examined the neurotropism of SARS-CoV-2 in cortical organoids by identifying the cell types susceptible to SARS-CoV-2 infection, viral infection levels, viral replication, and the consequential effects on infected cells. We next determined the mechanisms by which neuroinflammation causes cellular alterations in cortical organoids by evaluating cellular integrity and neuronal networks. This study aims to reveal novel insight into the human-specific cellular etiology of potential neuropsychiatric disorder development from prenatal COVID-19 exposure, potentially contributing to future therapies and interventions.

Disclosures: C.L. McMahon: None. **H. Staples:** None. **M. Gazi:** None. **R. Carrion:** None. **J. Hsieh:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.02

Topic: A.03. Stem Cells and Reprogramming

Support: NICHD grant P50 HD093079

Title: Molecular and cellular mechanisms regulating brain overgrowth in autism

Authors: *S. CHETTY;
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Abstract: Approximately 15-20% of individuals with Autism Spectrum Disorder (ASD) have disproportionate megalencephaly (ASD-DM), with disproportionate enlargement in both gray and white matter volume. Individuals with ASD-DM have more severe behavioral and cognitive problems and are less responsive to standard therapeutic interventions, leading to very poor prognoses relative to

individuals with ASD and normal head circumferences. Increases in brain size often precede clinical symptoms, suggesting that understanding the underlying mechanisms regulating brain overgrowth could provide a window of opportunity for intervention or mitigation of symptoms. Here, we generated ~40 human iPSC lines from cohorts of children (2-4 years old) with complete clinical and phenotypic data, including A) ASD subjects with disproportionate megalencephaly, ASD-DM; B) ASD subjects with normal sized brains, ASD-N; C) Typically developing (TD) subjects with disproportionate megalencephaly, TD-DM; and and D) TD subjects with normal sized brains, TD-N. We differentiated each of the iPSC lines into neural progenitor cells (NPCs) and oligodendrocyte progenitor cells (OPCs) and investigated changes at the molecular and cellular levels contributing to brain overgrowth. In the differentiated neural and glial progenitor cells, we observe increased proliferation and suppressed phagocytosis of NPCs/OPCs by macrophages in ASD-DM. RNA-sequencing of the differentiated progenitor cells reveals important signaling mechanisms related to the neuroimmune system in regulating cellular phagocytosis. In prior work, we have demonstrated that CD47 (a 'don't eat me' signal) is overexpressed in both NPCs and OPCs in 16p11.2 deletion carriers with macrocephaly contributing to reduced phagocytosis in vitro and in vivo. Treatment of 16p11.2 deletion NPCs and OPCs with an anti-CD47 antibody to block CD47 restores phagocytosis to control levels in cellular and mouse models. Here, we show that similar neuroimmune mechanisms commonly implicated in cancer regulate cellular homeostasis in idiopathic forms of autism. Furthermore, we highlight new forms of therapy for selected autistic individuals with brain overgrowth early in the disease.

Disclosures: S. Chetty: None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.03

Topic: A.03. Stem Cells and Reprogramming

Support: NIH R01NS115965
Howard Hughes Medical Institute
Allen Discovery Center
Simons Center for the Social Brain Postdoctoral Fellowship
Surpina and Panos Eurnekian Bio Fund Fellowship

Title: Loss of Atypical Kinesin KIF26A Causes Brain Malformations via Aberrant Radial Migration and Increased Apoptosis

Authors: *X. QIAN[1,2], E. M. DEGENNARO[1,2], M. TALUKDAR[1,2], A. LAI[1,2], S. AKULA[1,2], C. A. WALSH[1,2];
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Abstract: Kinesins (KIFs) are molecular motors that transport cargo along microtubules intracellularly, and may serve as modulators of signaling pathways by altering the localization of signal-associated

factors. KIF26A, an unconventional kinesin that lacks ATPase activity, can bind to and sequester Grb2 and focal adhesion kinase (FAK) onto microtubules, suppressing their activity in signal transduction. Mice with homozygous deletion of Kif26a developed megacolon with enteric nerve hyperplasia. Nevertheless, the role of KIF26A in the central nervous system has not been characterized. We recently discovered a patient cohort with homozygous frameshift or compound heterozygous mutations in the KIF26A gene. The affected individuals displayed a spectrum of brain malformations including polymicrogyria, schizencephaly, cerebral atrophy and ventriculomegaly. Analysis of bulk and single-cell RNA sequencing (scRNA-seq) datasets of human fetal and postnatal cerebral cortex revealed KIF26A is specifically expressed in the first and second trimesters of gestation by migrating excitatory neurons. To investigate KIF26A's function in human brain development, we created KIF26A knockout (KO) human induced pluripotent stem cell (hiPSC) lines and generated forebrain organoids to compare with isogenic controls. We found KO organoids exhibited altered lamination of the subventricular zone (SVZ) and cortical plate (CP), and showed aberrant excitatory neuron radial migration, a FAK-dependent process. In KO organoids, migrating neurons were stalled in the SVZ, unable to reach the CP, and apoptotic cell death was elevated. In mouse embryonic cortex with shRNA knockdown of Kif26a, we observed similarly arrested radial migration in a cell-autonomous manner, but the knockdown didn't induce increase in apoptosis. To explore the underlying molecular mechanisms, we performed scRNA-seq on these organoids and discovered cell type-specific transcriptional changes in migrating and maturing excitatory neurons upon loss of KIF26A. Consistent with KIF26A's function as a Grb2 inhibitor, genes related to MAPK and p53 signaling were among the top differentially expressed genes. Gene set enrichment analysis further revealed dysregulation of MYC and E2F pathways, underscoring KIF26A's functions in modulating multiple signaling cascades related to cell survival. Together, our work uncovered the novel role of KIF26A in human brain development and diseases. Combining hiPSC-derived models and animal model, our multi-dimensional investigation illustrated that KIF26A regulates excitatory neuron migration and survival, and provided platforms for further mechanistic studies.

Disclosures: X. Qian: None. **E.M. DeGennaro:** None. **M. Talukdar:** None. **A. Lai:** None. **S. Akula:** None. **C.A. Walsh:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.04

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant MH125528

Title: Uncovering the cellular mechanism of Schizophrenia associated gene SETD1A loss-of-function in a human neural model

Authors: *X. SU[1], Y. HONG[2], H. ZHANG[3], S. ZHANG[3], H. SONG[2], J. DUAN[4,3], G.-L. MING[2], Z. P. PANG[1];
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Abstract: Uncovering the cellular mechanism of Schizophrenia associated gene *SETD1A* loss-of-function in a human neural model

Xiao Su[1], Yan Hong[2], Hanwen Zhang[3], Siwei Zhang[3], HongJun Song[2], Jubao Duan[3,4], Guo-li Ming[2], Zhiping P. Pang[1]
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Rare loss-of-function (LoF) mutations in *SETD1A* are strongly associated with schizophrenia (SZ), a debilitating mental disorder affecting 1% of the population, and other severe neurodevelopmental disorders. *SETD1A* encodes a component of the histone methyltransferase complex producing mono-, di, and trimethylated histone H3 at Lysine 4 (H3K4). H3K4 trimethylation (H3K4me3) and H3K4me1 are epigenomic marks of active gene transcriptional promoters and enhancers, respectively. Interestingly, histone methylation has also been suggested as one of the most enriched gene pathways in common variant-based genome-wide associations studies (GWAS) of major psychiatric disorders. However, the detailed molecular mechanism by which it causes neuronal dysfunction is still unclear. Recent advances in stem cell biology have allowed the efficient conversion of human stem cells into defined neuron subtypes allows to address this question. Using CRISPR/Cas9 gene editing, we have generated isogenic hiPSC lines carrying heterozygous LoF mutations on different genetic backgrounds of *SETD1A*. Preliminary results showed that mutant lines were defective in neuronal development with premature neuronal differentiation at early developmental stages. Furthermore, morphological, electrophysiological and transcriptomic analyses of hiPSC neurons carrying *SETD1A* LoF mutation showed defective synaptic neurotransmission. Ongoing experiments are evaluating *SETD1A* LoF with functional, morphological, biochemical and genomic parameters to understand the cellular mechanisms that how *SETD1A* LoF contributes to the pathogenesis of SZ. The study enables us to perform a well-controlled assessment of the impact of *SETD1A* LoF mutations on the molecular and cellular mechanisms underlying deficits in early neurodevelopment and synaptic properties.

Disclosures: X. Su: None. **Y. Hong:** None. **H. Zhang:** None. **S. Zhang:** None. **H. Song:** None. **J. Duan:** None. **G. Ming:** None. **Z.P. Pang:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.05

Topic: A.03. Stem Cells and Reprogramming

Support: Start up Funding from University of California San Diego, Antropology Dept

Title: Examining AUTS2 deficiency on human neurons

Authors: *C. MARCHETTO[1], V. M. CEREDA[2], A. SHARMA[3], J. T. WHITELEY[4];
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Abstract: The *Autism susceptibility candidate 2* (AUTS2) gene has been implicated in neurodevelopment and as a candidate gene for numerous neurological disorders, including autism spectrum disorders and intellectual disability. Individuals with mutations in this gene commonly show microcephalic features, craniofacial abnormalities and repetitive behaviors. Additionally, the genomic structural variants and single nucleotide polymorphisms in the *AUTS2* locus are also associated with a wide range of other neurological disorders such as epilepsy, schizophrenia, attention deficit hyperactivity disorder, dyslexia and depression as well as addiction-related behaviors, implicating that *AUTS2* is broadly involved in neurodevelopment. While *AUTS2* is often disrupted in patients with neurodevelopmental conditions above mentioned, the mechanisms underlying the neuronal pathogenesis in developing human neurons are still unclear. To bridge this gap, we use CRISPR/ Cas9 DNA editing technology to knockdown *AUTS2* gene on human stem cell lines and study the mechanistic consequences of lack of AUTS2 expression on transcriptomics and neuronal function. Our initial data analysis show that Wnt and Hippo signaling pathways are significantly affected on *AUTS2* knockdown human neuronal progenitors. We will present data characterizing unique phenotypical properties of *AUTS2* knockdown human neural progenitors. Understanding the cellular dysfunction and molecular pathways involved in AUTS2 deficiency could shed a light on the neuropathology of neurodevelopmental conditions such as ASD, ID and others.

Disclosures: C. Marchetto: None. **V.M. Cereda:** None. **A. Sharma:** None. **J.T. Whiteley:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.06

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R37 NS076752-08

Title: Human induced pluripotent stem cell model to study the role of SCN1B p.R89C gene variant in SCN1B-linked developmental and epileptic encephalopathy

Authors: *I. VERMA[1], L. T. DANG[2], L. F. LOPEZ-SANTIAGO[3], Y. YUAN[3], P. SWAMINATHAN[1], G. LIN[1], S. VAID[4], M. UHLER[5], L. L. ISOM[6], J. M. PARENT[7];
[1]Dept. of Neurology, and Michigan Neurosci. Institute, Michigan Med., [2]Dept. of Neurology, Michigan Neurosci. Institute, and Dept. of Pediatrics, Michigan Med., [3]Dept. of Pharmacology, Michigan Med., [4]Dept. of Pediatrics, Michigan Med., [5]Michigan Neurosci. Institute, and Biol. Chemistry, Michigan Med., [6]Dept. of Neurology, Dept. of Pharmacology, and Dept. of Mol. and Integrative Physiol., Michigan Med., [7]VA Ann Arbor Healthcare Sys. and Dept. of Neurology, and Michigan Neurosci. Institute, Michigan Med., Univ. of Michigan, Ann Arbor, MI

Abstract: *SCN1B*-linked developmental and epileptic encephalopathy (DEE) is characterized by pharmacoresistant seizures and sudden unexpected death in epilepsy (SUDEP). A subset of DEE patients exhibits homozygous putative loss of function variants in *SCN1B*, the gene that encodes the voltage-gated sodium channel (VGSC) β1 subunit. These *SCN1B* gene variants negatively affect neuronal development and alter neuronal excitability, leading to seizures and severe intellectual disability. We aim to understand how mutations in the *SCN1B* gene cause DEE to identify precision therapies. To this end, we generated induced pluripotent stem cells (iPSCs) from fibroblasts/blood of two patients with homozygous *SCN1B* p.R89C variants and healthy controls (one parent and one unrelated control). These iPSCs were differentiated to form excitatory neurons using dual-SMAD inhibition as well as induction with *NGN2* expression. Electrophysiological recordings showed that, as compared to control, *SCN1B* mutant excitatory neurons exhibit increased transient sodium current (I_{Na}) and spontaneous firing suggesting neuronal hyperexcitability. We hypothesize that *SCN1B*-linked DEE patient-derived inhibitory neurons will exhibit reduced excitability, hence leading to further neural circuit instability and seizures. Our previous study using a mouse model of *SCN1B*-linked early infantile DEE (EIEE52) supports this model (Hull et al., 2020). We generated cultures of mature GABAergic inhibitory neurons from control and patient-derived iPSCs using a small molecule-directed differentiation protocol. Additionally, we used an induced differentiation approach based on the expression of transcription factors *ASCL1* and *DLX2*, resulting in the rapid generation of a homogeneous population of GABAergic interneurons. We confirmed the GABAergic identity of generated neuronal cultures based on real-time qRT-PCR analysis of *GAD65*, *GAD67*, and *VGAT* (n=3). Immunostaining analysis revealed the generation of multiple GABAergic interneuron subtypes including somatostatin- and calbindin-positive interneurons. Using calcium imaging and electrophysiological recordings, we are examining the mutant cultures of inhibitory interneurons to investigate whether they have altered excitability. This work offers the potential for delineating the mechanisms underlying cortical dysfunction in *SCN1B*-linked DEE and for developing precision therapies designed to alleviate seizures and cognitive dysfunction in patients with *SCN1B*-linked and other DEEs.

Disclosures: I. Verma: None. **L.T. Dang:** None. **L.F. Lopez-Santiago:** None. **Y. Yuan:** None. **P. Swaminathan:** None. **G. Lin:** None. **S. Vaid:** None. **M. Uhler:** None. **L.L. Isom:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; A portion of Dr. Isom's research is funded by a grant to the University of Michigan from Stoke Therapeutics.. **J.M. Parent:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.07

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R01 NS113516
NIH Grant R21 AG66496

Title: Uncovering a neurodevelopmental role for fAD linked PSEN1 mutations

Authors: *E. HURLEY[1], R. DOBROWOLSKI[2], J. HSIEH[3];
[1]Biol., Univ. of Texas San Antonio, San Antonio, TX; [2]Biol. Sci., Rutgers Univ., Newark, NJ; [3]Biol., The Univ. of Texas At San Antonio, San Antonio, TX

Abstract: Mutations in Presenilin1 (PSEN1), the catalytic subunit of gamma secretase, account for over 80% of familial Alzheimer's Disease (fAD). Another substrate of the gamma secretase is Notch1, a critical signaling molecule with roles in neural progenitor maintenance, neurogenesis and gliogenesis. Previous reports suggest that mutations in PSEN1 reduce Notch signaling and lead to premature neurogenesis. However, it is not clear whether altered neurogenesis is linked to AD related pathology and neurodegeneration. Using human induced pluripotent stem cell (iPSC) derived 3D cortical organoids, we focus on PSEN1 mutations that have not been widely studied in the literature. We perform CRISPR/Cas9 editing in an isogenic control iPSC line to generate distinct PSEN1 mutations predicted to cause a loss or gain of function in the gamma secretase complex. In contrast to previous reports, we observe increased Notch signaling, an increase in neural progenitor cells and reduced neuronal differentiation in PSEN1 mutant organoids. We also observe increased size and morphological changes in cortical organoids harboring PSEN1 mutations, which is blocked by treatment with a Notch1 specific inhibitor, consistent with Notch signaling defects that depend on gain of function PSEN1 mutations. We will be determining if any of the neurodevelopmental changes due to PSEN1 mutations have further effects on AD-related neuropathology. Using this human cell-based model, these findings suggest that fAD mutations alter neural progenitor expansion and neurogenesis during development, possibly predisposing neurodegeneration.

Disclosures: E. Hurley: None. **R. Dobrowolski:** None. **J. Hsieh:** None.

Poster

P039. Stem Cell Approaches in Neurodevelopmental Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P039.08

Topic: A.03. Stem Cells and Reprogramming

Support: State of Pennsylvania CURE grant
Charles Henry Leach Fund

Title: Neurotropic infections impair neural stem cell activity in the pediatric central nervous system

Authors: *Y. S. KAMTE, M. N. CHANDWANI, A. G. FADARE, L. A. O'DONNELL;
Duquesne Univ., Pittsburgh, PA

Abstract: Outcomes of a viral infection in the CNS are often age-dependent. Several neurotropic viruses lead to profound neuropathology in younger hosts compared to older hosts. In pediatric mice, key neurodevelopmental processes such as synaptogenesis, myelination, and pruning are still underway. Neural stem cells (NSCs) are multipotent progenitor cells that populate the brain with neurons, astrocytes, and oligodendrocytes. The NSC pool contracts with age and is restricted to two neurogenic niches in the brain [hippocampus and sub-ventricular zone (SVZ)]. Thus, we hypothesized that a viral infection at the pediatric age could disrupt ongoing physiological development in the brain, potentially through changes

in the NSC pool. To test this hypothesis, we determined the effect of a viral infection and anti-viral immunity on NSCs in transgenic NSE-CD46+ pediatric mice (postnatal day 10), where measles virus (MV) only infects neurons and NSCs are spared from the infection. MV (2 X 10^4 PFU/ml) and mock-infected mice were evaluated for illness, viral antigen expression, and neural cell populations at 9- and 90-days post infection (dpi). Flow cytometric analysis revealed increased innate and adaptive immune cells in the CNS at 9 dpi while only B cells were present at 90 dpi. However, MV antigen was detected at both 9 and 90 dpi in the hippocampus. Thus, the pediatric anti-viral immune response fails to control the virus within the time frame of our studies. Additionally, the anti-viral immune response led to a drastic decrease in the NSC pool (Nestin+) in both the hippocampus and SVZ at 9 dpi, but NSC numbers were unchanged at 90 dpi. Oligodendrocyte progenitor cells (OPCs; O4+) increased at 9 dpi only in the hippocampus but increased in both the neurogenic niches at 90 dpi. These studies showed that both the NSC and OPC pool are perturbed during infection, but the OPCs are increased long-term. In the hippocampus, immature neurons (DCX+) decreased at 9 dpi while immature glia (A2B5+) increased at 90 dpi, suggesting a shift in NSC commitment to new neural cells. In the SVZ, mature neurons (β-III tubulin+) and immature glia (A2B5+) increased at 9 dpi and immature neurons (DCX+) decreased at 90 dpi, implying long-term changes in neurogenesis. Thus, the pediatric anti-viral immunity impairs neural cells not only during infection but also long-term. As neurons are the target cells of MV infection in our model and synaptogenesis is ongoing during the pediatric period, our current studies focus on understanding whether synaptic impairment occurs after infection. Our future experiments aim to understand whether long-term impairments in behavior occur after infection in pediatric mice.

Disclosures: Y.S. Kamte: None. **M.N. Chandwani:** None. **A.G. Fadare:** None. **L.A. O'Donnell:** None.

Poster

P041. Autism: Behavioral Analysis II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P041.01

Topic: A.07. Developmental Disorders

Support: Burroughs Wellcome Fund
Vanderbilt Kennedy Center
Vanderbilt University McGavock Chair

Title: Impact of bedding material on tactile behavioral phenotypes of a Camk2a E183V mutant mouse model of ASD

Authors: *J. R. THOMAS[1], R. J. COLBRAN[2];
[1]Mol. Physiol. and Biophysics, Vanderbilt Univ., Nashville, TN; [2]Dept Molec Physiol & Biophysics, Vanderbilt Univ. Sch. Med., Nashville, TN

Abstract: Impaired social communication and restricted behaviors are primary hallmarks of autism spectrum disorder (ASD). However, individuals with ASD also display abnormal tactile sensitivity and responses to sensory inputs, but underlying molecular mechanisms are poorly understood. Here, we assessed tactile phenotypes of an ASD mouse model with a Glu-183 to Val CaMKIIα catalytic domain

mutation (E183V-KI mice) which display abnormal social and motor behaviors[1]. The impact of raising mice in cages with cob or paper bedding was assessed. In von Frey filament tests, homozygous (HOM) E183V-KI mice were less sensitive to touch compared to wild-type (WT) and heterozygous (HET) mice, and this phenotype was exaggerated in HOM mice raised on cob bedding compared to paper bedding. Tactile discrimination was then assessed using three tests. **1.** Texture preference (TP) test: Mice freely explore a novel open field arena containing two visually-similar solid white plastic cubes with rough or smooth surfaces for 10 min. WT mice, but not HOM mice, raised on cob bedding spent significantly more time exploring a rough cube rather than a smooth cube. However, mice raised on paper bedding had no preference for the rough vs. smooth cubes, independent of genotype. **2.** Sandpaper (SP) test: Mice freely explore a novel open field arena with two equal floor zones covered with either coarse sandpaper or smooth paper for 30 min. During the first 10 min. (the TP test duration), WT mice raised on either paper and cob bedding spent more time in the rough floor zone. HET and HOM mice raised on cob bedding retained a significant preference for the rough floor zone, but HET and HOM mice raised on paper bedding spent equal amounts of time in the rough and smooth floor zones. However, the zone preference of HOM, but not HET or WT mice, raised on cob bedding was lost during the last 10 min. of the SP test. **3.** Textured novel object recognition (tNOR) test: To assess interactions between texture and cognition, mice are habituated to open field arenas containing either two rough or two smooth cubes on days 1 and 2, and on day 3 one of the cubes is replaced with a cube of the opposite (novel) texture, such that equal numbers of mice within each group were tested with novel rough or smooth cubes. WT mice, but not HET or HOM mice, raised on cob bedding explore the novel cube more than the familiar cube. However, none of the mice raised on paper bedding discriminated between novel and familiar cubes. Taken together our data demonstrates that tactile sensitivity and discrimination is impaired in HOM E183V-KI mice and can be modulated by environmental factors, such as bedding. 1. Stephenson et al., 2017. J Neurosci. 37(8): 2216, PMC5338762

Disclosures: J.R. Thomas: None. **R.J. Colbran:** None.

Poster

P041. Autism: Behavioral Analysis II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P041.02

Topic: A.07. Developmental Disorders

Support: 5R21MH118685-02
NSF 19-597 FAIN 2011039

Title: Modeling phenotypic heterogeneity in autism spectrum disorder by leveraging a mouse model of global genetic diversity, the Collaborative Cross Genetic Reference Panel, with Chd8 haploinsufficiency.

Authors: M. TABBAA[1,2], A. KNOLL[1,2], P. LEVITT[1,2];
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Abstract: An individual's combination of rare and common genetic variants interact with experience to impact risk for clinical disorders. For example, children with identical mutations in disease-causing genes show significant heterogeneity in symptom occurrence and severity. Thus, clinical heterogeneity remains a major challenge for developing effective models of treatment efficacy. This is highly relevant to disorders characterized by marked behavioral heterogeneity, such as in autism spectrum disorder (ASD). Currently, behavioral measures are largely conducted in a limited number of inbred rodent strains which can result in findings that are not generalizable due to a lack of understanding the effects of genetic variability on complex behaviors. Towards addressing this issue, we have embarked on a systematic analysis of risk gene penetrance using mouse models of global genetic diversity, the Collaborative Cross (CC) and BXD genetic reference panels, with mutations in a high-confidence ASD risk gene, *CHD8*, to identify how genetic background impacts risk and resilience. In clinical populations, functional mutations in *CHD8* are associated with ASD, intellectual disability, anxiety, and macrocephaly with variable penetrance and severity. These effects are replicated in C57BL/6J (B6) mice heterozygous for *Chd8* (*Chd8*$^{+/-}$) with variability for some phenotypes across studies. In this study, B6-*Chd8*$^{+/-}$ dams were mated with sires from 27 CC strains and 5 BXD strains. The resulting F1 wildtype (WT; n=8) and *Chd8*$^{+/-}$ (n=8) male and female littermates were phenotyped deeply. Dam and pup behaviors were recorded during litter observations, and adult social behaviors, contextual fear learning, anxiety-like and ambulatory behaviors were measured. Body weight trajectories and brain weights were also recorded. Strain impacted litter size, maternal care, pup behavior, and body weights. We also show an expansion of adult phenotypes in WT mice. The occurrence and severity of *Chd8* heterozygosity varies by strain and sex. Specifically, *Chd8* heterozygosity was highly penetrant for macrocephaly, body weight loss, social dominance, and reduced activity levels, with variable severity across strains. Additionally, we observed diverse sex- and strain-specific effects of *Chd8* heterozygosity on fear acquisition, expression and extinction. Resilient strains for specific phenotypic deficits also were identified. The B6-CC1 F1 strains thus revealed expanded mouse behavioral and physiological spectrums and differential susceptibility to *Chd8* heterozygosity. This effort creates potentially new models for determining factors that influence clinical heterogeneity.

Disclosures: M. Tabbaa: None. **A. Knoll:** None. **P. Levitt:** None.

Poster

P041. Autism: Behavioral Analysis II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P041.03

Topic: A.07. Developmental Disorders

Title: Study of autistic behaviors in transgenic mouse model with compromised Wave Regulatory Complex (WRC) function

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Abstract: *De novo* truncating variants in WAS protein family member 1 (*WASF1*) cause a rare form of intellectual disability with autistic features and seizures. *WASF1* encodes the protein WAVE1, one of five

components comprising the Wave Regulatory Complex (WRC). The WRC mediates interactions of membrane receptors with the actin cytoskeleton to regulate crucial developmental steps such as neural adhesion and migration. WRC is activated by different classes of ligands including the recently identified group of proteins containing the WRC interacting receptor sequence (WIRS). Over 40% of the identified proteins containing the WIRS domain are high confidence or strong candidate autism risk genes. Previous studies showed that *Wasf1* knockout mice exhibited reduced viability and behavioral abnormalities, such as poor balance, reduced coordination, and impaired learning and memory. To study WRC function more closely while circumventing the reduced viability observed in the conventional *Wasf1* knockout mouse model, we introduced point mutations in Abi2, another component of the WRC, to disrupt the WIRS binding motif that mediates WRC recruitment to cell membrane partners. Abi2$^{\Delta WIRS}$ mice showed no reduced viability. This study reports the characterization of anxiety, repetitive, and compulsive-like behaviors, cognitive performance, and seizure susceptibility in Abi2 $^{\Delta WIRS}$ mice. We also investigated brain anatomy, neuronal morphology and arborization to uncover the potential function of the WIRS/WRC interaction during brain development, and the suitability of the Abi2 $^{\Delta WIRS}$ mice as a model to study downstream signaling that would contribute to relevant neurodevelopmental disorders phenotypes.

Disclosures: G. Yang: None. **J.M. Rakotomamonjy:** None. **A.D. Guemez-Gamboa:** None.

Poster

P041. Autism: Behavioral Analysis II

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Program #/Poster #: P041.04

Topic: A.07. Developmental Disorders

Support: ANPCYT, PICT-2016-2202
ANPCYT, PICT-2019-1279
UBA, UBACYT2020-20020190100102BA

Title: Female mice postnatally exposed to estradiol show altered autism related behaviors

Authors: *A. SEIFFE[1,2], M. RAMIREZ[1,2], L. M. DI GUARDIA CASELLA[1,3], C. BARRIOS[1,2], M. M. ALBARRÁN[1,3], A. M. DEPINO[1,4];
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Abstract: Autism spectrum disorders (ASD) are characterized by reduced sociability, diminished communicative skills and repetitive behaviors. Notably, the proportion between boys and girls diagnosed with ASD is about 4 to 1. A striking difference between males and females in humans and other mammals is that males suffer a process of brain masculinization, due to the early exposure to gonadal hormones. In rodents, this developmental organization of the brain is essential for the proper display of sexual behaviors in adulthood, but it also determines other sex differences in brain function and behavior. Our first aim was to evaluate whether this process of brain masculinization influences the performance in behaviors relevant to ASD. To this aim, we studied sex differences and the effect of neonatal 17β-

estradiol benzoate (E2) treatment of female mice (CF1 outbred) on different ASD-relevant behaviors. On postnatal days (PND) 2, 5 and 8, female pups were injected (s.c.) with estradiol (50 µg; E2, n = 19) or vehicle (OIL, n = 12). On adulthood (from PND60), we found that the sex differences observed in exploration (distance in the Y maze, one-way ANOVA $p = 0.001$; and open field, one-way ANOVA $p = 0.014$), repetitive behaviors (self-grooming, one-way ANOVA $p = 0.020$), and depression-related behaviors (immobility in the forced swim test, one-way ANOVA, $p = 0.004$) are largely reduced when females are neonatally treated with E2. Recently, we observed that the prenatal exposure at gestational day 12.5 to 600 mg/kg valproic acid (VPA) results in decreased sociability of male offspring, while female littermates express normal levels of social interaction. Our second aim was then to identify the biological mechanisms involved in this differential impact of VPA in male and female mice. Our hypothesis is that brain masculinization is necessary for prenatal VPA exposure to affect autism-related behaviors, neuronal alterations and gliosis. To test this hypothesis, we studied the effect of postnatal exposure to E2 in female mice of the VPA model of autism, analyzing four experimental groups: SAL-OIL (n = 13), SAL-E2 (n = 17), VPA-OIL (n = 12) and VPA-E2 (n = 14). Our results show that only VPA-E2 females present no habituation to the stimulus mouse throughout the four consecutive presentations (three-way ANOVA followed by Fisher's LSD test, presentation 1 vs 4 $p > 0.05$). These results demonstrate that the combination of prenatal VPA exposure and postnatal E2 treatment results in altered sociability in female mice. Further studies of the VPA-E2 mice could help us identify possible biological mechanisms underlying the higher incidence of ASD observed in boys.

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Poster

P041. Autism: Behavioral Analysis II

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Program #/Poster #: P041.05

Topic: A.07. Developmental Disorders

Support: ProMedica Foundation Gift

Title: Social Transmission of fear in prairie voles

Authors: *D. GAMBOA PABON, S. K. PATEL, J. P. BURKETT, E. ANDARI;
Univ. of Toledo, Toledo, OH

Abstract: Autism is a neurodevelopmental disorder characterized by deficits in social communication, social interaction, and repetitive behaviors. Social deficits are characterized by impairments in social reciprocity, empathy, and social recognition. Prairie voles are social species that are monogamous and able to form social bonds with their partners. Here, we are developing a behavioral assay of social learning by being inspired by the social transmission of fear paradigm that has been used in rats. The goal of this test is to assess social learning in prairie voles. We were able to find that following habituation, prairie voles show partner-directed grooming toward the stressed partner following fear conditioning. We were also able to find that the non-shocked observer shows significantly more freezing to tones following

exposure to the stress of the partner compared to the control observer that was exposed to the non-stressed partner. Therefore, we believe that it is possible to socially condition prairie voles via the stress of the partner. These findings will help provide new outcome measures to study social cognition in rodents and future pharmacological manipulations.

Disclosures: D. Gamboa Pabon: None. **S.K. Patel:** None. **J.P. Burkett:** None. **E. Andari:** None.

Poster

P041. Autism: Behavioral Analysis II

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Program #/Poster #: P041.06

Topic: A.07. Developmental Disorders

Support: NSF grant #1640909

Title: Ai deep learning motor diagnostic analysis of neurodevelopmental disorders

Authors: *J. JOSE[1], **K. DOCTOR**[3], A. PHADNIS[2], D. WU[4], J. I. NURNBERGER[2], M. H. PLAWECKI[2];
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Abstract: We have studied the motor abilities of individuals with Neurodevelopmental Disorders (NDD). In particular, 12-ASD subjects with Autism Spectrum Disorder (ASD), 9 comorbid ASD plus ADHD (ASD+ADHD) vs 7 Typically Developing (TD). We used *XSENS* high definition kinematic sensors, (www.xsens.com), to measure the angular *velocity plus linear acceleration* of arm *movements. T*he subjects performed a reaching task moving their arms towards touch screen targets appearing intermittently on the monitor. We implemented a supervised deep neural network to predict NDD conditions based on the raw kinematic sensors data, without any preconceived assumptions about the data. Our hypothesis is that movement contains latent hidden physiological information about cognitive neurodevelopment abilities. We assumed that the sensors raw kinematic data would contain such NDD classification information that would unravel when using AI Deep Learning techniques. We generated training sets with, typically, 75% of the full NDD plus TD data measured with the sensors to train a neural network. To model the temporal signal, we used Long Short-Term Memory (LSTM) cells as the neurons of the network. To transform the memory-based output from the LSTM layer into a representation capable of predicting NDD conditions, we passed the LSTM output to a Linear Layer used to model a linear relationship between inputs plus outputs using the learned parameters defining a line (slope plus bias). Each of these output neurons are trained to represent a different NDD condition. The predicted strength of the individuals having that condition is proportional to the activation of the output neuron. Thus, to make a prediction of an individual's NDD condition we transformed the output of the Linear layer to a probability distribution by normalizing their activations plus selecting the NDD condition with the maximum probability. We could show that the network was not overfitting through the accuracy on the held out set that was never used to train the network. Given the small size of the dataset, we applied K-Fold Cross Validation to further train the network. The final accuracy on the held out set

was 71.4% (5 out of 7 individuals). This shows that DL is indeed able to correctly identify the diagnostics of most of the remaining NDD subjects without any *a priori* information about their cognitive abilities. It also clearly separates the NDDs from the TDs. This remarkable DL motor predictive power could be used as an early step in diagnosing the condition that is so needed for potential young NDD subjects' treatments.

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Poster

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Title: Rethinking the McGurk Effect in autism: Hierarchical drift diffusion modeling reveals decision-making differences in autistic and neurotypical children and adolescents

Authors: *S. G. VASSALL[1,2], R. A. STEVENSON[7,8], M. T. WALLACE[1,3,4,5,6];
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Abstract: Broken into its simplest components, decision-making comprises three general phases: accumulation of sensory evidence over time, reaching a decision, and initiating a motor action. Using hierarchical drift diffusion modeling (HDDM) and Bayesian analyses, a dataset from prior research by Stevenson et al. (2014) was reanalyzed in order to elucidate differences in decision-making processes between autistic and neurotypical children and adolescents ages 6-18 years performing a modified McGurk task. Using these methods, we expanded upon prior findings to reveal differences in decision-making processes across both age and diagnostic group. We found that on unisensory trials, autistic children displayed significantly faster rates of evidence accumulation (i.e., drift rate) compared to neurotypical children in response to visual-only stimuli, an effect that was amplified in the younger cohort. However, under multisensory conditions, in children with autism this advantage disappeared, and drift rate was slower than that of the neurotypical groups. Importantly, we observed that the diagnostic group differences in drift rate increased with age. A principal component analysis also revealed an age-dependent relationship between clinical measures of autism and estimates of drift rate. Specifically, for

both unisensory and multisensory conditions the Social Responsiveness Scale, 2nd Edition Social Communication Impairment (SRS SCI) subscale was identified as the first principal component. However, while high SRS SCI scores predicted superior unisensory drift rate in younger autistic children and lower unisensory drift rate in older autistic children compared to neurotypical groups, no significant predictive relationship was observed for multisensory trials. From this evidence, we propose that accumulation of auditory and visual information slows in older children with autism. Furthermore, we put forward that slowed auditory and visual drift rate in older autistic children is predictive of increased social communication impairments as quantified by standardized clinical measures.

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Poster

P041. Autism: Behavioral Analysis II

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Topic: A.07. Developmental Disorders

Support: NIMH R01 MH100028; PI: K.A.P.
Autism Speaks Postdoctoral Fellowship, Grant ID 11808; PI: G.A.M.

Title: Increased volume of amygdala nuclei in autistic youth with elevated anxiety

Authors: *G. A. MCQUAID[1], A. JOB SAID[2], A. JACK[1], K. A. PELPHREY[3], G. L. WALLACE[2]; [1]George Mason Univ., Fairfax, VA; [2]George Washington Univ., Washington, DC; [3]Univ. of Virginia, Charlottesville, VA

Abstract: Introduction The amygdala plays a central role in processing socio-emotional information and thus has been featured prominently in some pathophysiological models of autism spectrum disorder (ASD). Nevertheless, findings have been mixed regarding ASD-related differences in amygdala structure. One factor in these mixed findings may be frequently co-occurring anxiety symptoms and disorders in ASD. A handful of studies to date have linked anxiety symptoms/disorders with amygdala volume in autistic youth. However, these studies have used global metrics of amygdala morphometry. Recent advances enable more fine-grained examination of amygdala structure (i.e., nuclei), which promise to advance our understanding of amygdala morphometry in ASD and its links with anxiety symptoms. **Method** 130 ASD (47.8% female) and 126 typically developing (TD) (50.8% female) youth aged 8-18 years (ASD: M=13.0 $\pm$ 2.8; TD: M=13.6 $\pm$ 3.0) completed a T1-weighted structural magnetic resonance imaging (MRI) scan. MRI data processing was carried out in FreeSurfer, generating not only cortical & subcortical volumes, but also 9 amygdala nuclei volumes via a specialized pipeline. Parent report on the Childhood Behavior Checklist (CBCL) was used to assess anxiety symptoms and to subgroup ASD participants into those who were high anxiety (HI-ANX, n=65; T score ≥65) or low anxiety (LO-ANX, n = 65; T score <65). Multivariate analysis of covariance (MANCOVA) accounting for the effects of age, sex, total intracranial volume, and scan site were conducted. Dependent variables were volume of the 9 amygdala nuclei. The independent variable was group: ASD HI-ANX, ASD LO-ANX, TD. **Results** Using Pillai's Trace, the MANCOVA revealed a significant effect of group (F(18,474) = 2.1, p =

.006, $V = .15$). Regions significant in follow-up ANCOVAs were the Basal ($p = .018$); Medial ($p = .020$); Cortical ($p = .03$); and Paralaminar ($p = .005$) nuclei, with only the last of these surviving FDR correction. These group differences were driven by greater volume in the HI-ANX compared to the LO-ANX group. **Discussion**Autistic children and adolescents with elevated anxiety had larger amygdala nuclei volume compared to their autistic peers with lower levels of anxiety. In particular, four amygdala nuclei show these effects. To our knowledge this is the first study to show differences in amygdala nuclei volume for autistic youth with elevated anxiety compared to those with lower anxiety levels. The reported granularity in amygdala morphometry differences may inform models of co-occurring anxiety in ASD.

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Poster

P041. Autism: Behavioral Analysis II

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Program #/Poster #: P041.09

Topic: A.07. Developmental Disorders

Support: NICHD funded IDDRC P50 (P50HD103526)
Interdisciplinary Intercampus (IDIC) Research Program grant from the University of Missouri system

Title: Maternal Antibody Response in Mothers of Children with ASD: The Role of Prenatal Stress and Genetics

Authors: *A. N. COSTA[1], B. J. FERGUSON[1], A. COMAN[3], E. HAWKINS[1], J. SCHAUER[4], A. RAMIREZ-CELIS[4], Z. TALEBIZADEH[5,2], J. A. VAN DE WATER[4], D. Q. BEVERSDORF[1];
[1]Univ. of Missouri, Columbia, MO; [2]Univ. of Missouri, Kansas City, MO; [3]Grinnell Col., Grinnell, IA; [4]Univ. of California - Davis, Davis, CA; [5]Children's Mercy Hosp., Kansas City, MO

Abstract: Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by challenges in social communication and the presence of restrictive and repetitive behaviors. Environmental and genetic factors have been shown to contribute to ASD, but the interaction between them is less understood. Previous research indicated that presence of a short allele of the promotor region of 5-HTTLPR was associated with an increased vulnerability to anxiety under stressful conditions, and higher levels of stress in pregnant mothers were associated with ASD. Additionally, previous studies found immune dysregulation during pregnancy to be associated with a diagnosis of ASD in the child. However, the relationship between prenatal stress exposure, maternal genetic stress susceptibility, and maternal antibodies in mothers whose children are diagnosed with ASD is unclear. **Methods:** This study examined whether the maternal antibody response was related to prenatal stress in their association with ASD. Additionally, the study examined whether the interaction between prenatal stress and the 5-HTTLPR polymorphism correlated with maternal antibody response. Samples from 53 mothers who have at least one child diagnosed with ASD were examined. Maternal antibody presence, stress level during pregnancy (high or low), and maternal 5-HTTLPR polymorphism (presence or absence

of at least one copy of the short allele) were recorded and used to conduct statistical analyses. Four groups were created for the allele x prenatal stress interaction (short allele present and high stress, short allele present and low stress, short allele absent and high stress, short allele absent and low stress). **Results:** A chi-squared analysis indicated that the association between maternal antibody presence and prenatal stress was not significant (p=0.709, Cramer's V=0.051). Furthermore, a chi-squared analysis to examine the association between maternal antibody presence and the interaction between 5-HTTLPR genotype and stress was not significant (p=0.729, Cramer's V=0.157). **Discussion:** The results revealed that prenatal stress, and the interaction between the 5-HTTLPR polymorphism and prenatal stress, were not associated with presence of maternal antibodies, in their association with ASD. These results are interesting, given the known associations between ASD diagnosis and prenatal stress, 5-HTTLPR polymorphism, and immune dysregulation. These results point to the notion that prenatal stress and immune dysregulation are independently associated with a diagnosis of ASD.

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Poster

P041. Autism: Behavioral Analysis II

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Program #/Poster #: P041.10

Topic: A.07. Developmental Disorders

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Title: Investigating common gene networks underlying sensory over-responsivity and habituation impairments in Autism Spectrum Disorders

Authors: *L. D. KEPLER[1], C. H. RANKIN[2];
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Abstract: The genetic complexity and phenotypic heterogeneity of Autism Spectrum Disorder (ASD) pose significant challenges to our ability to understand disorder etiology and identity effective treatments. Alterations in sensory processing and habituation (a type of learning where one learns to stop responding to repetitive stimuli) are reported in up to 90 percent of ASD cases. The high presence of sensory processing and habituation impairments suggests that ASD-associated genes may be acting together to control these behaviours, offering a unique opportunity to investigate commonly affected pathways underlying ASD. Our lab recently published an in-depth phenomic database of 135 *C. elegans* strains with loss-of-function mutations in 98 ASD risk gene orthologs. Here, we used the data generated by our high-throughput machine vision tracking system to investigate the relationships between phenotypes such as mechanosensory hypo or hypersensitivity and altered habituation to mechanosensory stimuli. By exploring our dataset, we identified subsets of ASD risk genes that similarly affected initial responsivity

and degree of habituation for response probability, duration, and speed. Alternations in initial response duration and habituation of response duration showed a strong positive correlation, suggesting a high degree of mechanistic overlap underlying these phenotypes. Identifying common pathways contributing to sensory processing and habitation alterations provides a unique opportunity to investigate why sensory and learning impairments occur when different ASD-associated genes are affected and aid in identifying new therapeutic targets to help individuals with these behavioural and learning difficulties.

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Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P157.01

Topic: B.11. Glial Mechanisms

Support: NIH Grant DA048241
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Title: Hippocampal Astrocytes Regulate Heroin Withdrawal and Future Enhanced Fear Learning

Authors: *S. V. PAREKH, J. E. PANICCIA, G. A. BARKELL, L. O. ADAMS, K. J. REISSNER, D. T. LYSLE;
Psychology and Neurosci., Univ. of North Carolina, Chapel Hill, NC

Abstract: Converging evidence suggests the neural immune system is altered following opioid use and withdrawal and post-traumatic stress disorder (PTSD). Using an innovative rodent model that combines escalating heroin administration and spontaneous withdrawal with enhanced fear learning, we demonstrated neuroimmune alterations mediate withdrawal-induced fear learning. Specifically, heroin withdrawal enhanced fear learning is driven by dorsal hippocampal (DH) interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) signaling, and withdrawal from escalating heroin administration induces both DH IL-1β and TNF-α expression. Moreover, the IL-1β and TNF-α involved in heroin withdrawal enhanced fear learning is primarily expressed in hippocampal astrocytes. Interestingly, we found that heroin withdrawal upregulates hippocampal glial fibrillary acidic protein (GFAP), a marker for astrocyte reactivity. Astrocytes critically modulate the neural environment and opioid-induced changes in astrocyte physiology may contribute to heroin-related behavioral maladaptation. To better understand the role of DH astrocytes in heroin withdrawal-induced fear learning, we investigated whether astrocyte activity is causally related to heroin withdrawal enhanced fear learning and if withdrawal from chronic heroin altered astroglial structure and synaptic interactions. Thus, Experiment 1 employed G_i-coupled designer receptors exclusively activated by designer drugs (DREADDs) to manipulate astrocyte signaling *in vivo*. Male rats were infused with AAV8-GFAP-hM4D(Gi)-mCherry into the DH, and underwent the chronic escalating heroin administration paradigm. Clozapine-n-oxide (3 mg/kg, s.c.) or vehicle was administered

0-hour, 24-hours, and 48-hours into heroin withdrawal, and animals were then exposed to the enhanced fear learning paradigm. Experiment 2 used an established method to visualize DH astrocytes in detail using a membrane-tagged GFP, advanced microscopy, and image analysis. Male rats were administered bilateral intra-DH infusions of AAV5-GFAP-Lck-GFP, and underwent the chronic escalating heroin administration paradigm. Tissue was collected 24-hours into heroin withdrawal. Using high resolution confocal microscopy and analysis of 3-dimensional cellular reconstructions, astrocyte surface area, volume, and colocalization with postsynaptic density-95 were quantified to assess the consequence of chronic heroin and spontaneous withdrawal on astrocyte structure and neuronal interactions. Together, these studies examine the role of hippocampal astrocytes in heroin withdrawal-enhanced fear learning.

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Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

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Topic: B.11. Glial Mechanisms

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NIH Grant DA007244

Title: Sex-differences in heroin withdrawal enhanced fear learning behavior

Authors: *L. O. ADAMS, S. V. PAREKH, J. E. PANICCIA, G. A. BARKELL, D. T. LYSLE; Psychology and Neurosci., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Opioid use disorder (OUD) and post-traumatic stress disorder (PTSD) are highly comorbid in clinical populations. However, the biological mechanisms underlying this relationship are not fully understood. Our laboratory has established that chronic escalating heroin administration and withdrawal produces future enhanced fear learning and induces expression of dorsal hippocampal (DH) interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α). Further, heroin withdrawal enhanced fear learning is blocked by inhibiting DH IL-1β and TNF-α signaling. Excitingly, blockade of DH TNF-α signaling mitigated withdrawal-induced weight loss, suggesting that TNF-α signaling may drive neurobiological changes resulting in PTSD/OUD comorbidity. However, previous experiments have studied only male rats and it is currently unknown whether these findings extend to females. There are substantial gaps in knowledge about the effects of opioids in females, and it is imperative to explore heroin-enhanced maladaptive behaviors across sex. Thus, the current study examined sex differences in heroin withdrawal enhanced fear learning. Experiment 1 tested whether chronic escalating heroin administration produced a withdrawal phenotype and an enhanced fear learning response in female Sprague Dawley rats. Rats underwent the escalating heroin administration in which they received 3 injections of heroin per day for

10 days. The dose was increased every 2 days, culminating to a final dose of 10 mg/kg. Animals then underwent the enhanced fear learning paradigm, and estrous cycle stage was assessed on each test day. Females displayed comparable withdrawal behaviors to males, however, did not display heroin withdrawal-enhanced fear learning. As we have previously established a role for hippocampal cytokine signaling in the development of heroin withdrawal-enhanced fear learning in male rats, we sought to determine whether sex differences were present in brain cytokine expression. In Experiment 2, female rats underwent the chronic escalating heroin administration paradigm and tissue was collected 24-hour into withdrawal. DH IL-1β and TNF-α were assessed, as elevated levels of these cytokines may indicate that the mechanism underlying the females' fear learning response to heroin is different than that of males, or that females may have a protective factor that mitigates the effect of elevated cytokines. Collectively, these experiments provide the first evidence that female rats may possess a protective biological factor that lessens the effects of heroin administration and withdrawal on future fear learning, potentially by suppressing neuroinflammatory pathways.

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Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

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Title: Chronic Ethanol Consumption Exacerbates Future Stress-Enhanced Fear Learning and Alters Neuroimmune-Related mRNA Expression

Authors: *G. A. BARKELL, S. V. PAREKH, J. E. PANICCIA, A. J. MARTIN, T. E. THIELE, D. T. LYSLE;
Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly comorbid in clinical populations. While it is hypothesized this comorbidity is a result of alcohol use to cope with PTSD symptomology, it is still unknown whether a prior history of chronic alcohol consumption alters the development of a PTSD-like phenotype. The neuroimmune system has been implicated in regulating both AUD- and PSTD-related behaviors, as well as being influenced by ethanol consumption and stress exposure. Our laboratory has developed a novel rodent model to explore the outcome of prior chronic

ethanol consumption and withdrawal on the development of a PTSD-like phenotype, and uncover the neurobiological mechanisms driving this relationship. In Experiment 1, adult male Sprague Dawley rats were given either ethanol (5% w/v) or control formula of low-fat Lieber-DeCarli liquid diet for 15 days. This 15-day exposure produced withdrawal behaviors and blood ethanol concentrations (BECs) above 80 mg/dL. Subsequently, all animals were placed on control diet. Twenty-four hours post ethanol removal, rats were exposed to a novel context (Context A) for 90 min where they received a severe stressor (15 scrambled footshocks (2 mA, 1s) on a 6 min variable interval schedule) or remained unshocked controls. One week later, all animals were placed into a distinctly different context (Context B) and administered a mild footshock (1 mA, 1 s). On test days, conditioned freezing behavior to Context B was quantified. Animals with a prior history of chronic ethanol and severe stress exposure displayed increased conditioned freezing behavior relative to all other animals, demonstrating enhanced fear learning behavior. Experiment 2 examined the neuroimmune consequences of chronic ethanol combined with severe stress exposure using a 2 (drug) x 2 (stress) design. Male rats were given ethanol (5% w/v) or control diet for 15 days and placed into Context A 24-hours post ethanol removal. In Context A, animals either underwent the severe footshock stress or remained as unstressed controls, and tissue was collected 24 hours post shock. Using RT-qPCR we detected ethanol-induced increases in glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, in both the dorsal and ventral hippocampus and amygdala. Additionally, we observed stress-induced decreases in the neuroimmune targets CD68 and TNF-α, as well as neuropeptide Y in the dorsal hippocampus. Collectively, results indicate prior ethanol exposure and severe stress result in the development of a PTSD-like phenotype, and alter neuroimmune targets across multiple brain regions.

Disclosures: G.A. Barkell: None. **S.V. Parekh:** None. **J.E. Paniccia:** None. **A.J. Martin:** None. **T.E. Thiele:** None. **D.T. Lysle:** None.

Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P157.04

Topic: B.11. Glial Mechanisms

Support: NIH F32NS110481
NIH K99AA028579
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Title: Assessing the computational power of Ca2+ transients in astrocyte microdomains of the visual cortex

Authors: *J. SHIH[1], G. O. SIPE[1], N. M. LE[1], E. S. BOYDEN[2], M. SUR[1];
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Abstract: Astrocytes are the most abundant glial cell type in the brain. Increasing evidence shows that they respond to and influence neuronal function at the synaptic, cellular, and network levels, and that this

relationship may be reflected in transient astrocytic calcium (Ca2+) activity. These Ca2+ transients are spatiotemporally diverse, particularly the microdomain Ca2+ events in astrocyte fine processes, which are closely associated with synapses. Astrocyte fine processes contain a number of neurotransmitter reuptake transporters and ion channels, which contribute to how astrocytes shape synaptic transmission and neuronal signaling. Transporter function and ion channel flux are dependent on concentration gradients of monovalent and divalent cations across the astrocytic cell membrane, particularly the sodium gradient, which drives key mechanisms such as glutamate uptake and sodium-calcium exchange. How ion flux and transporter function at astrocyte fine processes affect microdomain Ca2+ transients and correlate with neuronal activity in complex cortical circuits has not been characterized. We hypothesize that astrocytic Ca2+ transients in microdomains encode neuronal activity and behavioral task parameters in the visual cortex, and that this encoding feature is disrupted when ion concentration gradients, particularly the sodium gradient, is perturbed. We first measured and characterized neuronal and astrocytic Ca2+ activity in the primary visual cortex of awake mice using in vivo two-photon microscopy during passive visual stimulus presentation and used generalized linear models to determine the encoding power of microdomain Ca2+ activity. We then used the sodium selective channelrhodopsin variant ChromeQ to show that alteration of sodium flux across the astrocyte membrane increased Ca2+ microdomain events. These preliminary results suggest that perturbation of sodium flux in astrocytes in vivo may allow us to target Ca signaling in a specific compartment of the astrocyte domain to determine their contributions to visual processing and encoding.

Disclosures: J. Shih: None. **G.O. Sipe:** None. **N.M. Le:** None. **E.S. Boyden:** None. **M. Sur:** None.

Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P157.05

Topic: B.11. Glial Mechanisms

Support: CT (1P20GM130459)

Title: Serotonin and Norepinephrine Modulate Vascular and Astroglial Activities During Sensory Stimulation in Awake Mice

Authors: *K. SHARMA, C. TRANTHAI;
Univ. of Nevada Reno, Reno, NV

Abstract: Serotonin and Norepinephrine Modulate Vascular and Astroglial Activities During Sensory Stimulation in Awake Mice
Kushal Sharma and Cam Ha T. Tran
The brain possesses control mechanisms to regulate blood flow to meet metabolic demands. Neurovascular coupling (NVC) is one of those essential processes in which all members of the neurovascular unit including neurons, astrocytes and vascular cells, coordinatively respond to increases in neuronal activity to enhance cerebral blood flow. Studies showed behavioral state of the animal affected astrocytic Ca2+ dynamics. Wakefulness, increases in arousal or engagement are often associated with the

release of a number of neuromodulators including serotonin, acetylcholine, and norepinephrine. Previous work demonstrated that norepinephrine mediated astrocytic responses to increases neuronal activities. Whether these neuromodulators contribute to NVC remains poorly understood. Our objective was to uncover the role of serotonin and norepinephrine in NVC during sensory stimulation in fully awake, behaving mice. A craniotomy over the barrel cortex with the dura removed was performed. Two-photon imaging was used to image the vasculature and astrocytes Ca2+ from either C57Bl/6 mice or Aldh1l1Cre ERT x GCaMP6f mice. Fluorescein isothiocyanate dextran conjugated or Rhodamine B isothiocyanate dextranconjugated was used to visualize the vasculature while synthetic Ca2+ indicator (i.e. Rhod2-AM) or genetically engineered Ca2+ indicator (i.e. GCaMP6f) was used to examine astrocytic Ca2+ responses to 5s whisker stimulation. We found that blocking serotonin and norepinephrine receptors as well as manipulating the release of these neurotransmitters by neurotoxin differentially affected sensory-induced functional hyperemia and astrocytic Ca2+ dynamics. Our data introduce the contributions of neuromodulators to NVC and propose that these neurotransmitters act in conjunction with glutamatergic signaling pathway to regulate NVC and consequently cerebral blood flow.

Disclosures: K. Sharma: None. **C. Tranthai:** None.

Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

Location: Virtual Only

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Program #/Poster #: P157.06

Topic: B.11. Glial Mechanisms

Support: CAMH Discovery Feed Fund
Labatt Family Research Fellowships in Depression Biology
Campbell Family Mental Health Research Institute

Title: Chronic stress induces astroglial atrophy in the prefrontal cortex of rodents

Authors: *S. A. CODELUPPI[1], D. CHATTERJEE[1], T. D. PREVOT[1], Y. BANSAL[1], K. A. MISQUITTA[1], E. SIBILLE[2], M. BANASR[1];
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Abstract: Neuromorphological changes are consistently reported in the prefrontal cortex (PFC) of patients with stress-related disorders and in rodent stress models, but the effects of stress on astrocyte morphology and potential link to behavioral deficits are relatively unknown. To answer these questions, transgenic mice expressing green fluorescent protein (GFP) under the glial fibrillary acid protein (GFAP) promotor were subjected to 7, 21 or 35 days of chronic restraint stress (CRS). CRS induced behavioral effects on anhedonia- and anxiety-like behaviors were measured using the sucrose intake and the PhenoTyper tests, respectively. PFC GFP+ or GFAP+ cells morphology was assessed using Sholl analysis and associations with behavior were determined using correlation analysis. CRS-exposed male and female mice displayed anxiety-like behavior at 7, 21 and 35 days and anhedonia-like behavior at 35 days. Analysis of GFAP+ cell morphology revealed significant atrophy of distal processes following 21 and 35

days of CRS. CRS induced similar decreases in intersections at distal radii for GFP+ cells, accompanied by increased proximal processes. In males, the number of intersections at the most distal radius step significantly correlated with anhedonia-like behavior (r=0.622, p&lt0.05) for GFP+ cells and with behavioral emotionality calculated by z-scoring all behavioral deficits (r=-0.667, p&lt0.05). Similar but not significant correlations were observed in females. No correlation between GFP+ cell atrophy with anxiety-like behavior was found. Overall we found that, chronic stress exposure induces a progressive atrophy of cortical astroglial cells, potentially contributing to maladaptive neuroplastic and behavioral changes associated with stress-related disorders. Current work aims to investigate the consequences of region specific astroglial manipulations on stress-related behavioral and cellular deficits.

Disclosures: S.A. Codeluppi: None. **D. Chatterjee:** None. **T.D. Prevot:** None. **Y. Bansal:** None. **K.A. Misquitta:** None. **E. Sibille:** None. **M. Banasr:** None.

Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

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Program #/Poster #: P157.07

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Title: Coordinated neuron and astrocyte activity in developing sensory domains

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Abstract: Spontaneous neuronal activity in developing sensory systems enables periodic, coordinated firing of neurons that will eventually process similar aspects of sensory information. This burst firing is conserved between species, resistant to perturbation, and important for both neuron survival and circuit refinement. Astrocytes secrete factors that promote synapse maturation and mature in parallel with neurons in the developing brain. However, little is known about the mechanisms that coordinate the maturation of astrocytes and neurons during this critical developmental period. Using *in vivo* calcium imaging in awake neonatal mice from both sexes, we show that bursts of neuronal activity passing through sound processing networks in the midbrain and cortex reliably induce calcium transients in astrocytes before the onset of hearing. Astrocyte transients were dependent on high levels of neuronal

activity and constrained to regions near active synapses, ensuring close spatial and temporal coordination of neuron and astrocyte activity. Using *in vivo* pharmacology and astrocyte-specific knock-out mice, we determined that astrocyte responses were induced by synergistic activation of two metabotropic glutamate receptors, mGluR5 and mGluR3, which promoted IP3R2-dependent calcium release from intracellular stores. This spatially and temporally coordinated neuron-astrocyte activity was restricted to the pre-hearing period, as sound induced activation of neurons in auditory cortex did not elicit calcium increases in nearby astrocytes, consistent with the developmental decline in expression of mGluR5 by astrocytes. Single-nucleus RNA sequencing of the auditory midbrain from mice in which astrocyte calcium signaling was selectively abolished during development, revealed that this activity influences the expression of genes within astrocytes that are involved in neurotransmitter clearance and cytoskeletal reorganization, suggesting that periodic, coordinated neuron-astrocyte calcium signaling during development promotes the structural and functional maturation of astrocytes within sound processing circuits.

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Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P157.08

Topic: B.11. Glial Mechanisms

Support: NIH Grant AG029493
NIH Grant C03RR0306551
East Tennessee State University Research Development Committee-Major Grants Program

Title: Female-specific role of ciliary neurotrophic factor in the medial amygdala in regulating chronic stress responses

Authors: *C. JIA[1], D. W. GILL[2], C. LOVINS[2], R. W. BROWNS[2], T. HAGG[2];
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Abstract: Ciliary neurotrophic factor (CNTF) is produced by astrocytes and is known for its neuroprotective and neurogenic actions. Recent evidence implicates astrocytes in the regulation of stress responses. Whether CNTF affects stress responses is unknown. We previously identified a striking sex-specific effect of CNTF on stress-coping behavior in the forced swim test. CNTF promotes passive stress coping, i.e., immobility time, in female mice while reducing it in males. Female mice have higher levels of CNTF in the amygdala than males, suggesting the CNTF effect may be through mechanism(s) involved in the amygdala. Here, we further defined the region-specific CNTF effect within the amygdala. CNTF neutralizing antibody was stereotaxically injected into the medial, central or basolateral amygdala of female and male C57BL/6 mice. CNTF antibody reduced intracellular signaling of STAT3 (Y705), which is downstream of CNTF, at 24 and 48 h post-injection. Injecting CNTF antibody in the medial

amygdala reduced immobility time in the forced swim test at 24 h post-injection in female but not male mice, or in the central or basolateral amygdala. These data reveal a female-specific effect of CNTF in the medial amygdala on promoting passive stress-coping behavior. To test the roles of CNTF in chronic stress responses, we performed 4 weeks of chronic unpredictable stress (CUS) in female and male wild type CNTF+/+ compared to CNTF-/- littermate mice. In females, CUS increased passive stress-coping in the forced swim test and reduced sucrose preference in CNTF+/+, but not CNTF-/-, mice. Following CUS, a 5 min of immobilization restraint induced plasma corticosterone in female CNTF+/+ but not CNTF-/- mice. These CUS effects were also found in male mice but without genotype differences. Further, CUS increased CNTF expression in the medial amygdala of female but not male mice. CUS did not alter CNTF in the female hippocampus and hypothalamus. These data suggest a female-specific role of CNTF in promoting chronic stress-induced stress-coping deficit, behavioral anhedonia and neuroendocrine response, which could be involved in the medial amygdala. No CNTF-specific roles were found in the exploratory behavior and sensory-motor function measured by the elevated T-Maze and pre-pulse inhibition tests, respectively, in both female and male control and CUS mice. This suggests that a different mechanism other than CNTF may underlie these behaviors. Together, this study reveals a novel CNTF-mediated female-specific mechanism in stress response and points to opportunities for female-specific treatments for stress-related disorders, e.g. CNTF inhibitors or antagonists.

Disclosures: C. Jia: None. **D.W. Gill:** None. **C. Lovins:** None. **R.W. Browns:** None. **T. Hagg:** None.

Poster

P157. Astrocytes: Roles in Circuit Function and Behavior

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Program #/Poster #: P157.09

Topic: B.11. Glial Mechanisms

Support: NIH Grant 5R01NS047325-15
Funding from PKU 2019M660306

Title: Astrocytic calcium modulates cortical neuronal activity during the REM sleep-wake transition

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[1]Skirball Inst., New York Univ. Langone Med. Ctr., New York, NY; [2]Peking Univ. Shenzhen Grad. Sch., Shenzhen, China

Abstract: Recent studies have suggested that astrocytes play an important role in modulating sleep duration and pressure. To better understand the role of astrocytes in sleep regulation, we performed in vivo two-photon Ca^{2+} imaging of cortical astrocytes while monitoring animals' sleep-wake cycles. We observed highly synchronized Ca^{2+} activity in astrocytes using AAV5-gfaABC1D-cyto-GCaMP6f across different cortical regions immediately after REM sleep. This increased astrocytic Ca^{2+} was independent of animals' locomotion activity. Simultaneous recording of astrocyte and pyramidal neuronal Ca^{2+} showed that this increase in astrocytic Ca^{2+} was associated with a decrease in neuronal activity during the REM-wake transition. When astrocytic Ca^{2+} was suppressed by using IP3R2 KO mice, bath application of prazosin or chemogenetic manipulation, we observed increased activity of pyramidal neurons during this

transition period, under both resting and forced running conditions. Together, these findings reveal a role of astrocytes in transiently reducing cortical neuronal activity during the REM sleep-wake transition, which may reduce information processing before the brain switches to a fully awakened state.

Disclosures: B. Lai: None. **W. Gan:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.01

Topic: C.03. Parkinson's Disease

Support: Supporting Talent in ReSearch Unipd (https://www.unipd.it/en/stars-grantee-greggio)

Title: The parkinson's disease kinase lrrk2 orchestrates dendritic spines dynamics via bdnf signaling pathway

Authors: *G. TOMBESI[1], G. FAVETTA[1], A. MARTE[2], I. BATTISTI[1], S. COGO[3], L. IANNOTTA[1], N. PLOTEGHER[1], G. ARRIGONI[1], F. ONOFRI[2], E. GREGGIO[1];
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Abstract: Dendritic spines (DS) are small protrusions originating from neuronal dendrites. These structuresconstitute the postsynaptic element of excitatory synapses and possess the ability to change theirnumber, density and morphology within short timeframes, representing highly dynamic and plasticelements. DS are particularly rich in some classes of neurons, such as medium spiny neurons (MSNs),the most abundant cell type in the striatum. In this brain region, which receives dopaminergicprojections from the substantia nigra pars compacta, the structural plasticity of dendritic spines isinfluenced by brain derived neurotrophic factor (BDNF). Accumulating evidence indicates thatsynaptic vulnerability, including alterations in DS, is a common feature of neurodegenerativedisorders. In Parkinson's disease (PD) synaptic dysfunction is an early event that precedes neuronaldeath and disease clinical manifestation.Starting from the well-established role of the PD-associated kinase LRRK2 at the synapse, here weinvestigated the possible link between LRRK2 and BDNF signaling in regulating DS dynamics. Byperforming Golgi-Cox staining, immunofluorescence and electron microscopy analysis on striatalbrain slices, we carried out a longitudinal characterization of striatal synapse morphology, numberand ultrastructure in developing, mature and aged brains of Lrrk2 wild-type and knockout (KO) mice.One-month old Lrrk2 KO mice display an increased amount of immature DS and reduced synapticcontacts, an effect that disappears in older animals. From the functional point of view, we collectedevidence that LRRK2 phosphorylation at Ser935 is quickly increased upon BDNF stimulation indifferentiated SH-SY5Y neuroblastoma cells and primary mouse neurons. Conversely, primary LRRK2KO neurons display attenuated BDNF signaling (ERK1/2 and AKT phosphorylation) and bluntmorphological response to 24 hour-BDNF treatment, which fails to promote the formation of newsynaptic contacts as it occurs in WT neurons. An unbiased proteomic analysis suggested that severalLRRK2 interactions are re-shaped upon 15 minutes of BDNF stimulation, providing

further evidenceof a functional involvement of LRRK2 in BDNF signaling. Of note, we found that two mouse modelscarrying the most common LRRK2 PD mutation (knockin G2019S and BAC overexpressing murineLrrk2 G2019S) display morphological alterations of striatal spine morphology during aging, furthersupporting a mechanism whereby LRRK2 activity is important in synaptic structure and function.Overall, our data uncovered a novel role for LRRK2 in orchestrating spine dynamics via the BDNFsignalling pathway.

Disclosures: G. Tombesi: None. **G. Favetta:** None. **A. Marte:** None. **I. Battisti:** None. **S. Cogo:** None. **L. Iannotta:** None. **N. Plotegher:** None. **G. Arrigoni:** None. **F. Onofri:** None. **E. Greggio:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.02

Topic: C.03. Parkinson's Disease

Title: Highly potent LRRK2 inhibitors show different potencies, kinetic properties and cellular activities on WT vs. G2019S LRRK2

Authors: A. SAVA[1], C. GRIFFANTE[1], L. MENGATTO[1], E. TORCHIO[1], ***L. CABERLOTTO**[1], H. J. CARLISLE[2];
[1]Aptuit, an Evotec company, Verona, Italy; [2]ESCAPE Bio, San Francisco, CA

Abstract: Genetic and biochemical evidence support the hypothesis that elevated LRRK2 kinase activity is pathogenic in familial *LRRK2* Parkinson Disease (PD) and potentially in sporadic PD, suggesting that LRRK2 kinase inhibitors may have broad therapeutic value for PD. In this study, we characterized the biochemical activity, binding affinity, and cellular potency of four widely studied LRRK2 inhibitors (MLi-2, PFE-360, GNE-7915 and LRRK2-in-1) on both the wild type (WT) and pathogenic G2019S LRRK2 isoforms. Biochemical tests were carried out using purified truncated human LRRK2 enzymes. Inhibition of LRRK2-mediated phosphorylation of the peptide substrate, LRRKtide, was assessed using an HTRF assay. To overcome the lower limit of inhibitor potency detection, which is defined by the concentration of LRRK2 in the reaction, the Morrison equation for tight binders was applied to obtain functional pK_i values for picomolar potent compounds. From these biochemical studies, MLi-2 and PFE-360 were greater than 8 fold more potent on WT compared to the G2019S isoform, whereas GNE-7915 and LRRK2-in-1 showed comparable potencies at the two isoforms. To obtain kinetic parameters of the binding interaction between compounds and enzymes, the association of the Kinase Tracer 236 was followed in the absence or presence of inhibitor and analysed with the Motulsky & Mahan method. Interestingly, MLi-2 and PFE-360 also showed longer binding residence times on the WT isoform ($t_{1/2}$=38 min for MLi-2 and 23 min for PFE-360) compared to G2019S isoform ($t_{1/2}$=27 min for MLi-2 and 5 min for PFE-360). Cellular activity assays were carried out in HEK-293 cells overexpressing WT or G2019S LRRK2 after two hours incubation with compound. Inhibition of phosphorylation at S935 was assessed with a Cisbio HTRF kit following manufacturer instructions. Inhibition of the S1292 autophosphorylation site was assessed using Meso Scale Discovery technology. In WT LRRK2 cells, GNE-7915 and LRRK2-in-1 inhibited the pS1292 site more potently than the pS935 site (pS1292 IC50 =20 nM for both

compounds, pS935 IC_{50}=160nM for GNE-7915, pIC_{50}= 100 nM for LRRK2-in-1) while MLi-2 and PFE-360 showed similar potencies at the two phosphorylation sites. In G2019S LRRK2 cells, potencies at pS935 and pS1292 were aligned. In conclusion, these results suggest that the highly potent LRRK2 inhibitors MLi-2 and PFE-360 have differential activities and kinetic binding properties on WT vs. G2019S LRRK2. Furthermore, a differential inhibition of the pS935 and pS1292 sites on WT LRRK2, as observed with GNE-7915 and LRRK2-in-1, suggests that the two phosphorylation sites might be differently modulated by LRRK2 inhibitors.

Disclosures: A. Sava: None. **C. Griffante:** None. **L. Mengatto:** None. **E. Torchio:** None. **L. Caberlotto:** None. **H.J. Carlisle:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.03

Topic: C.03. Parkinson's Disease

Support: FAR 2020

Title: Constitutive silencing of LRRK2 kinase activity leads to early glucocerebrosidase deregulation and late impairment of autophagy in vivo

Authors: *F. ALBANESE[1], D. MERCATELLI[1], L. FINETTI[2], G. LAMONACA[3], S. PIZZI[3], G. BERNACCHIA[2], M. MORARI[1];
[1]Dept. of Neurosci. and Rehabil., [2]Dept. of life Sci. and biotechnology, Univ. of Ferrara, Ferrara, Italy; [3]Istitute for Biomedicine, Eurac Research-Affiliated Inst. of the Univ. of Lübeck, Bolzano, Italy

Abstract: Impairment of the autophagy-lysosome pathway (ALP) causes aberrant protein accumulation, a common feature of Parkinson's Disease (PD). Mutations in leucine-rich repeats kinase 2 (LRRK2), among which p.G2019S is the most prevalent, are associated with familiar and sporadic PD. Dysregulation of ALP has been proposed as a mechanism underlying LRRK2-related PD. Therefore, the role of LRRK2 in ALP regulation, its kinase- and age-dependence and relation with pSer129 α-synuclein inclusions were investigated *in vivo*. Striatal ALP markers were analyzed by Western blotting in 3 and 12-month-old LRRK2 G2019S knock-in mice (bearing enhanced kinase activity), LRRK2 knock-out mice, LRRK2 D1994S knock-in (kinase-dead) mice and wild-type controls. Chloroquine (CQ), a lysosomotropic agent, was administered to block the autolysosomes formation and, thus, measure the autophagic flux *in vivo*. Quantitative Real-time PCR was used to quantify the transcript levels of key ALP genes. The activity of the lysosomal enzyme glucocerebrosidase was measured using enzymatic assay. Immunofluorescence analysis was used to study the expression of LC3B puncta and pSer129 α-synuclein inclusions in striatal MAP2-positive and nigral TH-positive neurons. No differences in macroautophagy and chaperone-mediated autophagy markers were observed among genotypes at 3 months of age. Conversely, increase of LC3-I, p62, LAMP2 and GAPDH levels, decrease of p-mTOR levels and downregulation of *mTOR* and *TFEB* expression was observed in 12-month-old kinase-dead mice. Upon CQ administration, LC3-II/LC3-I ratio was reduced, suggesting a defective autophagic flux. G2019S

knock-in mice showed LAMP2 accumulation and a significant downregulation of several ALP genes: *MAP1LC3B*, *LAMP2*, *mTOR*, *TFEB* and *GBA1*. Both LRRK2 knock-out and kinase-dead mice displayed an increase in the striatal glucocerebrosidase activity at 3 and 12 months. *GBA1* expression was reduced only in 12-month-old G2019S knock-in mice. Immunofluorescence revealed no correlation between LC3B puncta accumulation and pSer129 α-synuclein inclusions in striatal and dopaminergic neurons of LRRK2-mutant mice. We conclude that LRRK2 kinase activity inhibits striatal glucocerebrosidase activity *in vivo*. Early deregulation of GCase activity precedes a late impairment of macroautophagy and chaperone-mediated autophagy in the striatum of mice devoid of LRRK2 kinase activity. In G2019S knock-in mice, striatal pSer129 α-synuclein accumulation observed under basal conditions appear unrelated to autophagy impairment.

Disclosures: F. Albanese: None. **D. Mercatelli:** None. **L. Finetti:** None. **G. Lamonaca:** None. **S. Pizzi:** None. **G. Bernacchia:** None. **M. Morari:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.04

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation
Alexander and Eva Nemeth Foundation

Title: Phosphorylated Rab12 reveals activity of the Parkinson's disease-related LRRK2 kinase in the Nucleus Basalis of Meynert.

Authors: *V. G. CHITTOOR-VINOD[1], ***J. SINGH**[2], N. NIKULINA[2], S. BUKHARI[1], P. CHU[1], C. GAJERA[1], O. BRAUBACH[1], T. MONTINE[1], J. NICHOLS[1], J. NICHOLS[1];
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Abstract: The Leucine Rich Repeat Kinase 2 (LRRK2) protein kinase is a large bifunctional enzyme with both GTPase and kinase activities. Mutations in the *LRRK2* gene are the most common familial genetic predisposition for Parkinson's disease (PD). LRRK2-PD patients present clinically similar to idiopathic PD (iPD) patients. All pathogenic mutations of LRRK2 increase their kinase activity against exogenous and endogenous substrates. Biochemical studies have identified a subset of Rab GTPases as bone fide substrates of LRRK2, that are hyperphosphorylated by LRRK2 PD mutants. The prevailing hypothesis is that LRRK2-PD mutant linked hyperphosphorylation of substrates underlies the onset of LRRK2 PD; due to clinical overlap, it is suspected that similar molecular pathogenicity may underly iPD. This presents two questions: 1) Where in the human brain and what type of cells exhibit LRRK2 signaling? and 2) Is LRRK2 kinase-related signaling enhanced in LRRK2 PD and/or iPD. To address in which brain region and cell type exhibit LRRK2 kinase signaling, we established immunocytochemical and immunohistochemical assays to detect substrate Rab phosphorylation in human autopsy brains. Though much work has elucidated the functional impact of Rab phosphorylation by LRRK2, we still lack spatial and cellular resolution of signaling events in the disease. In this study we examined the

LRRK2◊Rab12 signaling axis, in which Rab12 is phosphorylated by LRRK2 on Ser106. We validated a recombinant rabbit monoclonal antibody against Rab12 pSer106 in immunocytochemistry for responsiveness to genetic and pharmacological modulators of LRRK2 kinase activity, and found a strong correlation of pRab12 with LRRK2 kinase function. We next surveyed regions from throughout the human brain and found that although total Rab12 was detectable in multiple brain regions, pRab12 was only detected in the Nucleus Basalis of Meynert (NBM). Highly-multiplexed fluorescent imaging with the CODEX imaging technology was used to further correlate the localization of pRab12 in ChAT-positive cholinergic neurons of the NBM. Other regions, including substantia nigra which is a critical region in PD pathology, lack prominent pRab12 immunoreactivity across all of the experiments conducted here. We established ICC, IHC and CODEX multiplex imaging techniques to observe LRRK2 signaling in autopsy brains, and identified the NBM as a prominent site of LRRK2àRab12 signaling. The NBM is a region implicated in cognitive dysfunction in AD and PD. Thus, our study offers a potential link between PD-associated LRRK2 mutation and cognition, through Rab12 phosphorylation.

Disclosures: V.G. Chittoor-Vinod: None. **J. Singh:** A. Employment/Salary (full or part-time):; Akoya Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Akoya Biosciences. **N. Nikulina:** A. Employment/Salary (full or part-time):; Akoya Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Akoya Biosciences. **S. Bukhari:** None. **P. Chu:** None. **C. Gajera:** None. **O. Braubach:** A. Employment/Salary (full or part-time):; Akoya Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Akoya Biosciences. **T. Montine:** None. **J. Nichols:** None. **J. Nichols:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.05

Topic: C.03. Parkinson’s Disease

Support: NIH T32 AG020506
NIH R01 NS097901
Michael J Fox Foundation

Title: Function of LRRK2 in striatal cholinergic interneurons

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Abstract: Leucine-rich-repeat kinase 2 (LRRK2) mutations represent the most common monogenetic form of Parkinson’s disease (PD). The clinical similarity between LRRK2-linked and idiopathic cases suggests that LRRK2 mutations are a useful and valuable tool for understanding PD in general. LRRK2 is significantly enriched in spiny projection neurons (SPNs) in the dorsal striatum, in contrast to the

relatively low expression in midbrain dopaminergic neurons that degenerate and die in PD. Prior to the onset of overt neurodegeneration, LRRK2 mutations reduce evoked dopamine release from midbrain dopamine neurons and disrupt the glutamatergic synaptic inputs onto spiny projection neurons. Meanwhile, data from rodent models suggest that striatal cholinergic interneurons (CINs) are specifically vulnerable to LRRK2 mutation, and clinical evidence indicates cholinergic abnormalities in LRRK2-linked PD. We therefore sought to determine whether LRRK2 mutations influence the physiology of striatal CINs.
We first confirmed that LRRK2 is expressed in striatal CINs by immunostaining for LRRK2 and choline acetyltransferase (ChAT). We then investigated LRRK2 function in CINs by generating cholinergic-neuron-specific conditional Lrrk2 knockout and LRRK2-R1441C knock-in mouse lines generated by a crossing ChAT-Cre driver line to Lrrk2-Floxed and Rosa26 LRRK2-R1441C lines, respectively. Controls were generated by crossing ChAT-Cre mice to wild-type mice. We used AAV delivery of a Cre-dependent EGFP construct to target CINs for experiments in ex vivo brain slices. Experiments were performed on adult (8-16 weeks old) mice of both sexes. We found no differences in resting membrane potential, input resistance, action potential shape, sag potential, or excitability. R1441C overexpression increased the magnitude of the slow afterhyperpolarization . Dopamine and acetylcholine function in the striatum are tightly linked, as nicotinic acetylcholine receptors on dopaminergic terminals allow CINs to stimulate local dopamine release. Therefore, ongoing work will determine the effect of LRRK2 on neurotransmitter release using virally encoded optogenetics to target cholinergic neurons and virally encoded fluorescent sensors to measure extracellular acetylcholine and dopamine.
Overall, our data show that LRRK2 does not affect the membrane properties of cholinergic interneurons that determine their excitability and tonic activity. Future experiments will study the LRRK2-mediated neurotransmitter release from CINs and determine whether LRRK2 in CINs affects acetylcholine and acetylcholine-evoked dopamine release in the striatum.

Disclosures: P. Skelton: None. **C. Chen:** None. **Y. Kozorovitskiy:** None. **L. Parisiadou:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

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Program #/Poster #: P255.06

Topic: C.03. Parkinson's Disease

Support: R01 NS107512 NINDS
Michael J Fox Foundation 019048
FBI Sundaram Scholar Award

Title: Neural mechanisms driving comorbid Parkinson's and melanoma

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Abstract: Epidemiological studies have shown that people with Parkinson's disease (PD) have a significantly higher risk of developing melanoma and vice-versa. However, research on this comorbidity is sparse. One possible point of convergence lies in the sympathetic nervous system. Studies show that activating sympathetic axons residing in breast adenocarcinomas increases cancer growth and metastasis. Extending this, our preliminary data suggest that mice implanted with melanoma allografts and carrying a knock-in LRRK2-G2019S mutation, one of the most common genetic contributors to PD, have enriched populations of sympathetic axons in their tumor microenvironment. Therefore, we hypothesize that a PD environment produces an altered melanoma response by regulating the activity and innervation of sympathetic axons in the tumor microenvironment. To investigate this, we are characterizing melanoma progression and its neural microenvironment in WT and LRRK2-G2019S-knock in (GSKI) mice. The preliminary data show that the extent and pattern of melanoma growth is altered significantly in GSKI mice and that tumors have altered patterns of innervation and macrophage infiltration. These and additional data will be used to establish conditions and timing for testing whether LRRK2-G2019S-mediated alterations in melanoma growth lie downstream of local sympathetic axonal activity and to ascertain whether positive results can be reversed by LRRK2 kinase inhibition, which is significantly elevated with the G2019S mutation. Studying the downstream effects of sympathetic axonal activity and innervation in a tumor microenvironment will create a fuller understanding of the neural mechanisms connecting PD and melanoma.

Disclosures: P. Del Valle: None. **J. Di Martino:** None. **G.W. Huntley:** None. **J.J. Bravo-Cordero:** None. **D.L. Benson:** None.

Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.07

Topic: C.03. Parkinson's Disease

Support: R01NS097901

Title: Pathogenic LRRK2 mutations differentially regulate synapse structure and function in spiny projection neurons

Authors: *C.-Y. CHEN[1], G. SOTO[2], V. DUMRONGPRECHACHAN[2], N. M. BANNON[2], S. KANG[1], C. SMITH[1], Y. KOZOROVITSKIY[2], L. PARISIADOU[1];
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Abstract: Leucine-rich repeat kinase 2 (LRRK2) has a critical role in both inherited and idiopathic forms of Parkinson's disease (PD). LRRK2 is highly expressed in the spiny projection neurons (SPNs) of the striatum. Evidence suggesting a critical role for LRRK2 in regulating glutamatergic excitatory synaptic activity. Our previous findings showed that LRRK2 contributes to glutamatergic synaptic functions by directing PKA signaling events in SPNs, which resulted in altered GluA1 synaptic incorporation in the striatum of R1441C mice. To access how the two most common pathogenic mutations (R1441C and

G2019S) alter the structure and function of individual synapses on direct (d-) and indirect (i-) pathway SPNs, we conducted subcellular fractionation biochemistry super-resolution imaging and 2-photon glutamate uncaging of R1441C and G2019S knock-in mice. This study showed that R1441C but not G2019S dSPNs had altered synaptic GluA1 receptor distribution and larger single-spine glutamate uncaging-evoked ESPCs. Our data provide a coherent framework for understanding how the two distinct *LRRK2* pathogenic mutations selectively alter excitatory synaptic function in specific cell types.

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Poster

P255. LRRK2 Mechanisms, Targets, and Pathways

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P255.08

Topic: C.03. Parkinson's Disease

Title: Treatment of rotenone-induced Parkinsonism in G2019S*LRRK2 knock-in rats with LRRK2 inhibitor PF-06685360

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Abstract: Parkinson's disease (PD) is a disorder characterized by loss of substantia nigra pars compacta (SNpc) dopamine neurons that innervate the striatum. Mutations in *LRRK2* that increase kinase activity, exemplified by the G2019S variant, are associated with PD pathogenesis. Recent work suggests pharmacological inhibition of LRRK2 kinase activity reduces the neurodegenerative effects of toxin-induced Parkinsonism in rodents. We developed a rotenone-exposure model in G2019S*LRRK2 knock-in rats, and evaluated the potential neuroprotective properties of the LRRK2 kinase inhibitor PF-06685360 (PF360). Rotenone injections (2.8 mg/kg s.c. SID) in 5-6 month old male rats produced rapid onset of PD-like motor and postural symptoms, and loss of nigrostriatal tyrosine hydroxylase (TH, dopaminergic neurons). We applied our rotenone exposure procedure and investigation to male and female 13-15 month old G2019S*LRRK2 knock in rats (homozygous, heterozygous, and wild-type), with daily exposure to rotenone (2.0 m/kg s.c. SID) and treatment with PF360 (10 mg/kg p.o. BID). PF360 treatment inhibited pS935 LRRK2 in the striatum, confirming target engagement. Rotenone caused gait and locomotor deficits not corrected by PF360 treatment. Rotenone increased neurofilament light chain amounts in CSF which was reduced by PF360 in WT and G2019S homozygous males. Rotenone induced TH loss in striatum and SNpc. PF360 partially protected striatal TH loss in wild-type and heterozygous rats, but exacerbated TH loss in homozygous rats. Rotenone caused mild TH loss in male rat SNpc across all genotypes, which was partially suppressed by PF360. This report highlights animal model utility for detecting neuroprotective efficacy and genetic interactions.

All studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed.

Disclosures: M.K. Schultz: A. Employment/Salary (full or part-time):; GlaxoSmithKline. **G.A. Logan:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **S.L. Agrapides:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **J. Beavers:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **K.M. Dougherty:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **A.E. Zacco:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **T.M. Graczyk:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **Y. Pang:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **C.A. Caswell:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **F.D. Tattersall:** A. Employment/Salary (full or part-time):; GlaxoSmithKline.

Poster

P374. Spinal Circuits: Models and Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P374.01

Topic: D.02. Somatosensation

Support: 1R01NS092875

Title: Sensitrak Performs Reproducible Measurements of Rat Forepaw Sensory Function

Authors: D. YOO[1], *A. RAMAMURTHY*[1], J. LEE*[1], A. M. SLOAN[2], J. B. CARMEL[1];
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Abstract: There are currently no turnkey systems for behavioral testing and assessment of forelimb touch and loss of function. We developed SensiTrak, a semi-automated system that quantitatively assesses the sensitivity of rodents to vibration applied to the forepaw. Rats are trained to hold a lever and release it once they feel a vibration (a go/no-go task). The vibration duration is altered to determine the threshold for detection. Baseline criteria are met when rats reach: a true positive rate of at least 80%, a false alarm rate (releasing the lever during no stimulus trials) below 25%, and a steady increase in detection ability with longer stimulus durations. Rat performance is assessed by calculating the 50% threshold representing the vibration duration at which rats correctly identify the stimulus 50% of the time. Our rats achieved the 50% threshold at a stimulus duration of 21 +/- 6ms (3 to 5 stimuli at a frequency of 166 Hz). To determine the rat's sensitivity to vibration, we plot the response rate and the response time against the vibration length at 11 stimulus points. The resulting sigmoidal-shaped psychophysical profiles allow for reproducible sensory thresholds with good inter and intra-subject reliability. We found after testing seven rats, this task can operantly condition rats in 8 weeks to perform 50 outcome trials over 30-minute sessions with average hold times of 7-8 seconds. In addition to this relatively narrow range between rats, each rat showed stability within their respective thresholds as far out as 25 weeks after beginning testing. Control experiments including dampening materials, auditory masking, and injury/inactivation of sensory tracts suggest that this is a test of paw somatosensation and not auditory function. Backed by these results,

SensiTrak is a reliable measure of somatosensation in rats. Future studies will test the utility of this system for mice and other sensory modalities like proprioception and texture discrimination.

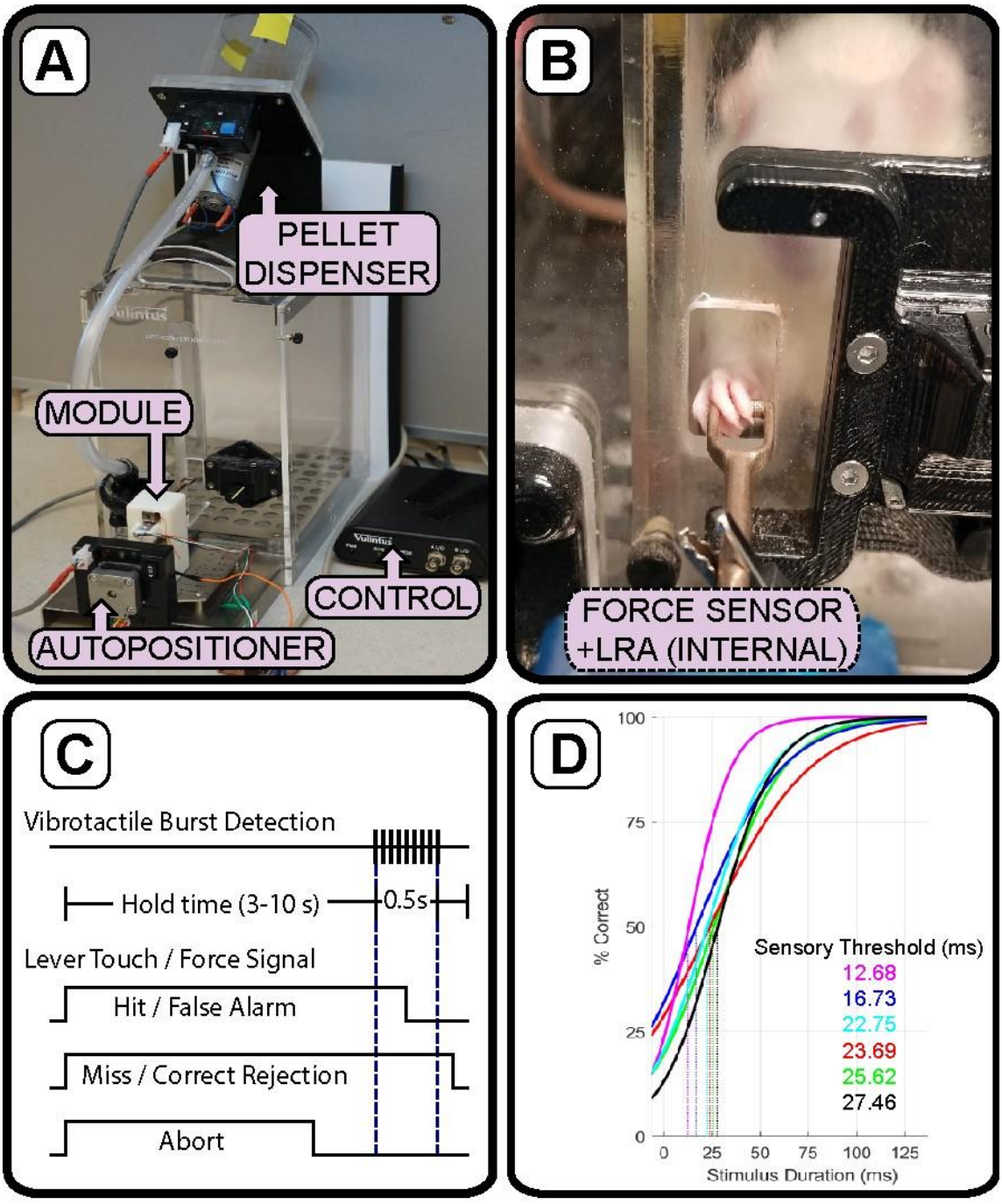


Figure: **A)** Sensitrak Hardware setup
B) Rat performing vibrotactile descrimination task
C) Variety of outcomes available for task
D) Reproducibility: 50% sensory thresholds, n=7

Disclosures: D. Yoo: None. **A. Ramamurthy*:** None. **J. Lee*:** None. **A.M. Sloan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.M. Sloan is CEO of Vulintus, Inc., a for-profit company which is developing products based on this work. **J.B. Carmel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jason Carmel is a co-inventor of a patent for the use of softening spinal electrodes. He also has equity in Backstop Neural, which seeks to commercialize the devices devices for humans..

Poster

P374. Spinal Circuits: Models and Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P374.02

Topic: D.02. Somatosensation

Support: NIMH Grant F32MH120873
NIMH Grant RF1MH121539

Title: Jaw movement-modulated activity of sensory neurons in the mesencephalic trigeminal nucleus during a directional licking task

Authors: *W. P. OLSON[1], M. VASS[1], V. B. CHOKSHI[2], D. H. O'CONNOR[3];
[1]Dept. of Neuroscience, Krieger Mind/Brain Inst., [2]Biol., Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Neurosci., The Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: While the activity of muscle spindle (MS) sensory afferents is known to be modulated by position and movement of the body, the movement coding of these neurons remains poorly defined in the context of voluntary behavior. Here, we record from MS afferents innervating the jaw musculature (located in the mesencephalic trigeminal nucleus, MEV) of mice performing a directional licking task. In this task, head fixed mice are trained to lick a moving ‘port’ through an arc of seven locations surrounding the mouse’s face to receive a water reward. This task elicits jaw trajectories along three anatomical axes (dorsoventral, mediolateral, anterior-posterior) that we can track in high speed video recordings of the face. To define the sensory coding of MS afferents, we isolate single units from MEV extracellular tetrode recordings and relate their neural activity to jaw kinematics. We furthermore validate MEV expression of a set of published molecular markers for MS afferent subtypes and present a strategy for imaging long-range MEV projections in cleared skeletal-muscular face samples. Taken together, these data will allow us to better define the ways in which the rich diversity of MEV in vivo physiological responses may be built from the subtype identities and/or long-range anatomies of single MEV neurons.

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Poster

P374. Spinal Circuits: Models and Disorders

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Topic: D.02. Somatosensation

Support: NIH Grant R34NS121875 (AO)
NIH Grant R01DA023281 (LT)
FAU Brain Institute Pilot Grant Award (AO)

Title: Characterization of chronic pain-dependently activated neurons in the spinal cord

Authors: *A. OZAWA, K. TARGOWSKA-DUDA, D. PETERS, J. L. MARCUS, G. ZRIBI, L. TOLL; Dept. of Biomed. Science, Charles E. Schmidt Col. of Med., Florida Atlantic Univ., BOCA RATON, FL

Abstract: Decades of efforts in elucidating pain mechanisms, including pharmacological, neuroanatomical, and physiological studies have provided insights into how nociceptive information transmits from the periphery to the brain and the locations receiving pain signals. However, little is known about which specific stimulus-dependently activated neurons, amongst heterogeneous neural environments, discriminatively evoke the cognate pain behavior. In this study, we shed light on activated neuron populations in the spinal cord to determine chronic pain-dependently activated neuronal subsets using Fos2A-iCreER (TRAP2) mice, which allow us to monitor reporter gene expression triggered by specific pain stimuli as reference for c-Fos expression, a neural activation marker. Using TRAP2 mice crossed with Ai9 (Cre-dependent tdTomato reporter) mice, we have found a larger number of neurons chronic pain-dependently activated (pain-TRAPed neurons) in the spinal cord in spinal nerve-ligated mice compared to sham. Further neuroanatomical analyses identified different subsets of spinal neurons that were activated by distinct pain modalities (i.e., mechanical allodynia vs. heat hyperalgesia) under chronic pain conditions. In addition to the neuroanatomical analyses, we also examined the functionality of these pain-TRAPed neurons in the context of the regulation of pain behavior using chemogenetic neuronal manipulation. Selectively inhibiting pain-TRAPed neurons via hM4Di receptors (an inhibitory DREADD, Designer Receptors Exclusively Activated by Designer Drugs) significantly reduced the response to the pain stimuli associated with chronic pain originally given to the animals. Interestingly, this reduction was not observed when mice were tested on the stimuli different from the original pain stimulation given the animals. These findings support the idea that spinal neuronal ensembles underlying pain transmission undergo dynamic changes regulating selective pain transmission. Altogether, the methods established here will be useful and represent a unique opportunity to further understand the roles of pain-dependently activated neural circuits regulating specific pain behaviors.

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Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.04

Topic: D.02. Somatosensation

Support: NIH Grant 1R01AT011447
NIH Grant 3K99DE028360

Title: Transformation of spinal sensory codes in neuropathic pain

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Abstract: Pathological pain states are defined by an abnormal input-output relationship within the somatosensory system. Under normal conditions, the nociceptive outputs of acute pain perception and protective behavioral responses are evoked only by intense stimuli that threaten or cause tissue damage, while in pathological states such as neuropathic pain, the same perception is triggered by normally harmless stimuli or by no stimulus at all. A primary locus implicated in this maladaptive plasticity is the spinal dorsal horn, which integrates, processes, and relays information regarding touch, temperature, and bodily harm from peripheral sensory neurons to the brain. Our current work aims to define, at a cellular resolution, how normal dorsal horn sensory coding evolves to a pathological state during the progression of neuropathic pain. We image neuronal population activity in the spinal cord of mice genetically engineered to express GCaMP in genetically and anatomically defined populations. These populations encompass spinal projection neurons giving rise to the anterolateral tract, the primary pathway transmitting pain and thermosensory signals from spinal cord to brain. A chronically implanted spinal window permits longitudinal imaging of population responses to mechanical and thermal stimulation of cutaneous receptive fields before, during, and after induction of neuropathic pain by spared nerve injury. Our results define the normal patterns of population response to somatosensory stimuli in the superficial dorsal horn and identify dorsal horn neuronal populations displaying altered function in neuropathic pain states. This approach may reveal targets and strategies to restore normal somatic perception and treat pain.

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Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.05

Topic: D.02. Somatosensation

Support: Hungarian Academy of Sciences (MTA-TKI 242)
Hungarian National Brain Research Program (KTIA_NAP_13-1-2013-0001)

Title: Glycinergic neurons in laminae I-IV of the mouse spinal dorsal horn: morphological and neurochemical characterization

Authors: C. MIRANDA[1], H. WILDNER[3], H. U. ZEILHOFER[4], *M. ANTAL[2];
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Abstract: It is becoming increasingly evident that glycinergic neurotransmission in the spinal dorsal horn plays an important role in the development of allodynia and hyperalgesia. However, how glycinergic neurons contribute to the formation of neural circuits underlying spinal pain processing is poorly understood. The lack of this essential knowledge makes the interpretation of the role of glycinergic neurons in spinal pain processing vague. Therefore, in our present experiments we investigated the morphological and neurochemical properties of glycinergic neurons in laminae I-IV of the spinal dorsal horn using a GlyT2::CreERT2-tdTomato transgenic mouse line. Most of the glycinergic neurons were found in laminae III-IV, whereas they were only sparsely distributed in laminae I-II. We unequivocally showed that in addition to GABA-glycine neurons there are also glycine-only neurons not only in laminae III-IV but also in laminae I-II. According to their morphological properties, we divided the glycinergic neurons into 3 and 6 groups in laminae I-II and laminae III-IV, respectively. Concerning the neurochemical characterization, we found that some of the glycinergic neurons co-express parvalbumin, neuronal nitric oxide synthase, RORb and RET, but further neurochemical properties need to be investigated. Our present results can contribute to a better understanding of the role of glycinergic inhibition in spinal pain processing.

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Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.06

Topic: D.02. Somatosensation

Support: NIH Grant 5R01NS118769

Title: Identification of the spinal circuit for cooling sensation

Authors: *L. HORWITZ, C. C. HOR, R. FUNG, B. DUAN;
Dept. of Molecular, Cell. and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: A healthy internal body temperature falls within a narrow window and is dependent upon homeostatic mechanisms of thermoregulation. It is vital then to detect even the slightest change in external temperatures. While progress has been made in characterizing temperature-sensitive neurons in the periphery, the molecular identity of cool temperature-sensing neurons in the spinal cord is not well defined. Using a combination of intersectional genetic strategies and chemogenetic tools, Calbindin 1::Cre (Calb1^{+}) neurons in the dorsal horn of the spinal cord were identified as essential for innocuous cool (15 - 20˚C) but not noxious cold (below 15°C) responses in mice. These results suggesting distinct neural pathways transmit cool and cold sensations. Calb1+ neurons present a heterogenous population of excitatory interneurons in the dorsal horn, and selectively ablating or silencing Calb1+ neurons in the dorsal horn results in several behavioral deficits, including loss of punctate mechanical pain and cooling

sensation. Further molecular quantification revealed a unique subpopulation of Calb1^{+}; SOM^{-}; Calb2^{-} neurons is responsible for relaying cool environmental temperature information, whereas Calb1^{+}; SOM^{+}; Calb2^{+} spinal neurons transmit punctate mechanical pain. Our studies uncover a distinct neural mechanism by which cool but not noxious cold temperatures or mechanical pain are transmitted in the dorsal horn of the spinal cord.

Disclosures: L. Horwitz: None. **C.C. Hor:** None. **R. Fung:** None. **B. Duan:** None.

Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.07

Topic: D.02. Somatosensation

Support: NSF GRFP Grant DGE1745303
NIH R35 5R35NS097344-05
The Hock E. Tan and K. Lisa Yang Center for Autism Research at Harvard University

Title: Distinct modes of spinal cord inhibition regulate tactile sensitivity in mouse models of autism spectrum disorders

Authors: *A. TASNIM[1,3], L. OREFICE[4,2], I. ALKISLAR[1,3], A. ABDELAZIZ[1,3], D. D. GINTY[1,3]; [1]Dept. of Neurobio., [2]Dept. of Genet., Harvard Med. Sch., Boston, MA; [3]Howard Hughes Med. Institute, Harvard Med. Sch., Boston, MA; [4]Dept. of Mol. Biol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Individuals with autism spectrum disorders frequently report altered reactivity to sensory stimuli, with many individuals displaying over-responsivity to tactile stimuli. Previous work in our lab revealed that appropriate feedback (or presynaptic) inhibition (PSI) of primary somatosensory neurons is critical for normal touch reactivity in adult mice, and loss of PSI drives tactile hypersensitivity in at least some mouse models of ASD (Orefice et al., 2016). In this study we found that genetic ASD models in which feedforward inhibitory (FFI) control of sensory inputs onto spinal cord neurons is disrupted also display tactile over-reactivity in adulthood. Interestingly, using a new measure of tactile reactivity in neonatal mice, we observed that ASD models that exhibit deficits in PSI of sensory neurons are over-reactive to light touch from birth, whereas animals with disruption to FFI of spinal cord neurons show normal tactile reactivity until late stages of postnatal development. Furthermore, though both PSI and FFI are critical for regulating tactile sensitivity in adults, animals that exhibit disruptions to PSI display aberrant anxiety-like behaviors, as previously described, but the same is not observed in mice with altered spinal cord FFI. Addressing the cellular and synaptic mechanisms underlying the development of PSI and FFI of somatosensory input to the spinal cord, we find that the differences in onset of tactile hyper-reactivity as well as comorbid behavioral consequences relate to the observation that PSI and FFI in the spinal cord mature at different stages: PSI develops by late embryonic or neonatal ages, whereas FFI develops late postnatally. These findings suggest that the precise timing of altered modes of inhibition of somatosensory input to the spinal cord determines the timing of aberrant sensory reactivity, and this in turn is a critical determinant in the genesis of other, comorbid ASD-associated behaviors such as anxiety.

Disclosures: A. Tasnim: None. **L. Orefice:** None. **I. Alkislar:** None. **A. Abdelaziz:** None. **D.D. Ginty:** None.

Poster

P374. Spinal Circuits: Models and Disorders

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P374.08

Topic: D.02. Somatosensation

Support: NSERC Discovery Grant

Title: Muscle stretch reflexes assessed in real and virtual environments

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Abstract: **Research Objective and Rationale:** Altered states of fear, anxiety, and postural (i.e., balance) control occur similarly when stressed with threatening real and virtual scenarios such as standing at height. However, mechanisms underlying neuromodulation of balance control in response to heightened threat remain unknown. Here we use Noisy Tendon Vibration (NTV) applied to the Achilles with a novel wearable device to characterise somatosensory reflexes during standing in real and virtual environments. The objective of this exploratory study is to examine threat-related changes in somatosensory reflexes as a possible mechanism of fear-induced changes to postural control.**Methods:** Preliminary data was collected from five (target sample size is 20 based on previous work) healthy young adults during quiet standing in real (eyes open, eyes closed) and VR (low, high) environments. In the virtual environment, subjects stood at the edge of a platform which was elevated from ground level (low) to 6m (high). NTV (40 to 120 Hz) was delivered to the right Achilles tendon throughout 120-second trials in each condition. Hoffman's reflexes (H-reflex) were delivered prior to and immediately following NTV. Muscle activity was monitored using surface electromyography (EMG) in the soleus, medial gastrocnemius, and tibialis anterior muscles, and ground reaction forces and moments (centre of pressure) were collected. Electrodermal activity (EDA) data was collected throughout testing to gauge anxiety levels objectively. Questionnaires assessed fear and anxiety subjectively. Eyes open and VR low conditions were compared to assess postural control and reflex modulation in real vs. virtual environments. The relationships between reflex modulation and postural control with altered threat perception was examined in the eyes closed, VR low, and VR high conditions. **Results:** Early results indicate an initial enhancement of reflex coupling in the Real Eyes Closed and both VR conditions compared to Real Eyes Open. There were no group effects of VR high on the stretch reflex compared to VR low, however individual differences showed some subjects increased while others decreased coupling or demonstrated no change. Further Investigation of the relationship between fear/anxiety and reflex coupling is pending additional data. **Conclusions:** Understanding the neuromodulation of balance control and reflexes in real and virtual setting is a crucial step towards developing wearable technologies to improve neuromuscular function and reduce injury risks in vulnerable populations. This research demonstrates the ability to assess muscle stretch reflexes using a novel wearable NTV system.

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Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.09

Topic: D.02. Somatosensation

Support: NIH R01 NS091031

Title: Effects of sensory spinal injuries on the dorsal and ventral horn in the primate

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Abstract: Our work examines the effects of focal spinal injuries affecting hand function and fine dexterity. Though it is known that even small sensory injuries induce plasticity across the neuraxis, the extent of different peripheral inputs to the spinal cord, and thus their potential to contribute to post-injury recovery, remains poorly defined. Understanding this is critical for correctly interpreting clinical injury extent, outcome, and for developing effective therapeutic approaches. To address this gap in our knowledge, we determined the extent of cutaneous and muscle afferent inputs to the cord in both normal and lesioned monkeys, at a greater resolution than previously reported.

Macaques (*M. cynomolgus*) were used, and the injury model comprised a unilateral combined dorsal root/dorsal column lesion (DRL/DCL), guided electrophysiologically and affecting just digits 1-3. Six months post-lesion, cholera toxin subunit B injections (CT-B) were made into either the distal pads of digits 1-3, or related muscles (first dorsal interosseous and abductor pollicis brevis), to label inputs to the cord bilaterally, as well as motor neurons within the ventral horn. Monkeys were euthanized 8 days later and tissue processed to visualize CT-B. Immunolabeling and confocal microscopy were used to analyze terminals, cell membrane and extracellular matrix proteins, as well as neurotransmitters of interest.

In controls, cutaneous afferents from digits 1-3 terminated in the dorsal horn from C1-T2, as reported previously. Proprioceptive afferents similarly projected to the dorsal horn between C1-T2. However, these muscle injections also resulted in a more focused retrograde labeling of ventral horn motor neurons, across just 2 segments (C7-8).

In lesioned monkeys, both cutaneous and muscle inputs to the dorsal horn were drastically reduced across all segments. Primary afferents directly contacting motor neuron cell bodies (i.e. VGLUT1+ terminals), also decreased by 50%, compared with the contralateral side.

On the cell membrane of affected motor neurons, excitatory neurotransmitters, monoamine input & KCC2 receptors all showed changes following DRL/DCL, even at this relatively chronic time point. Inhibitory neurotransmission and perineuronal net integrity, in contrast, showed no significant difference from baseline. Though our findings show just a snapshot in time, they indicate dynamic changes during recovery leading to longer term consolidation. Our findings underscore the considerable impact even a small, sensory injury has on the motor machinery of the spinal cord.

Disclosures: K. Fisher: None. **J.P. Garner:** None. **C.J. Darian-Smith:** None.

Poster

P374. Spinal Circuits: Models and Disorders

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Program #/Poster #: P374.10

Topic: D.02. Somatosensation

Support: F31NS111791
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Rita Allen Foundation

Title: Cellular and molecular architecture of the macaque dorsal horn

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Abstract: The spinal cord dorsal horn is composed of a large number of interneuron populations that serve to process peripheral somatosensory information prior to relaying it to the brain via dorsal horn projection neurons. However, our understanding of the functional organization of the interneurons and therefore, of the processing mechanisms is still limited. The functional organization of the spinal cord grey matter depends, in part, on the Rexed laminae (I-X), which are generally dorsoventrally oriented, non-overlapping layers of neurons, and also, by the termination patterns of distinct classes of primary afferents. Previous metrics for defining neuronal populations within these laminae included morphology, neuronal connectivity, intrinsic firing pattern as well as the expression of general molecular markers. More recent efforts include single-cell or nucleus RNA sequencing (scRNA-seq/snRNA-seq) studies of the mouse spinal cord and a meta-analysis that attempted to reconcile the differences arising from these studies. To achieve a consensus in the cell types and their organization, for the purpose of translating rodent dorsal horn studies to humans, we performed snRNA-seq of the macaque. From this, eight major cell types were identified including oligodendrocytes, neurons, astrocytes, oligodendrocyte precursor cells, microglia, meninges, ependymal and Schwann cells. The neurons (~22% of the total cells), were sub-clustered further into discrete excitatory (GLUTs1-11) and inhibitory (GABAs1-5) clusters with novel marker genes. Mapping these computationally defined clusters using *in situ* hybridization show that they largely reside within specific laminae. We also performed a comparative analysis between dorsal horn neurons of the macaque and those of the mouse meta-analysis. Clusters of each species are highly correlated and show a similar conservation of their laminar distribution. Interestingly, sub-clustering of the macaque GABA2 and GABA4 clusters resulted in a strong correlation with two of the mouse meta-analysis derived families (groups of similar clusters)- the Rorb and Adamts5. These two molecularly

distinct clusters, which reside in laminae III-IV, may therefore have concerted functional roles. Species-specific differences were also observed in select genes, such as an enrichment of *PIEZO2*, an ion channel important for light touch and proprioception, in the macaque GLUT8 cluster. Lastly, we examined the expression pattern of the major neuropeptides in the macaque and human dorsal horn and found that their laminar distribution is highly conserved across all three species with the interesting exception of cholecystokinin.

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Poster

P414. Stimulus Feature Response Properties: Peripheral

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Program #/Poster #: P414.01

Topic: D.04. Somatosensation – Touch

Support: NINDS Grant NS122333

Title: Neural basis of active touch and stereognosis

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Abstract: Manual interactions with objects are critically dependent on tactile and proprioceptive feedback from the hand, as evidenced by severe deficits that result from deafferentation. Indeed, signals from the skin, joints, and muscles, convey information about the state of the limb, its interactions with objects, and the objects themselves to support object manipulation. Three aspects of somatosensation relevant to manual dexterity have yet to be systematically investigated. First, perhaps more than any other sensory modality, touch occurs during active movements. Despite this, the neural basis of touch has been studied almost exclusively with stimuli delivered passively to the skin. Second, proprioceptive signals carry information not only about the time-varying conformation of the hand, but also about manually applied forces. While kinematic representations have received some recent experimental attention, their kinetic (force-related) counterparts remain to be characterized. Third, stereognosis - the sense of the three dimensional shape of objects - implies the integration of tactile and proprioceptive signals. At each point of contact with the object, tactile signals convey information about the object's local contours, for example curvature and edge orientation. Cutaneous signals about local geometric features are then interpreted in the context of where the contact points are relative to one another in space, information that is conveyed by proprioceptive signals. The study of active touch, hand proprioception, and stereognosis has been hindered by technical obstacles, such as characterizing contact events and tracking hand movements with sufficient precision and reliability. To overcome these obstacles, we have developed an experimental apparatus that allows us to simultaneously measure contact events, time-varying forces and

hand postures while monkeys grasp instrumented objects of varying sizes and orientations. We recorded neural responses evoked in the hand representation of the somatosensory cortex, including Brodmann's areas 3a, 3b, 1 and 2. We then fit generalized linear models (GLM) to individual neurons from each area to assess to what degree they encode kinematic and/or kinetic variables. We also examined tactile and proprioceptive representations at the population level to assess how features of objects and our interactions with them are encoded in the central nervous system.

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Poster

P414. Stimulus Feature Response Properties: Peripheral

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Topic: D.04. Somatosensation – Touch

Support: NIH R01 NS97344
Edward R. and Anne G Lefler Center for Neurodegenerative Disorders

Title: A cutaneous mechanoreceptor and its role in the detection of slip

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Abstract: Our sense of touch depends on low-threshold mechanoreceptors (LTMRs) that innervate hairy or glabrous (non-hairy) skin and form specialized mechanosensitive endings that are intimately related to their function. Meissner corpuscle associated Aβ RA-LTMRs that innervate glabrous skin respond to forces generated during slip and are hypothesized to provide critical feedback for grip control. We developed a mouse slip assay and demonstrated that glabrous skin tactile feedback is important for maintaining stable contact with an angled ramp. Unexpectedly, we find that mutants lacking Meissner corpuscles do not have slip avoidance deficits. To identify other populations of mechanoreceptors that underlie the avoidance of slip, we performed optogenetic receptive field mapping of A-fiber neurons that innervate glabrous skin and discovered an uncharacterized class of neurons with large (1 mm^2) receptive fields. Electrophysiological recordings indicated that these neurons correspond to a class of mechanoreceptors that respond to innocuous tangential forces that stretch the skin. To gain genetic access to this population, we generated a mouse line in which Cre recombinase is inserted into the Ptgfr locus and found that it can be used to selectively label these uncharacterized glabrous skin LTMRs. Sparse genetic labeling experiments revealed that $Ptgfr^+$ neurons innervate the skin and exhibit large terminal fields that occasionally span multiple digits. Central projections in the lumbar spinal cord terminate within the LTMR recipient zone of the dorsal horn, consistent with a mechanoreceptor function. Surprisingly, $Ptgfr^+$ neuron terminals in glabrous skin are free nerve endings (FNEs) that penetrate the epidermis, an anatomical feature that is often associated with nociceptors capable of signaling damaging

stimuli. Optogenetic activation of Ptgfr$^+$ neurons in awake behaving mice failed to elicit nocifensive responses, but instead triggered a gripping motion. As slip can be avoided through tactile feedback to actively manage the shear force between the body and an object at the contact surface, we hypothesize that this uncharacterized Ptgfr$^+$ mechanoreceptor functions to detect incipient slip through its unique sensitivity to tangential forces acting on glabrous skin.

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Poster

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Title: Tactile intensity perception is shaped by temporal integration: evidence from single afferent recording and stimulation in humans

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Abstract: In glabrous hand skin, four types of fast conducting mechanoreceptive afferent encode different aspects of touch interactions, e.g. pressure, edges, velocity, textural quality. Temporal firing patterns in these afferents reveal components relating to the stimulus quality, whereas the firing rate relates to the perceived intensity. However, intensity coding breaks down for short duration stimuli (<400 ms), where vibration of equivalent magnitude is perceived as weaker for shorter stimuli. We sought to use this phenomenon to study afferent intensity coding. We used broadband vibration reflecting real world tactile interactions, and found intensity ratings dropped markedly when stimulus duration was reduced below 400 ms. However, intensity was perceived as equivalent when increasing absolute stimulus magnitude. We combined single afferent recordings in humans using microneurography, with the perceptual equivalence judgements of intensity at different durations, and used different parameters in the afferent firing as predictors of perceived intensity. Firing rate gave a poor prediction of intensity, which was instead best predicted by binned firing rate across 100 ms time windows. Preliminary evidence of the specificity of this effect was gained by electrically stimulating individual afferents, combining single unit microneurography and intraneural microstimulation. Tactile percepts were evoked by stimulating both fast-adapting type I (FA-I, n=5) and slowly-adapting type I (SA-I, n=3) afferents using comparable spike trains to vibration. At the same frequency, intensity was perceived as lower at durations below 100 ms,

but delivering the same number of impulses produced equivalence. However, in FA-II (n=2) or SA-II (n=2) afferents, intensity judgements were also reduced at longer stimulus durations (>200 ms). These data suggest that tactile perception related to intensity judgment is integrated over short time windows for SA-I and FA-I afferents, but this might be different in type II afferents. This work relates to the concept of perceptual cycles, where stimuli must be separated perceived as separate events, only when during different cycles of somatosensory cortical oscillations, suggesting intensity representation may have a similar mechanism. Knowledge of the afferent determinants of the determinants of tactile intensity perception will aid in the design of artificial tactile feedback, such as with prostheses incorporating direct nerve stimulation.

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Poster

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Topic: D.04. Somatosensation – Touch

Support: NCI Grant R21CA226726
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Title: Characterizing the tactile acuity and sensitivity of the human breast

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Abstract: In the US alone, more than 100,000 women undergo mastectomy to treat or prevent breast cancer. This procedure involves amputating all breast tissue, including the cutaneous sensory nerves that mediate breast sensation, often leading to partial or complete numbness of the breast. In an effort to develop technologies to address this loss of sensation and its downstream effects, we set out to characterize the cutaneous sensitivity of the nipple-areolar complex (NAC) of healthy, intact breasts to gain some insights as to the underlying tactile innervation. We specifically aimed to evaluate (1) the spatial acuity of the NAC and breast compared with the back and hand, and (2) the vibrotactile thresholds of the nipple, areola, and breast skin. To these ends, we designed and constructed an experimental apparatus to passively deliver well-controlled tactile stimuli to the breast and NAC while subjects performed well-established psychophysical paradigms. First, to evaluate spatial acuity, we sequentially presented two skin indentations and asked subjects to indicate whether the second stimulus was above (closer to the head) or below (closer to the feet) the first. From these measurements, we computed the spatial just-noticeable difference (JND) - the distance at which subjects can reliably perceive a change in position. We found that these JNDs are highest in the breast and NAC - more than fivefold greater than those observed in the hand, and more than double those found on the back. Furthermore, the spatial acuity decreased with increased breast size. Second, to establish the vibrotactile sensitivity of the nipple, areola,

and breast tissue, we evaluated the minimum amplitude required for subjects to detect a vibratory stimulus applied to the skin to shed light on the nature of the underlying innervation, as different classes of nerve fibers exhibit different frequency sensitivity profiles. We tested this across a broad range of frequencies and compared these detection thresholds to those of the hand. We found that, while the spatial acuity in the NAC and breast is much lower than that of the hand, the vibrotactile sensitivity is similar, implying that the breast is innervated with the same tactile nerve fibers as the hand, but at a substantially lower density.

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Poster

P414. Stimulus Feature Response Properties: Peripheral

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Topic: D.04. Somatosensation – Touch

Support: NINDS Grant R01NS089652

Title: Investigating tactile innervation and unit responses in mouse tongue

Authors: *L. ZHANG[1,2,3], D. XU[1,2,3], W. P. OLSON[1,2,3], D. H. O'CONNOR[1,2,3];
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Abstract: The mammalian tongue is richly innervated with somatosensory, gustatory and motor fibers. These form the basis of sophisticated sensorimotor functions such as the determination of object shape and texture during active touch. Despite high tactile acuity and sensitivity revealed by human studies (Trulsson & Essick, 1997)[1], the response properties and underlying innervation patterns and ending types of the tongue remain largely unknown. In this study, we found that the anterior two-thirds of the dorsum of the mouse tongue is innervated by NFH-positive myelinated afferents, consistent with prior work (Moayedi et al., 2018)[2]. Unlike gustatory afferents, which innervate only taste buds (Fei et al., 2014)[3], sensory neurons in the trigeminal ganglion (TG) innervate both the fungiform papillae that host taste buds and the filiform papillae of the tongue. By screening Cre/CreER mouse lines, we identified 2 Cre markers (Pirt-Cre and VGlut2-Cre) that labeled myelinated afferents at the tongue surface. Optogenetic stimulation of the tongue during single-unit recordings from the TG of Pirt-Cre/+; Ai32/+ mice suggests that Pirt-Cre labels tongue low-threshold mechanoreceptors (LTMRs) in TG. Interestingly, by labeling terminal Schwann cells with S100β or PLP1-EGFP, we did not find any specialized sensory end organs in the mouse tongue, but rather only free nerve endings. In contrast, we identified corpuscular end organs at the dorsum of ferret tongue by immunostaining for NFH and S100β. Single-unit recordings from anesthetized mice showed that tongue LTMRs in TG are highly sensitive to static force stimulation or stretch and have small receptive fields (RFs, around 0.1 mm^2). The tongue LTMRs recorded so far (n = 12) exhibit either an intermediately adapting (IA) property or a rapidly adapting (RA) property, with the ratio between IA and RA units being 10:2. 10 of 12 recorded units had a Von Frey threshold equal to or less than 0.4 mN, and had a receptive field located near the midline or the tip or the edge of the tongue,

with the distance between the RF center and the midline/edge of the tongue less than 0.5 mm. In contrast, a unit with an RF located at the middle region of the left side of the tongue had a higher threshold of 0.7 mN. This suggests the possibility that tongue LTMRs innervating the edge, the tip and the midline regions of the tongue may be more sensitive to innocuous mechanical stimuli compared with those innervating the middle regions.

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Poster

P414. Stimulus Feature Response Properties: Peripheral

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Program #/Poster #: P414.06

Topic: D.04. Somatosensation – Touch

Support: Innovate Calgary Grant

Title: Clinical skin sensitivity assessed using a vibration-emitting smartphone application

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Abstract: Background: Peripheral neuropathy (PN) is a neurological condition involving thegradual death of sensory and motor neurons. Measures of cutaneous sensitivity,including the Semmes-Weinstein monofilament (SWMF) test and 128 Hz tuning fork(TF) test, detect higher-than-normal perceptual thresholds to inform a clinical diagnosisof PN. Whether these assessments are capable of providing valid and reliable estimatesof perceptual thresholds remains unclear. As an alternate, detection estimates derivedfrom computerized instruments demonstrate improved precision and reliability whencompared to manual assessments.**Rationale:** Smartphones contain well controlled vibrating motors capable of assessinghigh-frequency (128 Hz) perceptual thresholds at varying amplitudes. Assessment ofvibrotactile detection along a spectrum of preprogrammed amplitudes is suitable forperception threshold estimation for varying health conditions.**Objective:** This study aims to assess the validity and reliability of the SWMF, TF, and anovel vibration-emitting smartphone application (ie, Vibratus App or VA) against thegold-standard nerve conduction studies (NCS) on a sample of healthy adults andchemotherapy-induced PN (CIPN) patients.**Methods:** Preliminary data was collected from nine healthy adults assessed for skinsensitivity during SWMF, TF, and VA testing, in addition to peripheral nerve functionobtained from NCS. SWMF and VA thresholds were determined from a twenty-trial 4-2-1 stepping algorithm. VA threshold values are described as a percentage of the totalpossible amplitude delivered by the smartphone. The timed TF method was conductedand discrepancies between rater and participant perceived duration of vibration wererecorded. NCS analysis was comprised of sensory nerve action potential (SNAP)amplitude and latency. Ongoing research will determine assessment validity andreliability on a sample of healthy young and older adults (n=60, young: 18-45y, old:+65y) and CIPN patients (n=30, +18y).**Results:** Early findings suggest that these assessment methods correctly quantifyperceptual thresholds according to health status (SWMF = 0.02 ± 0.01 g, TF = 3.52 ±2.52 s, VA = 0.27 ± 0.18 au), as determined by NCS parameters (amplitude = 62.18 ±15.2 μV, latency = 3.11 ± 0.33 ms). Individual

differences in perception have beenidentified but must be explored further to determine cut-off values for the diagnosis ofPN.**Significance**: Smartphone-based testing will allow users to self-administer neurologicalexams as often as desired, empowering them as agents in their own healthcare team.

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Poster

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Topic: D.04. Somatosensation – Touch

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Berrie Foundation Initiative on the Neurobiology of Obesity
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Title: Functional classification of tongue-innervating mechanosensory neurons based on in vivo calcium imaging

Authors: *Y. MOAYEDI[1], S. XU[3], S. OBAYASHI[4], B. U. HOFFMAN[2], G. J. GERLING[3], E. A. LUMPKIN[4];
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Abstract: Lingual mechanosensory neurons provide essential information for guiding food choice, feeding ability, and speech. Yet, little is known about the identities of neurons that contribute to these daily tasks. In our previous work, we identified putative mechanosensory endings in the tongue with novel morphologies; the functions of these neurons in sensation are not known. To identify functional classes of lingual mechanosensory neurons, we employed in vivo calcium imaging of trigeminal ganglia (n>3 male and female mice/experiment). We first investigated calcium responses of tongue-innervating trigeminal neurons to thermal and mechanical stimulation (e.g. pressure, fluid flow, temperature changes). We found that around 17% of neurons responded to pressure, and that these pressure responders were significantly larger in size than neurons that only responded to temperature changes. To further investigate the cadre of functionally distinct mechanosensory neurons, we tested responses to brushing and sustained pressures and found that brush-sensitive neurons comprise the majority of tongue-innervating mechanosensory trigeminal neurons. We next developed an unbiased multilevel K-means clustering approach to classify calcium response characteristics to pressure stimulation. This approach revealed that mechanosensory neurons displayed five distinct stimulus-response profiles to pressure. These classes include neuronal populations with sustained and transient responses to force, as well as neurons with no response or negative responses to force application. These studies lay the foundation for defining functional differences between somatosensory neurons in the tongue and how they encode tactile features of foods and contribute to oral functions.

Disclosures: Y. Moayedi: None. **S. Xu:** None. **S. Obayashi:** None. **B.U. Hoffman:** None. **G.J. Gerling:** None. **E.A. Lumpkin:** None.

Poster

P414. Stimulus Feature Response Properties: Peripheral

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P414.08

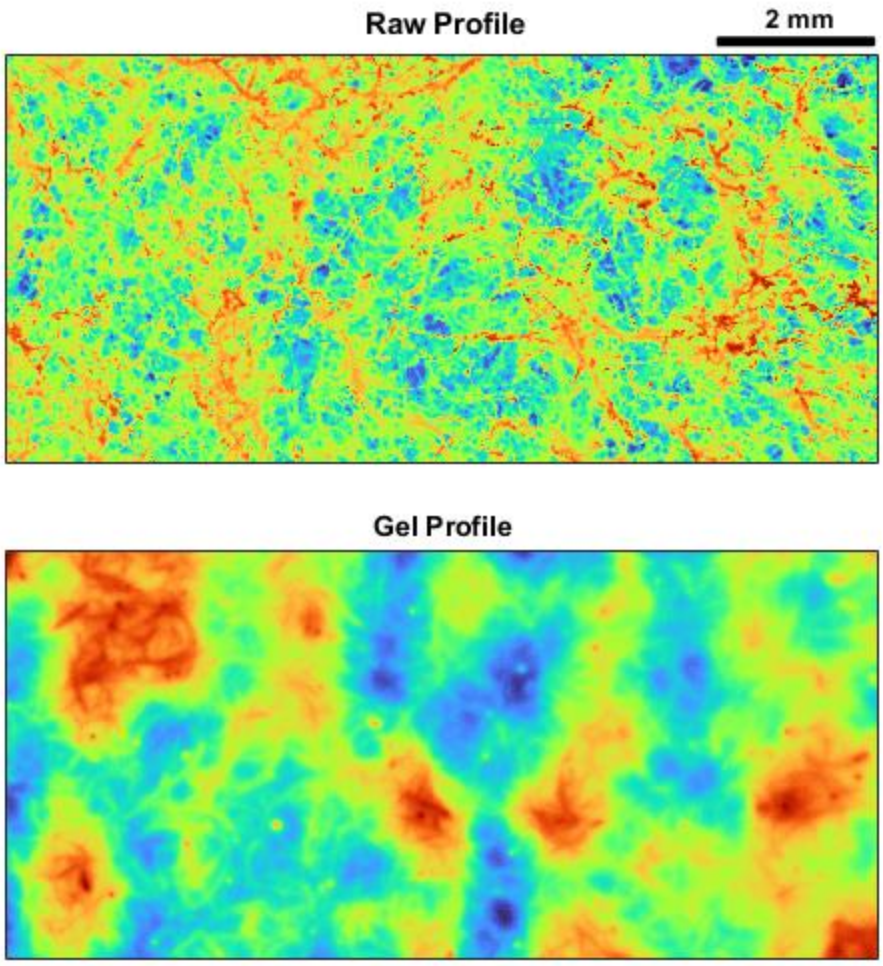
Topic: D.04. Somatosensation – Touch

Support: NINDS grant NS101325
NINDS grant NS122333

Title: Using a gel elastomer to characterize the neuromechanics of texture perception

Authors: *N. B. ORNSTEIN[1], C. M. GREENSPON[2], S. J. BENSMAIA[3];
[1]Organismal Biol. and Anat., [2]Dept. of Organismal Biol. & Anat., [3]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: We are exquisitely sensitive to texture: We can tell the difference between satin and silk and can discern features as small as 10 nanometers in size. While much is known about the neural mechanisms that mediate texture perception, the role of the skin in shaping the percept remains unclear. Surfaces often comprise compliant elements, which not only deform the skin but are themselves deformed by it, an interaction that is nearly impossible to characterize with most natural textures. It is therefore difficult to relate a textural percept and its neuronal representation to the stimulus because the latter is not suitably characterized. To overcome this problem, we constructed a silicone elastomer gel that mimics the mechanical properties of human skin. We then indent textured surfaces into this elastomer and measure the patterns of deformation produced in the elastomer using a laser profilometer. The patterns of elastomer deformation then serve as a proxy for the corresponding skin deformations, hitherto unknown. For example, fleece comprises small elements (top panel, max depth, 0.91 mm). The gel compresses those elements, revealing the corresponding skin deformations (bottom panel, max depth, 0.3 mm). We find that the measured deformations yield better predictions of psychophysical judgments of texture and better predictions of afferent responses to texture than do raw texture profiles. This study contributes to a growing literature on neuromechanics that seeks to elucidate how biomechanics shape our perception of the external world.



Disclosures: N.B. Ornstein: None. **C.M. Greenspon:** None. **S.J. Bensmaia:** None.

Poster

P414. Stimulus Feature Response Properties: Peripheral

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P414.09

Topic: D.04. Somatosensation – Touch

Support: NIH grant NS055159 (TR)
NIH grant F31NS100484 (JDR)
NIH grant F99NS113422 (JDR)

Title: Tmem120a/tacan inhibits mechanically activated piezo2 channel activity

Authors: J. S. DEL ROSARIO, **M. GABRIELLE**, Y. YUDIN, *T. ROHACS;
Pharmacology, Physiol. and Neurosci., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: Mechanically activated Piezo2 channels are key mediators of light touch and proprioception in mice and in humans. Relatively little is known about what other proteins regulate Piezo2 activity in a cellular context. TMEM120A (TACAN) was proposed to act as a high threshold mechanically activated ion channel in nociceptive dorsal root ganglion (DRG) neurons. Here we find that TMEM120A co-expression robustly reduced mechanically activated Piezo2 currents, but did not inhibit mechanically activated Piezo1 and TREK1 currents. TMEM120A co-expression did not affect cell surface expression of either Piezo1 or Piezo2 and it did not have major effects on the cortical actin or tubulin cytoskeleton. TMEM120A expression alone did not result in the appearance of mechanically activated currents above background. In addition, TMEM120A and Piezo2 expression in DRG neurons overlapped, and siRNA mediated knockdown of TMEM120A did not decrease the proportion of slowly adapting mechanically activated currents, but resulted in an increased proportion of rapidly adapting currents. Our data do not support TMEM120A being a mechanically activated ion channel, and identify it as a negative modulator of Piezo2 channel activity.

Disclosures: J.S. Del Rosario: None. **M. Gabrielle:** None. **Y. Yudin:** None. **T. Rohacs:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.01

Topic: D.07. Vision

Support: NSF Grant 1557820
NSF Grant 1557725

Title: Effects of glutamate on extracellular H+ in retinal slices of tiger salamander.

Authors: B. K. TCHERNOOKOVA[1], M. A. KREITZER[2], *R. MALCHOW[1];
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Abstract: Glutamate is thought to be the main excitatory neurotransmitter in the vertebrate retina. Powerful uptake systems are responsible for removing extracellular glutamate and terminating its effects on neuronal activity which in turn prevents excitotoxicity. We had previously shown that extracellular glutamate induces changes in extracellular H+ flux from isolated retinal Müller cells of the tiger salamander using self-referencing H+-selective electrodes. Here, we show that extracellular glutamate also induces changes in extracellular H+ from retinal slices from tiger salamander when self-referencing microelectrodes are positioned just over the outer plexiform layer (OPL). Recordings were made in a solution containing 1 mM HEPES as a pH buffer and without the added application of bicarbonate. Application of 300 μM glutamate induced a pronounced transient extracellular alkalinization followed by a sustained extracellular acidification. The glutamate uptake blocker DL-*threo*-β-benzyloxyaspartic acid (DL-TBOA) decreased the aklalinization induced by application of glutamate but not the acidification. When slices were bathed in the AMPA receptor blocker CNQX, a compound known to inhibit glutamate-

induced depolarization of second order retinal neurons, glutamate still induced an extracellular alkalinization, but the subsequent acidification event was diminished. We have previously shown that extracellular acidifications from isolated Müller cells as well as from retinal slices in response to extracellular ATP are mediated by the activity of purinergic receptors located on retinal Müller glial cells. Interestingly, the use of the P2 receptor blockers PPADS and suramin attenuates the acidification event following glutamate application, suggesting a potential role of purinergic signaling in the glutamate-induced changes in extracellular H+. The differential modulation of the biphasic response to extracellular glutamate suggests that different mechanisms govern the glutamate-induced alkalinization and acidification events, with the alkalinization likely being mediated by glutamate transporter activity and the acidification requiring activation of non-NMDA glutamate receptors.

Disclosures: B.K. Tchernookova: None. **M.A. Kreitzer:** None. **R. Malchow:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.02

Topic: D.07. Vision

Support: NIH #EY027970 issued to C. Linn

Title: Regeneration and functional ERG recovery in a mouse glaucoma model after treatment with an alpha7 nicotinic acetylcholine receptor agonist

Authors: *D. M. LINN[1], J. B. SPITSBERGEN[2], S. E. WEBSTER[2], C. L. LINN[2];
[1]Biomed. Sci., Grand Valley State Univ., Allendale, MI; [2]Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Eyedrop application of the selective α7nAChR agonist, PNU-282987, has been shown to induce bothneurogenesis and regeneration of retinal neurons in adult mammals. In this study, experiments wereperformed to evaluate structural and functionality recovery after PNU-282987 treatment in glaucoma-induced mice. Both sexes of mice (between 3 and 6 months) were injected with 1.2M hypertonic saline intothe episcleral vein to induce scarring and increase IOP. After the procedure, mouse eyes were treated oncedaily using eye drops containing 1mM PNU-282987/1mg/ml BrdU and weekly ERGs from light-adaptedanimals were recorded. At different time points, animals were euthanized, and retinas were removed,processed immunocytochemically with antibodies against BrdU and Thy 1.2, counterstained with DAPI,and viewed and analyzed using a Nikon confocal microscope. Hypertonic saline injections elicited asignificant increase in intraocular pressure four weeks post injection (an average of 15.8 mmHg ±1.2)compared to an average of 11.2 mmHg (±1.8; $p<0.05$) measured from the same animals before theprocedure. Induction of glaucoma also significantly reduced the cell density of Thy1.2+ RGCs by anaverage of 28.31% (±1.5; $p<0.05$) four weeks after injection. To assess the regenerative potential of PNU-282987, injected animals were treated with BrdU alone or with PNU-282987/BrdU. In the injected micetreated only with BrdU, no BrdU+ cells appeared despite an average loss of 30.88% (±3.4; $p<0.05$) RGCs.However, after agonist treatment following saline injection, Thy1.2/BrdU+ neurons

appeared in the GCL.After 7 days of agonist treatment, PNU-282987 significantly reduced the loss of Thy1.2+ cells associatedwith the glaucoma procedure to an average of only 12.4% (±0.8; $p<0.05$) compared to the near 30% averagethat are typically lost. Light-adapted ERG recordings from saline-injected mice exposed to PNU-282987for 3 weeks had a-wave amplitudes comparable to controls. However, significant increases in the b-waveamplitudes were recorded after glaucoma-induced animals were treated with PNU-282987 for 3 weeks byan average of 57% (±5; $p<0.05$). Peak oscillatory potentials (OP1, 2 and 3), that represent inner retinalactivity, all increased after inducing glaucoma by an average between 30 - 81% (± 14; $p<0.05$) due to PNU-282987 application. Lastly, the amplitude of the photopic negative response, which represents ganglioncell activity, significantly increased by an average of 78% (±12; $p<0.05$) after PNU-282987 treatment in
glaucoma induced animals. These are the first experiments to demonstrate regeneration and functionalrecovery in a glaucoma model using an α7 nAChR agonist.

Disclosures: D.M. Linn: None. **J.B. Spitsbergen:** None. **S.E. Webster:** None. **C.L. Linn:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.03

Topic: D.07. Vision

Support: NIH Grant T32NS105602

Title: Early diabetes-induced changes in retinal output neurons

Authors: *B. N. EBBINGHAUS, C. M. SORENSON, N. SHEIBANI, M. HOON;
Univ. of Wisconsin-Madison, Madison, WI

Abstract: Diabetes is a prevalent condition world-wide which often leads to visual impairment, a condition known as diabetic retinopathy. Retinal ganglion cells (RGCs), the output neurons of the retinal circuit undergo cell death during advanced stages of diabetic retinopathy with diabetes-induced vascular changes in the retina contributing to this process. Changes in RGCs prior to cell-death are not yet fully understood. In this study, we determined the impact of a short duration of hyperglycemia on RGC structure, function, and connectivity. We used a murine model (Ins2 Akita/+) of diabetes which spontaneously develops hyperglycemia at four weeks of age. We focused our analyses on the six-week time point (2 weeks after onset of hyperglycemia) and on four ‘alpha’ RGC subtypes that have been well-characterized in the mouse retina. We confirmed that RGC loss had not yet commenced at the time point of our analyses. Biolisitic transfections and immunohistochemistry were used to ascertain RGC morphology and synaptic distribution (excitatory and inhibitory) across RGC types. Single cell electrophysiology was used to determine RGC light response profiles. Interestingly RGC morphology and synaptic density was altered in a type-specific and region-specific manner. We also determined vascular density in the inner retina and found specific alterations at the time-point of our analyses. Thus, the early impact of diabetes is restricted to particular retinal circuits with certain subtype(s) of retinal output neurons being more susceptible to early diabetes-induced perturbations.

Disclosures: B.N. Ebbinghaus: None. **C.M. Sorenson:** None. **N. Sheibani:** None. **M. Hoon:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.04

Topic: D.07. Vision

Support: Wellcome [WT200804].

Title: An investigation of retinal and choroidal vasculature across the menstrual cycle using Swept-Source Optical Coherence Tomography

Authors: *M. E. WRIGHT[1], L. TERRY[2], S. DAVIES[1], A. CROFTS[1], J. J. STEVENTON[1], K. MURPHY[1];
[1]Cardiff Univ. Brain Res. Imaging Ctr. (CUBRIC), [2]Sch. of Optometry and Vision Sci., Cardiff Univ., Cardiff, United Kingdom

Abstract: Oestrogen has a neuroprotective effect against conditions such as dementia and glaucoma. One possible mechanism is oestrogen's vasodilatory influence on the cerebrovascular system. Considering the variation in oestrogen across a menstrual cycle, we hypothesise that changes in oestrogen hormone levels across the monthly cycle influence blood flow in both the brain and the eye.
With the increasing availability of Optical Coherence Tomography Angiography (OCT-A) for measuring retinal vasculature in clinical research, substantial changes in OCT-A derived metrics over a healthy cycle may effect clinical results. This study aims to investigate the influence of different menstrual cycle phases on retinal and choroidal vasculature using swept-source Optical Coherence Tomography (SS-OCT) and OCT-A.
The right eyes of 6 healthy, menstruating females (age mean[SD]= 22.0[2.3]; intraocular pressure mean[SD]= 12.6[3.2] mmHg; visual acuity mean[SD]= -0.1[0.1]) were tested during the early follicular (EF; day 1-4), late follicular (LF; day 10-12), and mid-luteal (ML; day 20-22) phase of their menstrual cycle. All sessions took place at the same time of day, after a fasting period of 4-6 hours. Due to the ongoing pandemic, not all participants have yet completed every phase (EF= 3; LF= 4; ML= 3).
3D macula scans were taken using a SS-OCT (Triton; TOPCON [Great Britain] Medical Limited, Newbury, UK). Choroidal thickness (inner and outer macula) was estimated by the instrument. OCT-A software in the same device was utilised to take a $3mm^2$ scan and measure retinal vascular density (superficial and deep layers); this was calculated using the ratio of vessels to non-vessels of the binarized image across a 2mm diameter ROI (centred on the fovea).
Qualitatively, choroidal thickness was thinner during the EF phase for inner (EF mean[SD]= 309.8[10.0] μm; LF mean[SD]= 329.1[56.9] μm; ML mean[SD]= 339.2[60.3] μm) and outer macula regions (EF mean[SD]= 288.3[18.8] μm; LF mean[SD]= 294.9[40.5] μm; ML mean[SD]= 302.4[44.4] μm). Vascular density was relatively stable across menstrual cycle phases for both the superficial (EF mean[SD]= 27.6[3.8]; LF mean[SD]= 27.1[2.0]; ML mean[SD]= 27.2[2.6]) and deep layers (EF mean[SD]= 33.1[4.5]; LF mean[SD]= 32.4[4.5]; ML mean[SD]= 33.3[3.4]).
These preliminary results suggest that OCT-A derived measures of retinal vascular density, in both

superficial and deep layers, are relatively stable throughout the menstrual cycle. The choroidal layer, however, appears thinnest during the EF phase, which mirrors the point of lowest oestrogen across the cycle and may provide a window into measuring cerebrovascular health.

Disclosures: M.E. Wright: None. **L. Terry:** None. **S. Davies:** None. **A. Crofts:** None. **J.J. Steventon:** None. **K. Murphy:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.05

Topic: D.07. Vision

Support: DBT, India

Title: Lipid metabolilizing genes modulate anti-vegf response in age related macular degeneration

Authors: *A. ANAND[1], K. SHARMA[2], R. SINGH[3], S. SHARMA[5], N. K. SHARMA[4];
[1]Dept. of Neurology, P.G.I.M.E.R, Chandigarh, India; [2]Neurol., [3]Opthalmology, [4]neurology, PGIMER, Chandigarh, India; [5]statistics, panjab university, Chandigarh, India

Abstract: Age related macular degeneration is a multifactorial disease. SNPs in certain genes have been associated with the disease. Wet form of the disease is treated by intra-vitreal administration of anti-VEGF injections . The response to the treatment varies among individuals depending upon unknown factors. In this study we have investigated the association between genetic variation and anti-VEGF response in AMD patients. For this study 78 AMD patients were recruited from Advanced Eye Centre, PGIMER Chandigarh. Details of Anti-VEGF treatment was noted for each patient. Blood sample was collected from the patients for isolation of serum and DNA. Retrospective record of administration of Anti-VEGF therapy was consulted for 11 patients. SNP genotyping (rs920915), LIPC (rs920915) and APOE (rs769449), pro-angiogenic genes including ADAMTS9 (rs6795735) and TIMP3 (rs5749482), regulatory genes e.g. B3GALTL (rs9542236), IER3 (rs3130783), HTRA1 (rs11200638) and SLC16A8 (rs8135665, monocarboxylic transporter protein) was done using Taqman assays and ELISA was used to estimate their proteins in Serum.We found that Alcohol intake and previous cataract surgery were modulators of Anti-VEGF response. B3GALTL and LIPC variants were associated with Anti-VEGF response in Indian AMD patients. Homozygous ‘CC’genotype of LIPC variant show enhanced expression of regulatory (HTRA1, B3GALTL and IER3), monocarboxylic transporter protein SLC16A8, and LIPC levels. We also found that APOE levels increased in patients with successive VEGF injections. The results show significance of lipid metabolizing molecules (including APOE and LIPC) in AMD which can influence the Anti-VEGF outcome in AMD patients.

Disclosures: A. Anand: None. **K. Sharma:** None. **R. singh:** None. **S. sharma:** None. **N.K. Sharma:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.06

Topic: D.07. Vision

Support: ORBITAL - European Innovative Training Network (ITN) funded by The Marie Sklodowska-Curie Actions (MSCA) in Horizon 2020. Grant agreement number: 813440
Dr. John P. and Therese E. Mulcahy Endowed Professorship in Ophthalmology (SK)

Title: Structure-function relationships in the Brown Norway rat streptozotocin-induced diabetic retinopathy model

Authors: *I. LELYTE[1,2], M. CERRADA-GIMENEZ[3], A. GHOSH[4,5], Z. AHMED[1], G. KALESNYKAS[3], S. KAJA[6,4];
[1]Inst. of Inflammation and Ageing, Univ. of Birmingham, Birmingham, United Kingdom; [2]R&D Division, Experimentica Ltd, Vilnius, Lithuania; [3]R&D Division, Experimentica Ltd, Kuopio, Finland; [4]R&D Division, Experimentica Ltd, Forest Park, IL; [5]Grad. Program in Biochem. and Mol. Biol., [6]Ophthalmology and Mol. Pharmacol. & Neurosci., Loyola Univ. Chicago, Maywood, IL

Abstract: The rat streptozotocin-induced model for diabetic retinopathy (DR) remains the most-commonly used experimental paradigm for drug discovery, as it recapitulates many of the complex phenotypes seen in patients. Advances in *in vivo* ocular imaging provide an opportunity to study early pathological processes in this model and to establish structure-function relationships. We recently performed a systematic literature review that included 662 records of preclinical STZ studies from the past 10 years. Of those, only one study was performed in pigmented rats, specifically Brown Norway (BN) rats. The BN strain is widely used in ocular drug discovery and the presence of pigmentation allows for the detection of potential confounding pharmacologic effects due to melanin binding. This highlights an urgent need for structure-function analysis of DR phenotypes in BN rats. BN rats (male, 3-4 months old) received two IP injections of STZ (65 mg/kg in citrate buffer, pH 4.5). Glucose levels and body weight were monitored twice per week. Rats were followed *in vivo* for 8-12 weeks by vitreofluorophotometry (VFP; OcuMetrics, Inc.), flash electroretinography (fERG; Diagnosys LLC), and spectral domain-optical coherence tomography (SD-OCT; Leica Microsystems, Inc.). Ocular tissues were collected for quantification of acellular capillaries and pericyte loss using trypsin digested retinal whole mounts, Evan's Blue (EB) extravasation assay and biomarker analysis. Majority of the rats developed hyperglycemia (>16 mmol/l) week 1 post-STZ ($p < 0.001$). Hyperglycemic rats presented significantly reduced body weight gain compared to the naïve rats by day 7 ($p < 0.001$). VFP showed mild progressive retinal leakage by week 3 post-STZ, which was statistically significant by week 5 ($p < 0.01$). fERG showed decreased photoreceptor responses by week 6 with increased latencies ($p < 0.05$). Inner retinal thickness measured by SD-OCT decreased by week 8-9 ($p < 0.001$). Pericyte ghosts increased significantly in diabetic animals compared to naïve rats ($p < 0.05$). EB levels in the retina showed a statistically significant increase, suggesting presence of blood-retinal barrier rupture. Our data demonstrate that the BN strain reproduces the known hallmarks of diabetic retinopathy, as seen in albino rat strains. Detailed analysis of the structure-function relationship in the BN rats reveal changes consistent with significant progressive pro-angiogenic vascular changes and retinal degeneration starting as early as

4 weeks post-STZ induction. The pigmented BN STZ model for DR offers unique opportunities for drug discovery.

Disclosures: I. Lelyte: A. Employment/Salary (full or part-time):; Experimentica Ltd. **M. Cerrada-Gimenez:** A. Employment/Salary (full or part-time):; Experimentica Ltd. **A. Ghosh:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Experimentica Ltd., K&P Scientific LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); eyeNOS, Inc.. F. Consulting Fees (e.g., advisory boards); Experimentica Ltd., K&P Scientific LLC. **Z. Ahmed:** None. **G. Kalesnykas:** A. Employment/Salary (full or part-time):; Experimentica Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Experimentica Ltd. **S. Kaja:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; AcuiSee, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Experimentica Ltd., K&P Scientific LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Experimentica Ltd., K&P Scientific LLC, eyeNOS, Inc.. F. Consulting Fees (e.g., advisory boards); Experimentica Ltd..

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.07

Topic: D.07. Vision

Support: 4VA -minigrant

Title: Characterizing early onset vision loss in the childhood neurodegenerative disease, Mucolipidosis type IV.

Authors: *N. CUBBAGE, M. PAMONAG, R. CISTULLI, M. T. WALKER;
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Purpose: In this study we are testing to identify the mechanisms that underlie photoreceptor function loss and cell death in Mucolipidosis type IV (MLIV). MLIV is a lysosomal storage disorder, which are the greatest causes of childhood onset neurodegeneration. MLIV results from loss of function mutations in the Mcoln1 gene that encodes the lysosomal cation channel (Trpml1). Loss of Trpml1 function has been shown to disrupt cellular autophagy and phagocytic activity, which contributes to the progessive motor neuron cell death in MLIV. In the retina it is not clear why the light response of photoreceptors in MLIV are sensitive to the loss of this lysosomal channel Trpml1. In many retinal degenerative diseases regardless of the genetic origin, retinas show some disruption in rhodopsin expression and trafficking that results in decreased photoresponse and increased photoreceptor death. We hypothesize that functional defects in photoreceptors of $Mcoln1^{-/-}$ mice is due to a disruption in trafficking of photoreceptor proteins across the connecting cilium of rod and cone cells. Methods: We use

electroretinogram recordings to measure age-dependent changes in photoreceptor activity in 4 and 6 week old mice. We also measure changes in photoreceptor protein expression and localization in the mouse retina. Results: Our results show an early decline in rod photoreceptor activity beginning between 4 and 6 weeks old. At low scotopic light intensities, Mcoln1$^{-/-}$ mice have a decreased A-wave latency. At 6 weeks these mice show a significant decrease in A-wave amplitude. This decline in light activation is accompanied by a 60% decrease in total rhodopsin in Mcoln1$^{-/-}$ retina. In our analysis of retinal proteins we discovered that Mcoln1$^{-/-}$ retinas also show a significant loss of the cilia forming protein BBS4. Mcoln1$^{-/-}$ mouse photoreceptors show morphological defects in the outer segment and disruption of rhodopsin translocation. Conclusion: Our data suggests that in addition to the disruption in autophagy, the loss of Trpml1 in photoreceptors also has a secondary effect on the expression and trafficking of phototransduction proteins across the primary cilium leading to functional loss and eventual cell death.

Disclosures: N. Cubbage: None. **M. Pamonag:** None. **R. Cistulli:** None. **M.T. Walker:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.08

Topic: D.07. Vision

Title: Endothelial heterogeneity in the inner and outer blood-retinal barrier

Authors: *S. KIM[1], J.-Y. KOH[2], Y. YOON[3], J. LEE[4];
[1]Dept. of Med. Sci., Asan Med. Inst. of Convergence Sci. and Technology, Asan Med. Center, Univ. of Ulsan Col. of Med., SEOUL, Korea, Republic of; [2]Neural Injury Res. Center, Asan Inst. for Life Sciences, Col. of Medicine, Univ. of Ulsan, Dept. of Neurology, ASAN medical center, Seoul, Korea, Republic of; [3]Ophthalmology, [4]Dept. of Ophthalmology, Div. of Vitreoretina, Asan Med. Center, Univ. of Ulsan Col. of Med., Seoul, Korea, Republic of

Abstract: The blood-retinal barrier (BRB) has two components: inner and outer barrier. The neurovascular unit of the retina and tight junctions between endothelial cells play key roles in the inner BRB. Choroid, the most highly vascularized tissue of the eye, is the major components of the outer BRB and provides oxygen and nourishment to the retina, which is crucial for maintaining visual function. Retinal and choroidal blood vessels come in different morphologies and have distinct organotypic characteristics that enable them to execute tissue-specific functions. In this study, we investigated molecular and functional differences between primary human retinal endothelial cells (HRECs) and human choroidal endothelial cells (HCECs) in terms of angiogenic and vasculogenic properties, permeability, and transcytosis. We performed tube formation assay, cell migration assay, in vitro permeability assay, microfluidic sprouting assay, and transcriptome analysis. HRECs showed higher proliferation and migration activity than HCECs, but the tube formation ability did not show a significant difference. HCECs displayed earlier sprouting angiogenesis but the overall speed was faster and more stable in HRECs under angiogenic stimuli. HRECs expressed higher tight junctional proteins than HCECs, but the transcytosis related genes were more in HCECs. Angiopoietin-2 and Tie2 were predominantly expressed in HRECs, but VEGF receptors were higher in HCECs. PDGFs were not

different between HRECs and HCECs despite the pericytes coverage is less in choroidal blood vessels. Our data indicate that HCECs is a quiescent endothelium but can be stimulated under the angiogenic environment, and have a specialized transcriptome for trans-endothelial molecular transport. In conclusion, retinal and choroidal blood vessels constitute two distinct BRBs under the endothelial heterogeneity: The outer BRB, size-selective barrier with vascular transcytosis for metabolic support, and the inner BRB, forming tight barriers, composes organotypic vasculature and maintains homeostasis in the eye.

Disclosures: S. Kim: None. **J. Koh:** None. **Y. Yoon:** None. **J. Lee:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

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Program #/Poster #: P457.09

Topic: D.07. Vision

Support: DOD Grant VR190034

Title: Neurogenesis and Functional Recovery of Adult Retinal Neurons in Mice using an Alpha7 nAChR Agonist after Blast Exposure

Authors: J. SPITSBERGEN, ***C. LINN**;
Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Eyedrop application of the selective α7 nicotinic acetylcholine receptor agonist, PNU-282987, has been shown to induce both neurogenesis and regeneration of retinal neurons in adult mammals. The objectives of this research include: 1) examination of the cellular and functional damage associated with ocular blast exposure, 2) evaluation of structural and functional recovery post PNU-282987 treatment. The hypothesis that application of PNU-282987 causes regeneration of new neurons in a blast damaged retina that leads to recovery of retinal function was evaluated using electroretinogram (ERG) recordings. Ocular blast damage was induced in adult mice (3-8 months old; both sexes) after exposure to a single blast of 35 psi to the left eye. Blast exposed mice were treated bilaterally daily, with an eyedrop containing 1mM PNU-282987 and/or 1mg/mL BrdU, post-blast for 4 weeks. Blast exposure of 35 psi caused a significant loss of cells in all retinal layers (15 to 40% compared to unblasted eye) after 4 weeks. Immunohistochemical analysis demonstrated BrdU incorporation in all layers of the retina in blast exposed mice treated with PNU-282987/BrdU eyedrops for 7 days. Agonist treatment induced an average of 15% (+/- 5) BrdU+ cells in the GCL, 25% (+/- 8) BrdU+ cells in the INL and 17% (+/- 5) BrdU+ cells in the ONL (n=5). ERG recordings were taken from untreated animals, from animals treated with PNU-282987 for 4 weeks only and from animals exposed to blast followed by 4 weeks of PNU-282987 treatment. Light adapted ERG recordings from blast exposed mice had significantly decreased a-wave (8.39 microvolts +/- 3.9) and photopic negative response (PhNR) (9.2 microvolts +/- 2.2) amplitudes as compared to recordings taken from the same mice prior to blast exposure (*n=5, p<.05*). Animals treated with PNU-282987 for 4 weeks showed a significant increase in a-wave (5.27 microvolts +/- 2.1**)**, b-wave (35.4 microvolts +/- 10.5) and PhNR (10.12 microvolts +/- 1.4) amplitude (*n=5, p*<.05). Under blast

exposed conditions, PNU-282987 alleviated the change of ERG waveform caused by blast, but it was not significant after only 4 weeks. (*p<0.07).* These are the first experiments designed to address recovery of functional changes in the retina after blast exposure using an α7 nAChR agonist.

Disclosures: J. Spitsbergen: None. **C. Linn:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.10

Topic: D.07. Vision

Support: University of Oklahoma, Vice President for Research and Partnerships

Title: Sensitivity of the pattern electroretinogram to variations in central dopamine in humans: A systematic review

Authors: M. CUPP[1], H. JAMSHED[1], T. PRUITT[1], ***M. J. WENGER**[2];
[1]Psychology, [2]Psychology, Cell. & Behavioral Neurobio., The Univ. of Oklahoma, Norman, OK

Abstract: Iron deficiency, even in the absence of anemia, has negative effects on cognitive performance, including working memory, selective attention, and other functions mediated by dopaminergic communication. Animal models of iron deficiency have documented negative effects of iron deficiency on D1 and D2 receptors, as well as on dopamine transporter. Directly measuring central dopamine levels in humans involves invasive techniques, including exposure to radiation or spinal puncture. Both animal studies and human studies have suggested that the pattern electroretinogram (PERG) may be a useful indirect approach to measuring central dopamine levels. The PERG is a non-invasive and economical method of measuring the function of retinal dopaminergic cells, and it has been suggested that the magnitude and latency of the PERG may be proportional to central dopamine levels. When measured in response to periodic patterns (e.g., checkboards or square-wave gratings), the PERG consists of a rapid negative deflection (the a-wave) followed by a larger positive deflection (the b-wave) and a set of oscillatory potentials. The present systematic review sought to determine the strength of the evidence in favor of the PERG is an indirect measure of central dopamine levels in humans. Eligibility criteria for inclusion in the systematic review included a focus on human participants, with varying dopamine levels such as occurs in patients with Schizophrenia, Parkinson's Disease, and ADHD, or studies in which dopamine levels were manipulated psychopharmacologically, published in English. Excluded were articles containing participant populations with glaucoma, depression, addictive drug use, or studies that did not include measurement of the PERG. Five databases were used for article search and selection. Articles were manually cross-examined for duplicates and excluded. Each abstract was reviewed by three judges before being included. A total of 28 conditions across 11 studies provided data for the analysis. We analyzed the standardized difference of the means (using Cohen's d) for the latency and amplitude of the b-wave and found the average difference between low and high dopamine conditions was 0.793 for latency and 1.029 for amplitude. This suggests the utility of the PERG as an indirect and noninvasive

measure of central dopamine and highlights its potential in understanding the mechanisms by which iron deficiency produces cognitive impairments in humans.

Disclosures: M. Cupp: None. **H. Jamshed:** None. **T. Pruitt:** None. **M.J. Wenger:** None.

Poster

P457. Retinal Circuitry IV

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P457.11

Topic: D.07. Vision

Support: 4VA-minigrant

Title: Characterization of sensory driven intrinsic iris constriction in mammals

Authors: *M. WALKER, R. CISTULLI, S. CHAMBERS;
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Purpose: The iris is the essential retinal protective muscular tissue in the eye that controls the amount of light entering the eye. Iris muscle activity is driven by neurological input in response to changes in ambient light. A subset of photosensitive retinal ganglion cells (ipRGCs) provide the principal pathway for all light input to the olivary pretectal nucleus which directs the neuronal input to drive iris constriction via the oculomotor nerve. In most vertebrates except primates, the iris has been shown to also have an intrinsic light response. It has been shown that in murine mammals, melanopsin is required to initiate this light response, but it is not clear how the signal is transmitted between cells across the iris tissue. Pharmacological inhibition experiments suggest that gap junctions are required to transmit the intrinsic signaling between cells across the iris. We have tested in iris for the expression and localization of connexin proteins that form that form intercellular gap junction channels. We hypothesize that in the intrinsic iris light response, gap junctions are required to propagate constriction across the tissue. Methods: We have designed an *ex vivo* culture assay to measure the light dependent mouse intrinsic iris construction. We used RT-PCR and immunohistochemistry to demonstrate connexin expression and localization, respectively. Results: We found that enucleated eyes show light-driven constriction independent of CNS input. We found that the enucleated eye does not dark adapt after light driven constriction has occurred. When we isolate the anterior region of the eye in culture the tissue can be dark-adapted and light-activated multiple times. Our tests of connexin expression in mice indicate the expression of Connexin 36 (Gjd2) in the iris. Immunohistochemistry with Connexin 36 antibody also shows expression in mouse and rat iris both show gap junction expression. Conclusions: Our results show that the intrinsic iris light responses in intact eye suggests that there is some inhibitory signal preventing the iris from dilating once activated. Once the iris is separated from the posterior eyecup, it can repeat multiple cycles of construction and dilation. Finally our expression and localization results suggest that Connexin 36 is involved in forming intercellular gap junction channels in the iris.

Disclosures: M. Walker: None. **R. Cistulli:** None. **S. Chambers:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.01

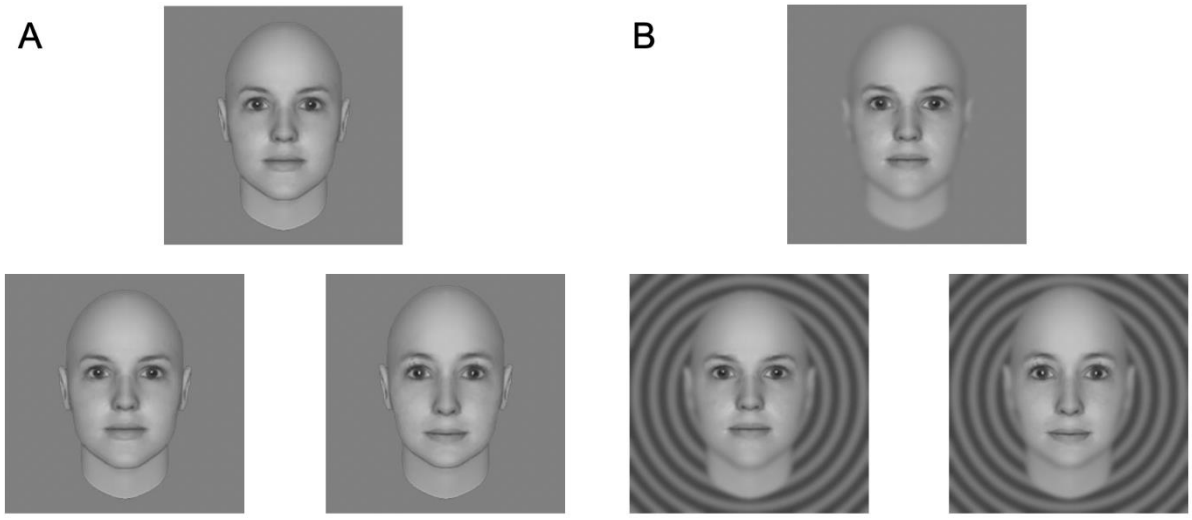
Topic: D.07. Vision

Support: NSF BCS 0617699
Dornsife Research Fund

Title: Given that large receptive fields are so important for face recognition, is their activity affected by the local visual context of a face?

Authors: *S. SAHA[1], I. BIEDERMAN[2], R. MELTZER[3];
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Abstract: Large receptive fields (r.f.s) in the first cortical visual stage (V1), critical for face recognition, enable the coding of subtle, ineffable metric variations of a face to yield unique configurations, distinguishing otherwise highly similar faces (Xu et al., 2014). Later face-selective areas, e.g., FFA, retain the V1 Gabor-like coding characteristic (Yue et. al, 2006). However, the large r.f.s, particularly those centered at the face's edges, would be affected by the face's local visual context, raising the question as to how accurate face recognition can be achieved independent of the local context. We assessed how the context affected face matching performance in a match-to-sample task that presented three similar computer-generated faces in a triangular display with a sample face on top and two test faces on the bottom, one of which matched the sample while the other was the foil (Figure 1). Independently varied was whether the faces' edges were blurred and if the adjacent context was empty (Fig. 1A) or populated with straight or curved contours (Fig. 1B) to provide noise to the large r.f.s extending past the faces' edges. Blurring a face's edges and adding adjacent contours produced a small but significant increase in mean correct reaction times (RTs) but had no effect on error rates, with the greater RT increases for curved compared to straight contours, consistent with Yue et al.'s (2011) finding that FFA shows more sensitivity to curved than to straight contours. The magnitude of the interference produced by the local context could be limited by attentional "shrink wrapping" as documented by Moran and Desimone (1985) in the r.f.s in V4, such that V1 cells may "shrink wrap" around a face's edges. How that modulation may be achieved is a problem that awaits resolution.
Figure 1. Stimuli from two illustrative trials where the sample is the upper face, the "match" to sample is the lower-left test face, and the "foil" is the lower-right test face. In trial A), the "foil" and "match" have no local contours or blur. In trial B), the "foil" and "match" have local curved contours and all three faces are blurred.



Disclosures: S. Saha: None. **I. Biederman:** None. **R. Meltzer:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.02

Topic: D.07. Vision

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NIH grant 2RO1 EY 022318
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Title: Distributed responses to visual categories in ventral temporal cortex become more similar across individuals during childhood development

Authors: *M. NORDT[1], J. GOMEZ[2], V. S. NATU[1], A. A. REZAI[1], D. FINZI[1], H. KULAR[1], K. GRILL-SPECTOR[1];
[1]Dept. of Psychology, Stanford Univ., Stanford, CA; [2]Princeton Neurosci. Institute, Princeton Univ., Princeton, NJ

Abstract: Ventral temporal cortex (VTC) contains distinct distributed representations to visual categories, which have a reproducible representational similarity across adult participants. However, it is unknown if representational similarity matrices (RSMs) become more or less similar across individuals during childhood development. Here we examined this question using longitudinal functional magnetic resonance imaging in 29 children. Children were initially 5-12 years old and were scanned on average 4.4±1.9 times over the course of 1-5 years. During scanning, children viewed images of 10 ecologically-relevant categories including faces, bodies, limbs, words, places, and objects while performing an oddball

task. We computed the RSM of distributed responses to these 10 categories in each functional session for lateral and medial VTC partitions in each hemisphere. Individual RSMs, which contained category information, were then compared across participants. We compared the similarity among RSMs (excluding the diagonal) across participants as a function of age, partition, and hemisphere. Results reveal that inter-participant-similarity among RSMs was higher in right compared to left VTC, and in medial compared to lateral VTC (Fig. 1). Interestingly, in lateral VTC inter-participant-similarity also increased with age. That is, distributed VTC responses to visual categories become more similar across individuals as they grow older. This developmental effect was independent of the temporal signal to noise ratio (tSNR) and is unaffected when excluding sessions that are outliers based on motion, task performance during scanning, or category reproducibility. These results suggest that shared visual experience may lead to more similar category representations in VTC with different levels of similarity across individuals in lateral versus medial, and left versus right VTC.

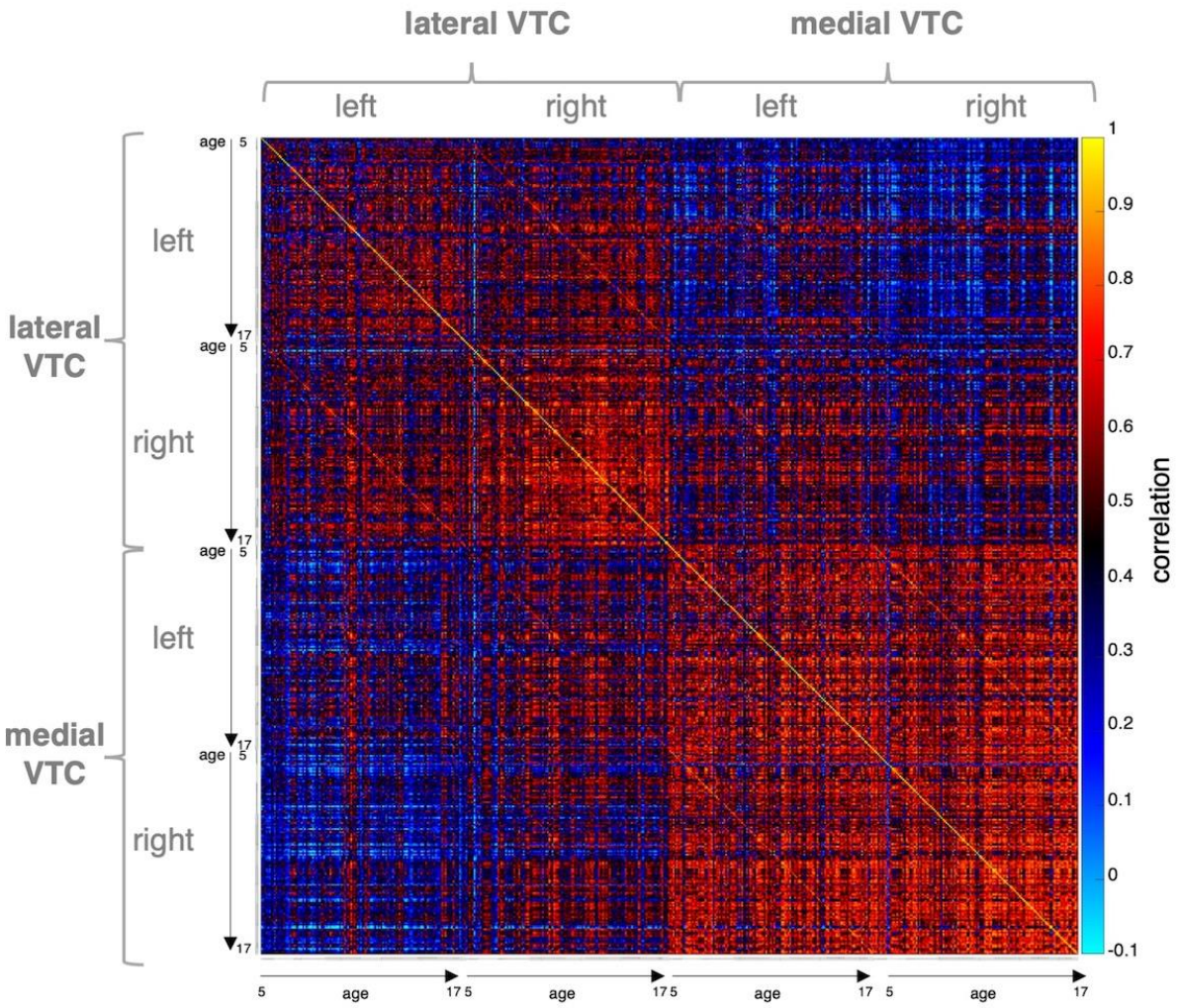


Fig. 1. Development of inter-participant-similarity among representational similarity matrices (RSM) in ventral temporal cortex (VTC). Each cell in this matrix represents the correlation (see color bar) between the lower triangle of RSMs of two sessions (n=128 sessions, 29 children ages 5-17, 18 female). The individual RSM represents the similarity between distributed representations to the 10 categories shown in the experiment (adult faces, child faces, bodies, limbs, words, numbers, cars, string instruments, corridors, houses). The inter-participant-similarity matrix is organized first by age, then by hemisphere, and finally by VTC partition (see notations on the left).

Disclosures: M. Nordt: None. **J. Gomez:** None. **V.S. Natu:** None. **A.A. Rezai:** None. **D. Finzi:** None. **H. Kular:** None. **K. Grill-Spector:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.03

Topic: D.07. Vision

Title: Face representation under partial occlusion in the inferior temporal cortex

Authors: *J. NOROOZI[1,2], M.-R. ABOLGHASEMI-DEHAQANI[3], E. REZAYAT[2], A. SHAHAMATI[2]; [1]Dept. of Physiol., Fac. of Med. Sciences, Tarbiat Modares Univ., Tehran, Iran, Islamic Republic of; [2]Sch. of Cognitive Sci., Inst. For Res. In Fundamental Sci., Tehran, Iran, Islamic Republic of; [3]Sch. of Electrical and Computer Engineering, Col. of Engin., Cognitive Systems Laboratory, Control and Intelligent Processing Ctr. of Excellence (CIPCE), Tehran, Iran, Islamic Republic of

Abstract: One prominent feature of biological visual systems, including our own, is the ability to recognize objects independent of various transformations, such as location and orientation. One of the most dramatic of these transformations is occlusion: While a massive body of previous studies focuses on the representation of occluded objects, only a few studies aimed to address how the challenge of partial occlusion is resolved in our brain. To fully understand how the neural system resolves occlusion, the representation of the occluded object, the occluder items, and their relationship should be distinguished. We examined the inferotemporal (IT) neural responses of macaque monkeys viewing partially occluded faces to address this. The two aspects of occlusion, including type and face identities, vary independently in the stimulus set. We directly addressed the representation of occlusion by investigating how the network of IT neurons process both occluder and occluded objects over time. We applied a combination of encoding and decoding methods to the single and population of recoded neural data to explore the role of the IT cortex in occlusion processing. We found an earlier distinguished representation of occluded **as opposed to** occluder **objects** in IT neurons. Responses of IT neurons to occluded against occluder objects are prominent. While the representation of occluder objects is mainly enhanced in the late time compare to the early time of IT neurons. These observations suggest that the other areas have played an essential role in occluded processing in the IT cortex. The greater cognitive demand of partially occluded object recognition hinted at the contribution of higher-order areas. Together, these results suggested evidence exists for effective feedback originating from the PFC or other areas to the IT cortex during the representation of occlusion.

Disclosures: J. Noroozi: Other; School of Cognitive Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran. **M. Abolghasemi-Dehaqani:** None. **E. Rezayat:** None. **A. Shahamati:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.04

Topic: D.07. Vision

Support: NIMH Intramural Research Program (ZIA-MH-002909)

Title: Interactions between amygdala and cortex during face presentation at fixation and in the periphery

Authors: *K. D. RANA, M. SARGEANT, J. TAUBERT, L. G. UNGERLEIDER, E. P. MERRIAM; Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Face processing is considered a function relegated to central vision. Supporting this notion are the behavioral observations that human participants tend to fixate on faces. On the other hand, it has also been shown that emotional faces are easily detected in the periphery, and the amygdala is engaged during the presentation of these peripheral faces. These findings suggest that some information about faces can be extracted from the periphery. Our goal was to investigate the functional communication between the amygdala and cortex while manipulating the screen location of faces, relative to fixation. To accomplish this, we measured brain activity using magnetoencephalography scanning during a task in which three images (size: 6 degrees across) were simultaneously presented to the observer, one image at fixation, flanked by two images 8 deg to the left and to the right of fixation. The images could either be a triplet of an object, face, and scene, or one of the aforementioned categories along with two noise images. The noise images were generated by phase-scrambling the images from the other categories. Decoding spectrotemporal activity revealed a bias for centrally-presented stimuli in the temporal lobes, which is consistent with the known central bias of the ventral visual pathway. In the amygdala, however, it was possible to decode between all stimulus locations with theta-band activity, supporting findings that it can discriminate peripherally presented faces. We used the weighted phase lag index measure to track the functional communication in the theta band between the amygdala and the cortex. We found significant theta-band connectivity between the amygdala and prefrontal cortex from 400 ms to 900 ms after stimulus onset. Our results show a delayed engagement between amygdala and prefrontal cortex in the theta band. This suggests a role of amygdala-prefrontal cortex communication in the conscious awareness of visual stimuli with greater socio-emotional meaning.

Disclosures: K.D. Rana: None. **M. Sargeant:** None. **J. Taubert:** None. **L.G. Ungerleider:** None. **E.P. Merriam:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.05

Topic: D.07. Vision

Support: NIMH Intramural Research Program (ZIA-MH-002909)

Title: Dynamic visual feature binding of face and body when perceiving emotional expression

Authors: *M. SARGEANT, K. D. RANA, J. TAUBERT, L. G. UNGERLEIDER, E. P. MERRIAM; Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: While both face and body expression are involved in the perception of emotion, their interaction is not fully understood. We investigated how face and body expression are integrated to influence emotional judgments. How do face and body expressions interact to influence the perception of emotion? What is the temporal evolution of this integration? To answer these questions, we conducted a behavioral experiment in which participants evaluated the emotional expression of images created by

joining faces and bodies. Face and body images were either emotionally congruent, with matching expressions (e.g., fearful body, fearful face), or emotionally incongruent, with unmatched expressions (e.g., fearful body, angry face). Each trial began when participants placed their mouse cursor at a fixed point at the bottom of the screen. The face and body composite image was then presented at fixation. Participants indicated their emotion expression judgment for that face/body combination by moving the mouse to one of the two targets. The trajectory of the mouse was recorded and used to infer the expression judgment over the course of the trial. Our results show that there is a preference for facial expression when identifying emotion on incongruent trials, consistent with previous findings (Solanas et al., 2018; Van de Riet & de Gelder, 2008). Moreover, the deflection of the mouse trace relative to a straight-line trajectory revealed biases in early weighting for both faces and bodies that differed from the eventual judgment on that trial. Our results reveal the utility of using dynamic mouse position for inferring emotional judgments and demonstrate that face and body expressions are dynamically weighted when participants evaluate emotional expressions.

Disclosures: M. Sargeant: None. **K.D. Rana:** None. **J. Taubert:** None. **L.G. Ungerleider:** None. **E.P. Merriam:** None.

Poster

P486. Representation of Faces and Bodies II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.06

Topic: D.07. Vision

Support: FWO Vlaanderen G0E0220N
ERC under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 856495)

Title: When the whole is equal to the sum of its parts: face-body integration in macaque inferotemporal cortex - fMRI study

Authors: *Y. ZAFIROVA[1,2], D. CUI[1,2], R. VOGELS[1,2];
[1]KU Leuven, Leuven, Belgium; [2]Leuven Brain Inst., Leuven, Belgium

Abstract: Social interactions involve an exchange of information between whole agents, and yet faces and bodies are processed in different brain areas and studied mostly separately (for a review, see Freiwald et al., 2016; Hesse and Tsao, 2020). How their integration unfolds on the neuronal level is unclear. To fill this gap, we conducted 2 fMRI experiments in 2 rhesus monkeys, employing static images on brown noise ($1/f^2$) background in passive fixation task. First, we identified the areas responding more to monkeys, monkey faces (without body), and headless bodies than to matching sets of carefully controlled objects. Face and body activations followed the classical face and bodies patches in the inferotemporal cortex (IT), with the monkey ones residing mainly in overlapping and/or neighboring voxels. In the second experiment, we examined the difference in activation between whole-agent natural (with the head in its original place) and unnatural composites (head attached to a different part of the upper body). Additionally, to estimate the contribution of the parts to the activations to the whole, individual faces and

headless bodies were presented separately, at the same position they appeared in the whole-agent images. We compared the activations to the natural versus the unnatural composites with the sum of the activations to the corresponding bodies and faces in the patches activated more strongly by monkeys compared to objects (ROIs defined with experiment 1). Only monkey patches in anterior IT, at the anterior-posterior level of face patches AL and AM, showed stronger activation to the natural compared to the unnatural composites which was not accounted for by the summed face-body activations. Importantly, the activation to the natural composites equaled the summed face-body activations in anterior IT, while the activation to the unnatural ones was less than the sum of their parts. The subadditive interaction of bodies and faces for the unnatural composites agreed with the classical divisive normalization mechanisms (e.g. Zoccolan et al., 2005). Subadditive activation to the natural whole-agents was found in the extrastriate to posterior IT regions. No evidence for superadditive face-body integration was found in the temporal cortex. In sum, these fMRI data suggest different integrating mechanisms for natural and unnatural composites of bodies and faces in anterior IT.

Disclosures: Y. Zafirova: None. **D. Cui:** None. **R. Vogels:** None.

Poster

P486. Representation of Faces and Bodies II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.07

Topic: D.07. Vision

Support: FWO Vlaanderen G0E0220N
ERC under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 856495)

Title: When the whole is equal to the sum of its parts: face-body integration in macaque inferotemporal cortex - Single unit study

Authors: *A. BOGNÁR[1,2], Y. ZAFIROVA[1,2], R. VOGELS[1,2];
[1]KU Leuven, Leuven, Belgium; [2]Leuven Brain Inst., Leuven, Belgium

Abstract: For successful social interactions, it is essential to exchange information between whole agents, however facial and body information are processed in different brain areas and studied mostly separately. Our study aimed to investigate the interaction between face, body, and whole-agent information in anterior inferior temporal areas of macaques. The targeted patch was identified in an fMRI study that employed the same subjects. The identified patches were activated more strongly by natural (NC) compared to unnatural (UC) composites of whole agents. In the UC stimuli, the face was attached to the wrong part of the upper body. The difference in activation between the NC and UC conditions could not be accounted for by the sum of the activations to the same faces and (headless) bodies that were part of the composites (Zafirova et al. SFN, 2021). The targeted patches were close to face patches AL and AM. We recorded 65 single units from 2 macaques during passive fixation. In the first test, we presented static images of 20 monkeys and 20 objects. The mean response to monkeys was higher than to objects. In the second test, we presented the same 20 NC and 20 UC as employed in the fMRI study. Consistent

with the fMRI activations, the mean response to NC was higher than to the UC stimuli. Based on the responses of this test, we selected 3 monkey stimuli, and manipulations of the one with the highest response was used for the present analyses. We recorded responses to conditions in which the 6 deg wide whole-agent images were centered according to the body or face and the images were mirrored along the vertical axis. Hence, the bodies and the faces were presented equally in the ipsi- and contralateral visual fields. In each condition, we presented NC and UC and the (headless) body and face stimuli that composed the NC and UC stimuli. The face and body-only stimuli were shown at the same position as in the composites. The average response was greater for the NC compared to the UC. To examine how the response to the whole-agent stimuli relates to those to the bodies and faces presented in isolation, we calculated a contrast index: [whole-agent - (body+face)] / [abs(whole-agent) + abs(body+face)] for NC and UC responses using the corresponding body and face responses. In both monkeys and conditions (images centered on bodies or faces), the mean contrast index for NC was higher than for UC. As for the fMRI data, the response to the NC stimuli was on average similar to those of the sum to the body and face responses, while the response to UC was smaller than the summed responses. These data suggest different integrating mechanisms for NC and UC in anterior inferotemporal cortex.

Disclosures: A. Bognár: None. **Y. Zafirova:** None. **R. Vogels:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.08

Topic: D.07. Vision

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Air Force Young Investigator Program Award 20RT0829
Dana Foundation Clinical Neuroscience Award
ORAU Ralph E. Powe Junior Faculty Enhancement Award
West Virginia University (WVU)
WVU PSCoR Program
NSF Grant OAC-1839909

Title: Feature-based encoding of face identity by single neurons in the human medial temporal lobe

Authors: R. CAO[1], J. WANG[1], C. LIN[4], E. DE FALCO[5], H. G. REY[6], A. G. TODOROV[7], U. RUTISHAUSER[8], X. LI[1], N. J. BRANDMEIR[2,3], S. WANG[1,9];
[1]Lane Dept. of Computer Sci. and Electrical Engin., [2]Dept. of Neurosurg., [3]Rockefeller Neurosciences Inst., West Virginia Univ., Morgantown, WV; [4]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [5]Lab. of Cognitive Neurosci., École Polytechnique Fédérale de Lausanne, Route Cantonale, Switzerland; [6]Dept. of Neurosurg., Baylor Col. of Med., Houston, TX; [7]Booth Sch. of Business, Univ. of Chicago, Chicago, IL; [8]Dept. of Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA; [9]Dept. of Radiology, Washington Univ. in St. Louis, St. Louis, IL

Abstract: Neurons in the human medial temporal lobe (MTL) that are selective for the identity of specific people are classically thought to encode a person's identity invariant to visual features (e.g., skin tone, eye shape). However, it remains largely unknown how visual information from higher visual cortical areas is translated into a semantic representation of an individual person. Here, we show that some MTL neurons are selective to multiple different face identities on the basis of shared visual features that form clusters in the representation of a deep neural network trained to recognize faces. Contrary to prevailing views, we find that these neurons represent an individual's face with feature-based encoding, rather than through association with concepts. The response of feature neurons did not depend on face identity, race, gender, or familiarity; and the region of feature space to which they are tuned predicted their response to new face stimuli. Our results provide critical evidence bridging the perception-driven representation of facial features in the higher visual cortex and the memory-driven representation of semantics in the MTL, which may form the basis for declarative memory.

Disclosures: R. Cao: None. **J. Wang:** None. **C. Lin:** None. **E. De Falco:** None. **H.G. Rey:** None. **A.G. Todorov:** None. **U. Rutishauser:** None. **X. Li:** None. **N.J. Brandmeir:** None. **S. Wang:** None.

Poster

P486. Representation of Faces and Bodies II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P486.09

Topic: D.07. Vision

Support: NIH 1U54-MH-091657 (HCP dataset)

Title: Microstructurally and functionally distinct fusiform face area(s) in over 1000 participants

Authors: X. CHEN[1], B. J. PARKER[2], Z. ZHEN[1], ***K. S. WEINER**[2];
[1]Beijing NormalUniversity, Beijing, China; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: Determining how visual categories are represented in the brain continues to be a highly debated topic with many different proposed theories. Theoretical debates aside - for example, the ever-popular arguments between modular vs. distributed processing, as well as the role of expertise - there is great interest in cortical networks selective for faces across species. In humans, the Fusiform Face Area (FFA) is a widely studied functional region that is causally involved in face perception. Even though the extended field has been studying the FFA for over two decades, we still lack answers to foundational questions regarding the structure and function of the FFA from a large (N>1000) group of participants. To fill this gap in knowledge, we quantified anatomical and functional features of fusiform face-selective regions in 1080 participants included in the Human Connectome Project (HCP) with a four-fold approach. First, we manually identified fusiform face-selective regions (4,221 in total) in all 2,160 hemispheres to determine incidence rates regarding how often a participant will have 0, 1, or 2 FFAs in a large group of participants for the first time. Second, we extracted macroanatomical (cortical thickness) and microstructural (myelination) features of each region. Third, we quantified functional features (face selectivity and functional connectivity fingerprints) of each region. Fourth, we examined the similarity in spatial patterns of each anatomical and functional feature between pairs of monozygotic (MZ) and

dizygotic (DZ) twins included in the HCP dataset. This approach revealed four main findings. First, ~2/3 of individuals have two FFAs that are macroanatomically, microstructurally, and functionally distinct. Second, pFus-faces/FFA-1 is more face-selective than mFus-faces/FFA-2, and the two regions also have distinct functional connectivity fingerprints. Third, pFus-faces/FFA-1 in the posterior FG is cortically thinner and more heavily myelinated than the more anterior mFus-faces/FFA-2. Fourth, face-selective patterns within each region were more similar in MZ than DZ twins and more so than anatomical gradients of thickness and myelination. Altogether, we show that fusiform face-selective regions are microstructurally and functionally distinct in over 1000 participants for the first time. As we share our areal definitions with the field, future studies can perform novel multimodal analyses that leverage the rich multimodal HCP dataset to explore how anatomical and functional features of these regions relate to cognitive and behavioral metrics also acquired in each participant.

Disclosures: X. Chen: None. **B.J. Parker:** None. **Z. Zhen:** None. **K.S. Weiner:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.01

Topic: E.09. Motor Neurons and Muscle

Support: NIH SC3 GM127195
NIH #5R25GM71381

Title: Stimulation of gamma motor neurons in vitro using optogenetics

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Abstract: Gamma motor neurons innervate the intrafusal fibers of the muscle spindle and control muscle spindle length and sensitivity of the muscle spindle afferents. It is challenging to independently stimulate the gamma motor neurons without also recruiting the alpha motor neurons that control the force generating extrafusal fibers. Optical stimulation in mice expressing the blue light gated Channel rhodopsin 2 (ChR2) in motor neurons led to alpha motor neuron recruitment from small to large diameter with increasing optical intensities (Llewellyn, et al., 2010). We hypothesized that gamma motor neurons, which are smaller than alpha motor neurons, will be recruited first in mice expressing ChR2 in ChAT positive motor neurons. The extensor digitorum longus muscle and sciatic nerve were dissected and placed in a tissue bath with oxygenated synthetic interstitial fluid. The sciatic nerve was attached to an extracellular suction electrode that recorded muscle spindle afferent activity. We used a light guide to deliver blue LED light (470nm; 0.5mW-5 mW) to the end of the nerve. We found that lower levels of optical stimulation recruited the gamma motor neurons as evidenced by an increased muscle spindle afferent firing rate. Higher optical intensities recruited alpha motor neurons to produce a twitch muscle contraction. Blocking neuromuscular transmission with alpha bungarotoxin blocked both the LED-induced twitch contractions and increases in muscle spindle afferent firing, eliminating the possibility of

direct optical recruitment of muscle spindle afferents. In some muscle spindle afferents with baseline firing, higher frequencies of optical stimulation led to greater increases in afferent firing rates as expected. Gamma motor neuron stimulation could recruit muscle spindle afferent firing in units that only fired during stretch, however, the recruitment was not always predictable and long lasting changes including the development of baseline firing was sometimes observed. Some of the variability we observed could be due to variable recruitment of dynamic and static gamma neurons or to the recruitment of alpha motor neurons which counteracted the gamma motor neuron induced stretch of the muscle spindle. We predict that a gamma motor neuron specific driver for ChR2 expression will decrease variability and are currently testing mice with ChR2 expression in Npas1 expressing cells, a recently identified gamma motor neuron marker (Blum, et al., 2021). The ability to stimulate gamma motor neurons in vitro will be valuable for studying gamma motor neuron function and screening for intrafusal fiber dysfunction in disease models.

Disclosures: R. Mandawe: None. **A. Karekal:** None. **S.K. Byri:** None. **D. Cheline:** None. **A. Occiano:** None. **S. Ortiz:** None. **S. Hochman:** None. **K. Wilkinson:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.02

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant 2T32GM007055-45
NIH Grant 2T32GM007055-44

Title: Nucleus Ambiguus Neurons Controlling Swallowing

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Abstract: Difficulty swallowing, or dysphagia, affects 1 in 25 adults in the United States annually and is a common complication of neurological conditions in the elderly. Neurological dysphagia can often lead to life-threatening conditions, such as infection, malnutrition, dehydration, choking, and aspiration pneumonia. Thus, there is a great clinical need to understand the neural control of swallowing and how to target its dysfunction. The nucleus ambiguus (nAmb), a region of the hindbrain that provides parasympathetic input to the pharynx, larynx, esophagus, lungs, and heart through the vagus nerve, mediates many different important functions, including swallowing, speech, respiration, and cardiac function. The nAmb's importance in swallowing has been studied; however, little is known about the cellular organization of the nAmb, including whether there are functional subtypes of neurons that may specifically control the esophageal and pharyngeal phases of swallowing. To address these questions, we characterized nAmb neurons based on their transcriptome-wide mRNA expression, anatomy, and ability to control swallowing muscles. Our single-cell transcriptomics analysis of 235 nAmb neurons pointed to three molecularly distinct nAmb neuron subtypes (differentially marked by the genes *Crhr2*, *Vipr2*, and *Tbx3*), which we validated and anatomically mapped by in situ detection of marker transcripts. Of note, the Crhr2 nAmb subtype was found predominantly in the rostral, "compact" nAmb, raising the possibility

that they were esophageal motor neurons. In contrast, the Vipr2 nAmb subtype was found in the caudal, "loose" nAmb, suggesting that they may instead provide pharyngeal/laryngeal control. To test these hypotheses, we used marker-driven genetic technology to label the axon projections of Crhr2 nAmb and Vipr2 nAmb neurons and imaged them in optically cleared esophagus and upper throat samples. Our results show that Crhr2 nAmb neurons project to the esophagus, whereas Vipr2 nAmb neurons innervate the upper esophageal sphincter. Furthermore, optogenetic stimulation of the cell bodies of Crhr2 and Vipr2 nAmb neurons under anesthesia activated swallowing-related muscles of the mouth and upper airway. Focal stimulation of the esophagus caused contractions only in Crhr2 nAmb neurons targeted mice. No change in heart rate or breathing were observed during stimulation of either Crhr2 or Vipr2 nAmb neurons. Together, these studies characterize the genetic, cellular, and functional organization of brainstem neural circuits for swallowing.

Disclosures: T. Coverdell: None. **S. Abbott:** None. **J. Campbell:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.03

Topic: E.09. Motor Neurons and Muscle

Support: Emory Computational Neuroscience Fellowship (O.F. Megwa)
Emory St Andrews Collaborative Research Grant (A.A. Prinz, S.R. Pulver)

Title: Tau from no Tau: Temporal dynamics of Na^+ pump mediated memory traces

Authors: *O. F. MEGWA[1], L. M. PASCUAL[1], S. R. PULVER[2], A. A. PRINZ[1];
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Abstract: Na^+ / K^+ ATPases (Na^+ pumps) mediate long-lasting, dynamic ion currents that provide a neuronal memory of previous activity than can last tens of seconds. The mechanisms controlling the dynamics of cellular memory are not well understood and can be counterintuitive. For example, long-lasting memory traces can arise from Na^+ pumps that instantaneously respond to Na^+ concentration changes in the absence of an explicit pump activation time constant. Here, we use computational modelling to examine how pump dynamics without time constants shape cellular memory traces.
In modelling a *Drosophila* larval motor neuron, we incorporated a Na^+ pump, a dynamic intracellular Na^+ concentration, and a dynamic Na^+ reversal potential. The pump current $I_p = I_{p,max} / \{1 + \exp[(NaH - Na)/NaS]\}$ is an S-shaped function of internal Na^+ concentration (Na) with three parameters: maximal pump current ($I_{p,max}$), half-activation concentration (NaH), and a slope factor (NaS) that determines the pump's sensitivity. This model does not include an explicit time constant *Tau* of pump activation. The pump shapes neuronal dynamics by generating an electric current due to an efflux of Na^+ ions and influx of K^+ ions while also changing the intracellular Na^+ concentration and thereby the Na^+ reversal potential. We find that despite the absence of an explicit *Tau*, the pump produces after-hyperpolarizations (AHPs) following bursts of action potentials that can last for multiple seconds, matching experimental data. This

‘*Tau* from no *Tau*’ arises from the interaction of the pump current, membrane currents and the Na^+ dynamics. The AHP duration depends on both parameters NaH and NaS. NaH primarily controls AHP amplitude and NaS controls the AHP duration. More vigorous spiking produces larger amplitude AHPs, but also - counterintuitively - reduces AHP duration. We further show that after the AHP - when the electrical effect of the pump has largely subsided - cellular excitability is still altered, suggesting a cellular memory for previous activity that is not driven solely by changes in membrane potential. This memory trace arises from interactions of the pump with membrane conductances and Na^+ concentration dynamics without slow molecular signaling cascades.
We conclude that even in the absence of an activation time constant *Tau*, Na^+ pumps can encode cellular memories of spiking dynamics. Our work provides testable predictions for physiologists and has implications for understanding information processing in neural networks and the neural control of animal behavior.

Disclosures: O.F. Megwa: None. **L.M. Pascual:** None. **S.R. Pulver:** None. **A.A. Prinz:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

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Program #/Poster #: P572.04

Topic: E.09. Motor Neurons and Muscle

Support: Royal Society Newton International Fellowship (NIF/R1/180091)
NSERC PDF (PDF-517295-2018)

Title: Persistent and hyperpolarization-activated inward currents shape fast and slow motoneuron recruitment during postnatal development

Authors: *S. A. SHARPLES, G. B. MILES;
Univ. of St Andrews, St Andrews, United Kingdom

Abstract: The fine control of movement is a prerequisite for complex behaviour and is mediated by the orderly recruitment of slow and fast motor units. The size principle was initially proposed to account for orderly recruitment; however, motoneuron size is a poor predictor of recruitment amongst functionally defined motor unit subtypes. While intrinsic properties of motoneurons are key regulators of motoneuron recruitment, the underlying currents involved are not well defined.
Whole-cell patch-clamp electrophysiology was deployed to study intrinsic properties, and the underlying currents, that contribute to the differential recruitment of fast and slow motoneurons (n = 261). Motoneuron subtypes were identified based on repetitive firing latency in response to a square depolarizing current pulse at rheobase. Motoneurons were studied during the first three postnatal weeks in male and female mice to identify key properties that establish orderly recruitment and contribute to the emergence of fine motor control during this period.
Data revealed that fast and slow motoneurons are functionally homogeneous during the first postnatal week and are recruited based on size, irrespective of motoneuron subtype. The recruitment of fast and slow motoneurons becomes staggered during the second postnatal week due to the differential maturation

of passive and active properties, particularly persistent inward currents (PICs). PICs measured in voltage clamp were larger and activated at a more depolarized voltage in fast compared to slow motoneurons. Subsequent blockade of either NaV1.6 channels with 4,9-anhdrotetrodotoxin (200 nM; n = 22) or L-type calcium channels with nifedipine (20 uM; n = 16) reduced PIC amplitude; however, only blocking NaV1.6 depolarized PIC activation voltage, which translated to an increase in recruitment current.
The current required to recruit fast motoneurons increases further in the third postnatal week, despite no additional changes in passive properties or PICs. This further staggering of recruitment currents reflects development of a hyperpolarization-activated inward current (Ih) in fast motoneurons that is active near resting membrane potential. Subsequent blockade of the resting Ih with ZD7288 (10 uM; n = 21) led to a decrease in the recruitment current and increase in the medium afterhyperpolarization of fast but not slow motoneurons.
Our results suggest that motoneuron recruitment is multifactorial, with recruitment order established during postnatal development through the differential maturation of passive properties and sequential integration of persistent and hyperpolarization-activated inward currents.

Disclosures: S.A. Sharples: None. **G.B. Miles:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.05

Topic: E.09. Motor Neurons and Muscle

Title: Understanding motor sequence generation across spatiotemporal scales

Authors: *A. D. ELLIOTT[1], R. VUONG[1], S. ROY[1], H. SHROFF[2], B. WHITE[1];
[1]NIH/NIMH, Bethesda, MD; [2]NIBIB, NIH/NIBIB, Bethesda, MD

Abstract: Behaviors are produced from a fixed set of neuromuscular connections, yet the brain produces a variety of movements for routine tasks and large number of adaptable responses to external stimuli. Neuromodulators and sensory feedback are two components known to tailor the activity of central pattern generators to adapt motor output to desired goals, though mechanistic detail of these processes remains limited. To investigate these processes, we have been studying a behavioral paradigm in *Drosophila* called the pupal ecdysis sequence in which motor activity can be monitored at single-muscle resolution while manipulating neuromodulatory and sensory input (Elliott et al, eLife, 2021). In this paradigm, sensory input plays a role in initiating behavior, individual movements are determined by a syllabary of co-active muscles, and certain syllables are sensitive to regulation by neuromodulators. Notably, the activity of individual muscles is recruited stochastically. This raised the question of how neuromodulators and sensory input differentially regulate motor output from the CNS. We hypothesize that these inputs operate in equilibrium to balance feedback from the moving body and output from central pattern generators. To test this hypothesis, we have built a custom lightsheet microscope that permits the effects of acute neuromodulatory and sensory manipulations on neural activity to be monitored at single cell resolution. We find that activation of specific proprioceptive inputs and neuromodulator-expressing cells causes distinct changes in motor output. To identify motor neurons that are sensitive to sensory input, we

have generated an expression atlas with lightsheet data aligning neuroanatomical markers and somata of subsets of motor neurons. We are currently measuring motor neuron calcium activity during fictive behavior both in an excised CNS and in a semi-intact fillet preparation that maintains sensory and motor neuron connections and registering the live data to our atlas to tease out which motor neurons are sensitive to sensory input. Our studies promise a detailed description of the regulatory roles played by neuromodulators and sensory neurons in shaping the output of the central pattern generators for an elemental behavioral sequence.

Disclosures: A.D. Elliott: None. **R. Vuong:** None. **S. Roy:** None. **H. Shroff:** None. **B. White:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.06

Topic: E.09. Motor Neurons and Muscle

Title: Does Estrogen Influence Fatigue Outcomes in Transcranial Direct Current Stimulation?

Authors: *J. R. DETERS, A. C. FIETSAM, C. D. WORKMAN, T. RUDROFF;
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Abstract: Transcranial direct current stimulation (tDCS) research is prone to high inter- and intra-subject variability, with approximately 50% of subjects not responding to tDCS or showing effects contrary to the expected response (e.g., inhibition after anodal stimulation). Biological sex may contribute to the marked inconsistency of results across the tDCS literature, possibly due to sex hormones that fluctuate significantly more in women than men. One of the main female sex hormones, estradiol (E2), has been found to endogenously increase cortical excitability. Therefore, administering anodal tDCS when estradiol is high might lead to overexcitation of the target area. Overexcitation may interfere with normal activation patterns in the cortex, thus resulting in decreased performance after tDCS administration. Accordingly, the aim of this study was to assess potential differences in leg muscle fatigability after tDCS administration when E2 was high versus when E2 was unknown. Twelve healthy young (aged 19-34) eumenorrheic women performed an isokinetic fatigue task (FT) after receiving 20 min of 4 mA anodal tDCS over the dominant leg M1 during the phase characterized by the highest E2 levels (late follicular). Subsequently, the subjects were age-matched from a previous study utilizing the same stimulation parameters in which hormone levels were not measured. A torque-derived fatigue index (FI) was calculated from the 40-repetition FT as follows: ([mean of first five reps-mean of last five reps]/mean of first five reps) *100. A higher FI represents a greater difference in torque output between the beginning and the ending of the FT, indicating an increase in fatigability. The results of this comparison revealed higher FI values when E2 levels were evaluated (i.e., the FT was performed when E2 levels were known to be high) versus when E2 was not measured (E2: 64.1 ± 7.77%, No E2: 52.4 ± 15.32 %; $p = 0.03$). Increased fatigability when E2 was high compared to when it was not evaluated indicates that E2 levels may alter functional outcomes in tDCS studies. E2 enhances excitability via increased concentration of glutamate, while tDCS induces excitation through downregulation of GABA levels. Thus, if tDCS is applied when endogenous cortical excitability is already upregulated via high E2 levels, overexcitation

may result in increased muscle fatigability. Importantly, differences in FI values in this study underscore the need to consider sex hormone levels as potential variables. Therefore, including methods for menstrual cycle phase identification into subject evaluations beforehand are critical to addressing the issue of variability in future tDCS studies.

Disclosures: J.R. Deters: None. **A.C. Fietsam:** None. **C.D. Workman:** None. **T. Rudroff:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P572.07

Topic: E.09. Motor Neurons and Muscle

Title: Personal Protective Equipment Alters Leg Muscle Fatigability Independent of Transcranial Direct Current Stimulation or Sex

Authors: *A. C. FIETSAM, J. R. DETERS, C. D. WORKMAN, A. L. COOPER, T. RUDROFF; Univ. of Iowa, Iowa City, IA

Abstract: In response to the COVID-19 pandemic, the use of personal protective equipment (PEE) has increased. However, mandating subjects to wear PPE during vigorous exercise might independently influence the fatigue outcomes in transcranial direct current stimulation (tDCS) studies. Sixteen young healthy subjects (8 females, age range: 20-26) wore PPE during an isokinetic fatigue task (FT) in conjunction with sham, 2 mA, and 4 mA tDCS conditions. The subjects were age- and sex-matched to sixteen subjects who did not wear PPE in our previous pre-pandemic study, in which right knee extensor fatigability significantly increased under these same conditions. A torque-derived fatigue index (FI-T) was calculated as: ([mean of first five reps - mean of last five reps]/mean of first five reps)*100 and a work-dervied fatigue index (FI-W) was calculated as: (total work performed in the last half of the FT/total work performed in the first half of the FT)*100. The results indicated that FI-T was higher (PPE: 60 ± 10%, No PPE: 50.4 ± 6.7%; $p = 0.01$) and FI-W was lower (PPE: 55.2 ± 10%, No PPE: 62.6 ± 5.1%; $p = 0.04$) for the right knee extensors in the sham condition, indicating greater performance fatigability in the PPE study compared to the No PPE study when stimulation was not applied. Additionally, there were no differences in knee extensor fatigability or muscle activity (EMG) between sham, 2 mA, or 4 mA tDCS in the PPE study, which contrasted with the results of the No PPE study. Therefore, a ceiling effect might have already been reached during the sham condition, which then resulted in the null effects of applying 2 mA and 4 mA tDCS and the significant contrast with the No PPE study. These results may also be influenced by the pandemic-altered research environment (i.e., both subjects and researchers wearing PPE) and psychological factors (e.g., anxiety). Moreover, there were no differences in the FI-T, FI-W, or average EMG of the right knee extensors in the PPE study when the responses between males and females were compared. Thus, PPE worn by subjects and researchers might have a detrimental effect on fatigue outcomes in tDCS studies irrespective of stimulation intensity or the sex of the subject.

Disclosures: A.C. Fietsam: None. **J.R. Deters:** None. **C.D. Workman:** None. **A.L. Cooper:** None. **T. Rudroff:** None.

Poster

P572. Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

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Program #/Poster #: P572.08

Topic: E.09. Motor Neurons and Muscle

Support: NIH RO1 NS069844

Title: Map kinase signaling is required for complement-associated clearance of synaptic inputs from injured motoneurons

Authors: *E. ASGHARI ADIB[1], J. SHADRACH[2], B. A. PIERCHALA[2,3], C. COLLINS[1];
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[3]Anatomy, Cell Biol. and Physiol., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Innate immune responses via the complement system and activated microglia have been found to direct the loss of synapses in both developmental and disease conditions. A major outstanding question in the field has been to understand how and why some synapses but not others are marked for clearance by complement; in particular, what are the cell-intrinsic mechanisms within neurons that lead to such marking? Our findings have implicated a neuronal kinase in triggering complement-associated synapse loss. Our study has focused on the loss of upstream excitatory inputs from axotomized motoneurons (MNs) following peripheral nerve injury (PNI). Termed 'synaptic stripping', this form of synapse loss is one of the oldest documented forms of microglial-associated synapse loss (Blinzinger K, Kreutzberg G. 1968) while the role of microglia in synaptic stripping has been debated (Alvarez FJ et al. 2020) prior studies have reported a critical role for complement component C3 (Berg A et al. 2012). We found that the deposition of the initiating factor C1q is dramatically induced around injured MN cell bodies following PNI, and that the Dual Leucine Zipper Kinase (DLK) is required cell autonomously in injured MNs for the activation of complement and associated microglial responses to PNI in the spinal cord. DLK is previously known as an axonally localized kinase the regulates multiple responses to nerve injury, including degeneration of the distal axon and the ability of the proximal axon to regenerate (Asghari Adib et al. 2018) MAP Kinase signaling downstream is thought to be mediated retrogradely through axons, placing DLK as an attractive upstream regulator of multiple responses to axonal damage. The activation of complement, innate immunity and synapse loss is a new role for DLK. However, it is consistent with an overarching role for DLK in promoting structural plasticity in the nervous system, enabling adaptive responses to axon damage. We are currently pursuing the mechanism, following a RiboTag approach that has identified genes strongly regulated by DLK in injured MNs following PNI.

Disclosures: E. Asghari Adib: None. **J. Shadrach:** None. **B.A. Pierchala:** None. **C. Collins:** None.

Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Program #/Poster #: P601.01

Topic: F.04. Stress and the Brain

Support: NIH R01 HD041469
National Defense Science and Engineering Graduate Fellowship

Title: Early-life stress may delay puberty in both sexes and alter corticosterone response to acute stress in males

Authors: *A. G. GIBSON[1], S. M. MOENTER[2];
[1]Neurosci. Grad. Program, [2]Mol. & Integrative Physiology, Intrnl. Medicine, and Obstetrics and Gyne, Univ. of Michigan, Ann Arbor, MI

Abstract: Both chronic and acute exposure to stress can alter the neuroendocrine regulation of reproduction. Adverse childhood experiences (ACEs) have profound consequences for physiological development and are important social determinants of health. In humans, ACEs can alter reproductive outcomes including age at menarche, engagement in risky sexual behaviors, and fertility. Early-life stress can also shape the way each physiologic system responds to stress in adulthood, promoting either resiliency or susceptibility to later stress. Adult stress has been independently demonstrated to disrupt fertility. We tested if a mouse model of early-life stress, the limited bedding and nesting (LBN) paradigm, altered reproductive development and the response of adults to an acute stress. CBA dams were crossed with B6 sires expressing GFP under control of the gonadotropin-releasing hormone (GnRH) promoter. Second litters were used to decrease pup loss. Litters were reared under standard conditions (STD) or the LBN paradigm from postnatal days (P) 4 to 11. Dam mass did not differ with treatment from P4 to weaning at P21 (p=0.57). Mean litter mass was the same for STD and LBN litters on P4 (p=0.11). In contrast, at the end of the LBN paradigm on P11, LBN-exposed offspring had a transiently lower body mass (p<0.001) that resolved by P21 (p=0.62). We monitored age at vaginal opening and first estrus in females or at preputial separation in males as external indicators of puberty. There was no difference in age at vaginal opening (p=0.27, n=32 STD, 29 LBN), but there was a trend for delayed first estrus in LBN offspring (p=0.06, n=29 STD, 29 LBN). Preputial separation was delayed by LBN (p=0.01, n=15 STD, 25 LBN). To test if LBN confers susceptibility or resilience to adult stress, we used an acute, layered, psychosocial stress (ALPS) paradigm that disrupts the preovulatory luteinizing hormone (LH) surge when given on the morning of proestrus. In preliminary studies, there was a trend for LBN to reduce the corticosterone response to ALPS in adulthood in male offspring (3-way interaction, p=0.06 n=4 STD-CON, 3 STD-ALPS, 6 LBN-CON, 6 LBN-ALPS). There were no treatment effects on baseline corticosterone levels (ps>0.999). ALPS treatment increased corticosterone in both STD and LBN groups (p<0.001). The interaction may stem from LBN blunting corticosterone response to ALPS (mean±SEM: 392±16.5 ng/mL STD-ALPS, 263±35.4 LBN-ALPS, p=0.22); animal numbers need to be increased to confirm this. Other future work will test the hypothesis that LBN female offspring are less susceptible to the effects of ALPS on corticosterone and that this renders them resilient to acute stress disruption of the LH surge.

Disclosures: A.G. Gibson: None. **S.M. Moenter:** None.

Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Topic: F.04. Stress and the Brain

Support: National Fund for Scientific, Technological, and Technological Innovation Development) (FONDECYT) and Word Bank (BM) grant # 025-2019 Fondecyt-BM

Title: Early-life resource scarcity environment alters maternal care and impacts offspring visual development trajectory and physical growth in two strains of inbred mice

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Abstract: Background. Early experiences, especially those related to impaired mother-infant interactions, impact the infant's neuronal and behavioral maturation. Recently, the early-life exposure of mice litters to the limited bedding nesting material (LNB) paradigm has been shown to reduce body weight and delay the eye-opening in offspring of both sexes, suggesting the critical role of early mother-infant experiences on the maturation of the visual system and somatic growth. To understand whether genetic factors also influence these changes, we exposed litters of mice from two inbred strains with phenotypic differences in stress susceptibility (C57BL/6NCrl and BALB/c) mice LBN paradigm. Then, we compare the dams maternal care profile and somatic growth and maturation of the visual system of the offspring. **Methods**. The maternal behavior of control and LBN dams was evaluated on 3 to 9 pups' days of life. During the postnatal day (PND) 2 to 9, a group of litters of both strains were exposed to the LBN protocol. From PND 10 to PND 22, pups of each litter were weighed daily and examined to verify the occurrence of eye-opening. **Results**. We found that LNB stress during PND 3-9 altered the maternal care profile of mice two strains differently. C57BL/6NCrl dams exposed to LNB significantly increased the presence in the nest, the exits from the nest (sorties), and nest-building behaviors. In contrast, BALB/c dams exposed to LBN increased the presence in the nest just during PND 5-7 with no changes in the sorties or nest-building behaviors. LNB exposed pups, for both strains, had their eye-opening occurring progressively between PND 12 and 21, although, for the BALB/c strain, this process began and ended earlier than for the C57BL/6NCrl strain. Exposure to the LBN protocol delays eye-opening in both strains, although significantly impacting the C57BL/6NCrl strain, which considerably delays the start and end of eye-opening, mainly in females. Likewise, exposure to the LBN protocol decreases body weight in the offspring of both strains, specifically during the periods PND 10-12 and PND 19-22, with a more significant impact on females of the C57BL/6NCrl strain. **Conclusions**. These data show that although both strain dams have slightly different maternal behavior profiles, both seem to deal differently with exposure to the LBN protocol. Exposure to an early adverse environment can alter specific neural circuits' trajectory and maturation rate in the genetic background sex-dependent manner of the offspring. These results can contribute to understanding individual variations in the long-term effects of stress in early life.

Disclosures: C. Becerra: None. **F. Delgado:** None. **L.F. Pacheco-Otalora:** None. **G.E. Pardo:** None.

Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P601.03

Topic: F.04. Stress and the Brain

Support: NIMH RO1MH096093
Harvey Family Endowment

Title: Early life adversity potentiates adult response to acute threat: A brain-wide imaging and behavior study

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Abstract: Adverse childhood experiences increase vulnerability later in life to stress-provoked mental illnesses, such as anxiety/depression and substance use disorders. How these experiences shape the brain in ways that lead to such disorders remains a mystery. Brain-wide imaging of neural activity in the adult raised with or without early life adversity (ELA) holds promise of finding clues. Longitudinal manganese-enhanced magnetic resonance imaging (MEMRI) provides a methodology to follow brain-wide neural activity dynamics over time in awake-behaving animals. Mn(II) delivered systemically is enters active neurons through voltage-gated calcium channels throughout the brain over 22-26h. Behavior is recorded in our custom arena during Mn(II) uptake. We capture an image of normal exploration at 22h, and then expose mice to predator odor (TMT, 2,3,5-Trimethyl-3-thiazoline), a naturalistic acute threat, and reimage at 26h (Uselman et al, 2020). Here we apply MEMRI paired with behavior to investigate ELA effects on responses to TMT in normally reared (n=12) and maternally deprived mice (n=24, ± ELA). Dams with newborn pups were deprived of adequate bedding from day P2-P9, which induces elevated cortisol in the pups (Rice et al., 2008). At 10 weeks of age, mice ± ELA were subjected to our paired behavior-MEMRI longitudinal procedure for both acute and delayed responses. After imaging, mice are sacrificed, brains perfusion-fixed and serial sections stained by immunohistochemistry. MEMRI images were skull-stripped, spatially co-registered, and intensity normalized. To measure the degree of activity and relationships between brain regions we performed statistical parametric mapping (SPM), segmentation of 110 brain regions, cross-correlation analysis, and Louvain community detection. Predator stress increased defensive/avoidance behavior for both groups ($p<0.05$, Tukey-Adjusted), attesting to the expected effect of the TMT. Basal neural activity of ELA mice resembled that of acute fear in normally reared mice, with increased activity in the basal forebrain and hindbrain. Additionally ELA resulted in decreased correlations of Mn(II) accumulations between brain segments, which fragmented further after acute threat. Staining for the norepinephrine transporter revealed clumping of distal projections, suggesting that neural activity dynamics could be due in part to ELA's effect on development of the noradrenergic system. Together our data find that ELA disrupts the arborization of noradrenergic projections and fragments neural activity in both basal state and during acute threat. Supported by NIMH RO1MH096093.

Disclosures: T.W. Uselman: None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Program #/Poster #: P601.04

Topic: F.04. Stress and the Brain

Support: CIHR
NSERC

Title: Effects of a maternal high-sucrose diet on fetal rat brain development

Authors: *D. R. SEIB, G. V. KACHKOVSKI, G. S. RUTLEDGE, H. W. CHEN, T. S. BODNAR, H. R. PRICE, A. C. COLLIER, K. K. SOMA;
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Abstract: Consumption of sucrose (table sugar) is high in much of the world. The effects of a maternal diet high in sucrose on the placenta and fetal brain remain unknown. In rats, maternal consumption of sucrose at a human-relevant level has effects on the mother's physiology and steroids, as well as long-lasting and sex-specific effects on the adult offspring's brain and behavior. In mothers, there are metabolic effects of sucrose intake, such as impaired glucose tolerance, increased liver lipids, and increased adipose inflammation. In mothers, sucrose intake also decreases corticosterone levels in the blood but not in the brain. In the adult male offspring, preference for a high-sucrose and high-fat diet increases due to maternal sucrose intake. Maternal sucrose intake also increases motivation for sugar rewards in a progressive ratio task in adult male offspring. In adult female offspring, corticosterone levels increase in the blood and brain as a result of maternal sucrose intake. In this study, we investigated the underlying mechanisms of the observed behavioral and endocrine effects in the adult offspring. Here, we examined cytokines and anti-inflammatory steroids in the placenta, amniotic fluid, and fetal blood and brain. In our model, we feed rat dams either a high-sucrose diet (26% of kCal) or an isocaloric, matched, control diet (1% sucrose) 10 weeks prior to and during gestation. At embryonic day 19 (E19), we collected maternal blood, placenta, amniotic fluid, fetal blood, and fetal brain. We use Palkovits punch to microdissect the placenta and fetal brain. Next, we use a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay, which is highly precise and specific, to measure multiple steroids (e.g. corticosterone, estrone, allopregnanolone). The method is highly sensitive, and we can measure neurosteroids in multiple regions of the fetal brain (e.g. prefrontal cortex, nucleus accumbens, hypothalamus, hippocampus). Moreover, we will examine steroidogenic enzymes and cytokines in the fetal brain and placenta. We will also examine neuronal proliferation, microglia and tyrosine hydroxylase immunoreactivity in the fetal brain. Current data show that maternal high sucrose diet leads to a 60% increase in dehydrocorticosterone (inactive metabolite of corticosterone) and a 100% increase in aldosterone in the dam's serum and amniotic fluid. Testosterone and androstenedione were significantly higher in the amniotic fluid of male fetuses than female fetuses. Ongoing experiments will examine how a maternal high sucrose diet affects brain development possibly by increasing inflammation.

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Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Topic: F.04. Stress and the Brain

Support: F31MH123041
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R01 MH119814
T32 DK059803

Title: Adolescent Stress Confers Resilience to Traumatic Stress in Adulthood: Role of the Prefrontal Cortex

Authors: *N. NAWREEN[1], E. M. COTELLA[1], R. D. MOLONEY[2], S. E. MARTELLE[3], K. M. OSHIMA[4], P. LEMEN[5], J. NIBLACK[5], R. JULAKANTI[5], M. FITZGERALD[5], M. L. BACCEI[7], J. P. HERMAN[6];
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Abstract: Stress during adolescence is usually associated with psychopathology later in life. However, under certain circumstances, developmental stress can promote an adaptive phenotype, allowing individuals to cope better with adverse situations in adulthood, thereby contributing to resilience. The aim of the study was to understand how adolescent stress alters behavioral and physiological responses to traumatic stress in adulthood. Sprague Dawley rats were subjected to adolescent chronic variable stress (adol CVS) followed by single prolonged stress (SPS) in adulthood. One week after SPS, animals were tested for acquisition, extinction, extinction recall and reinstatement of auditory-cued fear conditioning, with neuronal recruitment during reinstatement assessed by Fos expression. Patch clamp electrophysiology was performed to examine physiological changes associated with resilience. We observed that adol CVS blocked SPS-induced impairment of extinction learning (males) and enhancement fear reinstatement (both sexes). SPS effects were associated with a reduction of infralimbic (IL) cortex neuronal recruitment after reinstatement in males and increased engagement of the central amygdala in females, both of which were also prevented by adol CVS. We explored the mechanism behind reduced IL recruitment in male rats by studying the intrinsic excitability of IL pyramidal neurons. SPS reduced excitability of IL neurons and prior adol CVS prevented this effect, indicating that adolescent stress can impart resilience to the effects of traumatic stress by modification of IL output in males. Overall, our study suggests that prior stress exposure can limit the impact of a subsequent severe stress exposure in adulthood, effects that are mediated by sex-specific modification of infralimbic and amygdala signaling.

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Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Topic: F.04. Stress and the Brain

Support: NSERC Discovery Grant RGPIN-2019-04837
NSERC Discovery Accelerator Supplement RGDAS-2019-00033

Title: Intracerebroventricular infusion of corticosterone in neonatal mice

Authors: *H. BAJAJ[1], M. X. LI[1], K. M. GRAY[2], J. E. HAMDEN[3,4], M. SALEHZADEH[3,4], S. MCERLANE[5], K. K. SOMA[1,3,4];
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Abstract: Early life stress (ELS) has profound effects on brain development and function. Stressors activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased glucocorticoid (GC) secretion from the adrenal glands into the blood. Low GC levels in early life are crucial for normal neurodevelopment, and high GC levels lead to increased neuronal death and dendritic atrophy. Recent evidence suggests that, in early life, the brain can locally produce GCs, independently from the adrenal glands. Current ELS paradigms use manipulations that elevate circulating GC levels, such as maternal separation, endotoxin exposure, and systemic corticosterone administration (p.o., i.p. or s.c.). No study has delivered corticosterone directly to the developing brain. Here, we developed a simple and robust technique to administer corticosterone directly to the neonatal brain via a single intracerebroventricular (ICV) infusion into a lateral ventricle. Local anesthetic (lidocaine) was applied to the scalp of male and female postnatal day 5 (PND5) C57BL/6J mice. After 8 minutes, we administered 2 µL of either sterile saline (vehicle control) or corticosterone (5, 10, 15, or 45 ng/mL) (n=8/group) with a single ICV infusion. After 2.5 hours, we collected the brain, whole blood, and liver. Corticosterone concentrations were assessed via liquid chromatography tandem mass spectrometry (LC-MS/MS) in microdissected brain regions, whole blood, and liver. With higher doses of corticosterone, brain levels of corticosterone increased, whereas peripheral levels of corticosterone remained low. This study provides a novel paradigm to administer corticosterone directly to the brain without general anesthesia, which is a potent stressor. Our paradigm can be used to specifically manipulate levels of corticosterone, or other neuromodulators, in the brain of neonatal mice.

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Poster

P601. Early-Life Stress: Neural, Neurochemical, and Physiologic Effects

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Topic: F.04. Stress and the Brain

Support: NICHD T32-HD098066
NHLBI R01HL116585
IDDRC U54HD090257
CIHR MOP-81116

Title: Functional connectivity at term equivalent age predicts frequency of neonatal intensive care unit procedures in infants born very preterm using machine learning.

Authors: *K. M. COOK, J. DE ASIS-CRUZ, J.-H. KIM, N. ANDESCAVAGE, S. K. BASU, A. J. DU PLESSIS, C. LIMPEROPOULOS;
Children's Natl., Washington, DC

Abstract: Compared with full-term infants, Extreme and Very Preterm (EPT/VPT) infants born <32 gestational weeks (GW) are at increased risk of long-term motor, cognitive, and neuropsychological disorders, including autism, ADHD, and schizophrenia. The third trimester is a critical period for cortical development and the prematurely ex-utero neonatal intensive care unit (NICU) environment, which includes sensory overload and frequent stressful procedures (e.g., heel pricks, nasogastric tube placements, and catheterizations), is a putative contributor to the long-term neurodevelopmental sequelae of EPT/VPT survivors. To further address the role of NICU stress on brain connectivity at term equivalent age, we performed resting state fMRI at mean 39 GW in 62 EPT/VPT-born infants with no/minor brain injury. Using functional connectivity between 90 anatomically defined ROIs, we utilized linear support vector regression (SVR) to predict the total number of NICU stressful procedures (mean = 118.79, range = 55-197) between birth and term equivalent age. First, 20% of the sample (n=12) was withheld to perform feature selection through elastic net regularization, reducing the total number of connections to 122 (~3% of the original 4005). Subsequently, the remaining 80% of the data were split into 1,000 random 70%-10% (n=44/6) training-test sets. A separate SVR model was then trained for each split using 10-fold cross validation. Mean test accuracy across splits was $r = 0.646$ with a RMSE of 29.81 (20% of the range). Importantly, although there is a strong correlation between GW at birth and the number of NICU procedures ($r = -0.48$, $p < 0.001$), our SVR model was unable to reliably predict age at birth ($r = 0.09$, RMSE = 2.39) suggesting that we successfully isolated features sensitive to NICU stress, not those simply those related to GW at birth. The 122 edges were then characterized, calculating the mean model beta weights for across all 1,000 procedure prediction models. Across edges, 72 (60%) exhibited a negative relationship between connectivity strength and procedure number - heavily represented in the right inferior temporal gyrus and left precentral gyrus, paracentral lobule, and supplemental motor area. Positive relationships between connectivity and procedure number were observable in the fusiform gyrus and orbital frontal regions. Our results support the notion that NICU stress exposure is associated with altered functional brain connectivity in EPT/VPT infants at term age, independent of gestational age at birth, and may implicate mechanistic precursors to developmental deficits.

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Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P611.01

Topic: F.04. Stress and the Brain

Support: HHMI Gilliam Fellowship
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Title: Guanfacine acts upon BNST alpha2a adrenergic heteroreceptors to increase calcium activity in a pro-reinstatement circuit-specific manner

Authors: *J. A. BROWN[1,2], A. Y. JIN[1,2], S. W. CENTANNI[3,2], M. N. BEDENBAUGH[3,2], R. B. SIMERLY[3,2], D. G. WINDER[3,2];
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Abstract: Guanfacine, an alpha2a-adrenergic receptor (α_{2a}-AR) agonist, decreases anxiety associated with drug withdrawal and reinstatement behavior, but its mechanisms of action are unknown. We recently found that α_{2a}-ARs also play a role in driving reinstatement of drug seeking behavior, potentially through activation of the bed nucleus of the stria terminalis (BNST). We have shown that guanfacine activates and inhibits cells in the BNST and has pro-reinstatement effects. Here, we investigated the activity and circuitry of BNST cells activated by guanfacine, termed "guansembles". We applied a Fos-TRAP (*T*argeted *R*ecombination in *A*ctive *P*opulations) approach and validated this as a viable method to investigate guansembles by finding that repeated exposure to guanfacine activates overlapping cell populations. We combined this Fos-TRAP approach with cre-dependent GCaMP fiber photometry to record *in vivo* calcium dynamics in guansembles following exposure to guanfacine and during restraint stress. Guanfacine and restraint stress increased and decreased neuronal activity in guansembles, respectively. The effect of restraint stress on guansembles attenuated over time with repeated restraint. Next, we paired Fos-Trap with a cre-dependent PKA sensor, FLIM-AKAR, and used fluorescence lifetime photometry (FLiP) to record from guansembles *in vivo* to test the hypothesis that guanfacine regulates cAMP signaling in these cells. Results suggest that guanfacine inhibits PKA signaling in guansembles, consistent with activation of a Gi-coupled GPCR. We also observed a decrease in PKA signaling during acute restraint stress. To investigate the neural circuits in which guansembles participate, we utilized a FosTrap-guided retroviral rabies tracing approach to explore the monosynaptic connections onto BNST guansembles. Using tissue clearing and light sheet microscopy, we visualized and quantified BNST guansemble afferents. This approach revealed multiple areas including regions of the thalamus, hypothalamus, and the striatum. These results support guanfacine's activation of pro-reinstatement circuitry. Overall, this study identified Fos-TRAP as a viable method to study guansembles. Our *in vivo* neuronal activity studies support the hypothesis that guanfacine has an excitatory post-synaptic signaling effect on neuronal activity. Our tracing studies revealed guanfacine activation in a potentially novel pro-reinstatement circuit. Understanding the microcircuitry involving BNST guansembles has the potential to uncover the regulatory mechanisms underlying stress-induced reinstatement and α_{2a}-AR agonists as an effective therapeutic.

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Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P611.02

Topic: F.04. Stress and the Brain

Support: R37-AA019455
T32-NS007491

Title: Determining the role of BNST GluN2D expression in active coping bouts during repeated restraint stress

Authors: *M. A. DOYLE, J. A. BROWN, G. J. SALIMANDO, D. N. ADANK, D. G. WINDER; Vanderbilt Univ., Nashville, TN

Abstract: Alcohol use disorder (AUD) is a chronic, relapsing disease that is highly comorbid with anxiety and depression. These states of negative affect experienced during withdrawal are hypothesized to drive alcohol seeking and relapse behavior. The bed nucleus of the stria terminalis (BNST) is a brain region responsible for the integration of negative affect and alcohol-related behaviors, and it has been implicated in stress-induced ethanol seeking in rodent models. Our lab recently identified a significant decrease in BNST mRNA transcript expression of the NMDAR subunit GluN2D (*grin2d*) during protracted withdrawal from chronic ethanol in female mice, a timepoint at which these animals display increased anxiety- and depressive-like behaviors. Consistent with these data, mice lacking GluN2D show basal increases in anxiety- and depressive-like behaviors. Notably, our lab has shown that BNST knockdown of GluN2D is capable of inducing this phenotype, suggesting a role for BNST GluN2D-containing NMDARs in regulating negative affect; however, it remains unknown if GluN2D expression is capable of modifying behavioral responses during stressful stimuli. As coping strategies in response to stressors have been linked to stress susceptibility, we sought to characterize the effect of constitutive GluN2D knockout on active coping bouts measured during a repeated restraint stress paradigm in male and female mice. EthoVision and DeepLabCut were used to analyze movements. We found a significant Sex x Genotype interaction in both the total duration of time spent in active coping bouts and the average duration of these bouts, with a trend in total bout counts. Current work in the lab focuses on characterizing protein level changes in GluN2D expression, with preliminary data suggesting that BNST GluN2D levels may be decreased following acute and repeated restraint stress in male but not female mice. In parallel, ongoing studies seek to use pharmacological approaches to better define the potential implication of changes in active coping bouts. Future directions aim to characterize the role of GluN2D expression in the interaction of chronic ethanol exposure and stress, as preliminary data suggest that GluN2D constitutive knockout mice exhibit a deficit in BNST short term potentiation following chronic intermittent ethanol exposure. Together, given the restricted CNS expression of this subunit, exploration of GluN2D control of stress circuit actions may lead to a novel therapeutic target to consider in AUD treatment.

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Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

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Topic: G.04. Emotion

Support: NIH CNAP/COBRE Grant# P20GM113109
Human Frontiers Science Program HFSP (RGP0016/2019

Title: Zebrafish pallial eversion demystified: Lhx5- and vGlut2a-driven GFP-expressions in zebrafish identify missing links to the mammalian amygdala

Authors: *T. MUELLER;
Kansas State Univ., Manhattan, KS

Abstract: The telencephalon zebrafish, a carp-like (cyprinid) teleost fish, shows an outwardly-grown (everted) morphology, that looks very different from inwardly grown (evaginated) forebrains of mammals. For more than a century, comparative neurologists have struggled to explain how the everted forebrain can be compared with those of mammals in terms of homology and evolution. Some classical studies on the teleostean forebrain suggested that radial glia orientation and tela attachment sites speak in favor of a simple eversion process resulting in a telencephalic topology that is incomparable at large to the mammalian situation (Nieuwenhuys 2009). Likewise, recent fate mapping and genetic birth dating studies (Furlan et al. 2017) in zebrafish supported a simple outward-in pallial organization similar to those of classical studies and in support of the increasingly popular yet wrong idea that the teleostean/actinopterygian telencephalon strongly deviates from the prosomeric organization of tetrapods (Yamamoto, Bloch, and Vernier 2017).
Here, I will present results of a larger scale analysis of the distribution of molecular architecture versus *vGlut2a*- and *lhx5*-driven green fluorescent protein (GFP) expression in adult transgenic reporter lines in comparison to GFAP, which labels radial glia and their processes (Porter and Mueller 2020). The detailed analysis of these molecular expression patterns let us discover the missing evolutionary links between the evaginated and everted telencephalon ground plan allowing us to determine the true nature of major pallial and subpallial territories with respect to their homologies in tetrapods. Specifically, we identified previously overlooked parts of the thalamic eminence (EmT) and a subnucleus of the medial amygdala, which we called the posterior medial amygdala/rostral EmT (MeAp/EmTr). What is more, based on our analyses of both radial glia distribution and the tela attachment sites in relationship with the olfactory pallial divisions, we explained the topology of the everted telencephalon and re-defined pallial, subpallial, and EmT derivatives of the extended olfactory amygdala and in adult zebrafish. The results show that the teleostean telencephalon is the result of a complete and complex eversion. At large, our results indicate that a prosomeric amygdala ground plan as well as a homolog to the mammalian isocortex evolved in a common ancestor of teleosts and tetrapods.

Disclosures: T. Mueller: None.

Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

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Schmitt Program on Integrative Neuroscience (SPIN) GR504304

Title: Cortical granularity shapes the organization of afferent paths to the amygdala and its striatal targets in nonhuman primate

Authors: *A. C. MCHALE[1], Y. T. CHO[2], J. L. FUDGE[1];
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Abstract: The prefrontal cortex (PFC) and insula, amygdala, and striatum form interconnected networks that drive motivated behaviors. We previously found a connectional trend in which the relative granularity of the ventromedial and orbital PFC/insula predicted afferent connections to specific regions of the basal nucleus, and also the topography of efferent connections in amygdalo-striatal paths, in the same animal (Cho et al 2013). To further interrogate the relationship between cortex, amygdala, and striatum, and to better define the 'limbic (amygdala-recipient) striatum', we conducted tract tracing studies in two cohorts of primates (*macaque fasicularis;* Male n = 12, Female n = 1, mean weight = 4.46 kg, mean age = 4.9 years; Cohort 1: n = 8 animals & 11 total injection sites; Cohort 2: n = 6 animals & 6 total injection sites). We used an analytic strategy based on a cortical granularity index to define the topography of cortico-amygdalo-striatal (indirect) and cortico-'limbic' striatal (direct) paths originating in the entire PFC and insula. Using a quantitative approach, we found that the level of cortical granularity predicts the complexity and location of projections to both the basal nucleus of the amygdala and striatum. Remarkably, 'cortical-like' basal nucleus subdivisions also followed these rules in their projections to the striatum, defining the 'limbic' striatum. The ventral basal nucleus was the 'foundational' input, with progressively more dorsal basal nucleus regions gradually adding inputs as the 'limbic striatum' extended caudally. In both 'direct' and 'indirect' paths to the 'limbic' striatum, agranular cortices formed a 'foundational', broad projection, and were joined by inputs from progressively more differentiated cortices. Together, the 'indirect' and 'direct' paths follow consistent rules dictating projection strength and complexity to their striatal targets. Within this general rule, subtle differences in the indirect and direct paths were found. In cortico-amygdalo-striatal paths (indirect), we found that agranular cortices consistently dominate amygdala inputs to the striatum; in contrast, cortical (direct) inputs to these 'limbic' (amygdala-recipient) striatal sites create gradual shifts in connectivity fingerprints, with differences along the rostro-caudal axis of the 'limbic' striatum.

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Poster

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NIH MH122023 to SSN

Title: Localization and contribution of basal forebrain GABAergic input to the basolateral amygdala

Authors: T. TUNA[1], T. BANKS[2], M. STROUD[2], S. S. NAIR[2], *G. UNAL[1];
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Abstract: Basal forebrain (BF) GABAergic neurons from the medial septum selectively target GABAergic interneurons of the hippocampus, contributing to the excitability of the principal neurons (PNs). This projection is key for the generation of hippocampal theta oscillations (4-12 Hz), which correlate with hippocampal forms of learning and memory. There is a similar BF GABAergic projection to the basolateral amygdala (BLA) with unclear electrophysiological and functional role. We hypothesize that BF GABAergic projections carry out a similar neuromodulatory function in all of their target limbic structures by regulating local network activity via phase-dependent disinhibition of the principal cells. To test this hypothesis, we localized BLA-targeting BF cell groups by retrograde tract-tracing, and revealed their molecular profiles by fluorescent immunohistochemistry in male Wistar rats. The densest retrograde labeling was observed in the horizontal diagonal band (hDB), ventral pallidum (VP) and substantia innominata (SI) nuclei. We observed BLA-projecting parvalbumin (PV)-immunopositive or calbindin (CB)-immunopositive putative GABAergic neurons in the VP. The PV+ subgroup consisted of 5% of the retrogradely-labeled VP neurons and 12% of its PV cell population, whereas the CB+ subgroup was about 13% of the labelled neurons and 10% of the VP CB population. Anterograde tract-tracing with PHA-L suggest that both groups target putative GABAergic interneurons in the BLA. To shape and complement ongoing in vivo electrophysiological experiments, we developed a 1000-cell biophysical BLA model by incorporating tested properties of an earlier hippocampal network model (Hummos & Nair, 2017). Single cell models were created for PNs as well as PV+, somatostatin+, and calretinin+ BLA interneurons. The afferents comprised of excitatory thalamic/cortical inputs, rhythmic BF GABAergic projections, and modulatory BF cholinergic input introduced at three different states (low, baseline and high). Synaptic communication was modeled with AMPA, NMDA, $GABA_A$, and $GABA_B$ currents. To mimic the aforementioned phase-dependent disinhibition, 90% of the BF GABAergic input was given to the PV+ interneurons while 10% was directed to the PNs. As hypothesized, local theta oscillations arise when both the cholinergic and the GABAergic input from the BF are present in addition to the excitatory thalamic/cortical input. Following the case in the hippocampus, removing the cholinergic or the GABAergic BF input alone decreases the BLA theta power. The oscillation ceases completely when the GABAergic input is cut together with either the cholinergic or the thalamic/cortical input.

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Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P611.06

Topic: G.04. Emotion

Support: NIMH Grant MH097988,

Title: Activation of lateral parabrachial nucleus pituitary adenylate cyclase-activating polypeptide afferents in the bed nucleus of the stria terminalis increases anxiety-like behavior

Authors: *M. N. BOUCHER[1], S. K. MORIARTY[1], E. B. KOTLER[1], M. R. RICE[1], V. MAY[2], S. E. HAMMACK[1];
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Abstract: In order to improve treatments for stress-related psychiatric disorders it is important to understand the neural circuitry underlying emotional behavior. The bed nucleus of the stria terminalis (BNST) has been long studied for its role in many stress related pathologies, such as anxiety, pain, depression, and addiction. Our prior work has demonstrated that pituitary adenylate cyclase-activating polypeptide (PACAP) receptor activation in the BNST is both necessary and sufficient for many of the behavioral consequences of chronic stress, as well the stress-induced reinstatement of cocaine seeking behaviors. While the BNST contains local PACAP-expressing neurons, a major source of afferent PACAP is the lateral parabrachial nucleus (LPBn), and we have previously shown that excitotoxic lesioning of the LPBn substantially decreased PACAP immunostaining in the BNST. Here, we used chemogenetic techniques to selectively activate LPBn PACAP afferents in the BNST. We injected AAV2.hSyn.DIO.hM3D(Gq).mCherry, Cre-dependent AAVs containing excitatory designer receptors exclusively activated by designer drugs (DREADDS), into the LPBn of PACAP-IRES-Cre mice. Immediately before behavioral testing, CNO was infused directly into the BNST. We found that after selective activation of LPBn PACAP afferents in the BNST, mice spent significantly less time in the open arms of the elevated plus maze compared with controls, while total locomotor activity was not affected. These results indicate that activation of PACAPergic LPBn projections to the BNST may play an important role in producing anxiety-like behavior. On-going studies are examining whether the anxiogenic effect of LPBn PACAP afferent activation is dependent on BNST PACAP receptor activation.

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Poster

P611. Hypothalamus and Extended Amygdala in Stress, Fear, and Anxiety II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P611.07

Topic: F.04. Stress and the Brain

Title: The role of noradrenergic signaling from the solitary nucleus to the central amygdala in post-trauma threat responses and autonomic function

Authors: *C. E. STELLY[1], K. J. ANDERSON[1], A. M. HALL[1], J. P. FADOK[2], J. G. TASKER[3]; [2]Psychology and Tulane Brain Inst., [3]Cell and Mol. Biol., [1]Tulane Univ., New Orleans, LA

Abstract: After traumatic stress, a subset of individuals develop pathological changes in behavior and autonomic function. Norepinephrine (NE) signaling is implicated in the pathophysiology of post-traumatic stress; however, studies have focused primarily on one of two sources of NE projections, the locus coeruleus. The solitary nucleus (NTS) also provides noradrenergic innervation to subcortical structures, including the central amygdala (CeA), a key brain region for generating behavioral and autonomic responses to threat. Persistent fear responses that interfere with daily activities and hyperarousal are dissociable outcomes of trauma. We employed two stress paradigms to model these respective outcomes in mice and examine the contribution of noradrenergic NTS projections. Persistent, generalized fear was elicited with discriminative fear conditioning. In this paradigm, fear cues suppressed ongoing reward-seeking, and this conditioned suppression effect increased in magnitude and generalized to neutral cues over several weeks. Hyperarousal was elicited by a single traumatic footshock followed by repeated, brief exposures to a distinct but associated 'reminder' context. In this paradigm, a subset of mice (50%) displayed a sensitized acoustic startle response and an increased resting heart rate. To test the necessity of the NTS-CeA projection for these outcomes, Gi-DREADDs were expressed selectively in noradrenergic NTS neurons and activated by local agonist infusion in the CeA.

Disclosures: C.E. Stelly: None. **K.J. Anderson:** None. **A.M. Hall:** None. **J.P. Fadok:** None. **J.G. Tasker:** None.

Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.01

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH grant (NIA) AG032959
JPB Foundation
Robertson Therapeutic Development Fund
NIH grant DK120869
Kavli NSI Postdoctoral Fellowship

Title: Melanocortin 4 receptor stimulation prevents antidepressant-associated weight gain in mice caused by long-term fluoxetine exposure

Authors: *M. J. ORTUNO ROMERO[1], M. SCHNEEBERGER PANE[2], A. ILANGES[2], F. MARCHILDON[2], K. PELLEGRINO[2], J. M. FRIEDMAN[2], P. DUCY[1];
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Abstract: Contrasting with the predicted anorexigenic effect of increasing brain serotonin signaling, long-term use of selective serotonin reuptake inhibitors (SSRIs) antidepressants is correlated with body weight gain. This adverse outcome increases the risk of transitioning to obesity and interferes with treatment compliance. We show that orally administered fluoxetine (Flx), a widely prescribed SSRI, increases body weight by enhancing food intake in healthy mice at two different time points and through two distinct mechanisms. Within hours, Flx decreases the activity of a subset of brainstem serotonergic neurons by triggering autoinhibitory signaling through the serotonin Htr1a receptor. Upon longer treatment, Flx blunts serotonin Htr2c receptor expression/signaling, decreases the phosphorylation of Creb and Stat3 and dampens the production of pro-opiomelanocortin (POMC)/alpha-melanocyte-stimulating hormone (α-MSH) in hypothalamic neurons, thereby increasing appetite. According with the fact that α-MSH suppresses appetite by signaling through the melanocortin 4 receptor (Mc4r), exogenous stimulation of Mc4r by co-treating mice with Flx and lipocalin-2, an anorexigenic hormone signaling through this receptor, normalizes appetite and body weight. Flx and other SSRIs also inhibit CREB/STAT3 phosphorylation in a human neuronal cell line suggesting that these non-canonical effects could contribute to the weight gain observed in long-term users of SSRIs. By defining the molecular basis of the long-term SSRIs-associated weight gain our study proposes a therapeutic strategy to counter it.

Disclosures: M.J. Ortuno Romero: None. **M. Schneeberger Pane:** None. **A. Ilanges:** None. **F. Marchildon:** None. **K. Pellegrino:** None. **J.M. Friedman:** None. **P. Ducy:** None.

Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.02

Topic: F.09. Food and Water Intake and Energy Balance

Support: NIH Grant MH120498
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Title: Decreases in DNA 5-hydroxymethylation within the hypothalamus control weight gain in a sex-specific manner during the development of obesity

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Abstract: Obesity affects about 34% of the U.S. population and is a major contributing factor associated with health risks such as cancer, heart disease, and diabetes. Understanding the neurobiology of obesity is

crucial for responding to the etiology of this disease. The hypothalamus is responsible for controlling food intake and numerous studies have observed altered hypothalamic gene regulation in obesity models. However, little is known about the mechanisms controlling persistent changes in gene expression in the hypothalamus during obesity. Epigenetic mechanisms, such as DNA methylation, serves as powerful mechanisms of persistently controlling gene transcription throughout the lifetime of the individual. Yet little is known about whether hypothalamic DNA methylation changes contribute to the development of obesity. Here, we found that rats fed a high fat diet over the course of 7 weeks gained more weight per gram of food compared to rats that were fed standard rat chow with the overall percentage of weight gain being significantly higher in females than males. For DNA methylation levels, we found that male, but not female, rats fed a high fat diet had decreased global levels of DNA 5-hydroxymethylation (5-hmC), a potent transcriptional activator, within the hypothalamus. Importantly, correlational analyses revealed that within the hypothalamus of the male, but not female, rats fed a high fat diet there was an inverse relationship between body weight and DNA 5-hmC. This indicates that as DNA 5-hmC levels decreased, bodyweight increased. Consistent with this, only 3 weeks of exposure to the high fat diet, which was not sufficient to cause abnormal weight gain, decreased 5-hmC levels in the hypothalamus of male rats, suggesting that the decreases in DNA 5-hmC preceded significant weight gain. CRISPR-dCas9-VP64 mediated increases in expression of the DNA 5-hmC enzymes (*Tet1/2/3*) in the hypothalamus slowed weight gain in male rats fed a high fat diet relative to control injected animals, which resulted in a lower percentage of bodyweight gained over 7 weeks on the high fat diet. Conversely, CRISPR-dCas9-KRAB mediated reductions in the *Tet1/2/3* enzymes did not artificially stimulate weight gain in male rats fed a standard chow diet, suggesting that reductions in hypothalamic DNA 5-hmC contribute to, but are not sufficient to cause, abnormal weight gain. Collectively, these results indicate that decreases in hypothalamic DNA 5-hmC likely facilitate weight gain during the development of obesity in a sex-specific manner. Current experiments are underway to determine whether altered DNA 5-hmC occurs at genes that specifically regulate appetite.

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Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.03

Topic: F.09. Food and Water Intake and Energy Balance

Support: UW-Eau Claire Summer Research Experiences for Undergraduates
UW-Eau Claire Student-Faculty Research Collaboration Grants

Title: Does clozapine induce “hunger” in rats trained to discriminate between 2 and 22 hours food deprivation?

Authors: *S. D. PETIT, G. E. GROSLAND, E. K. CEDARBLOOM, K. D. NORMAN-KLATT, A. M. VIGIL, D. C. JEWETT;
Univ. of Wisconsin - Eau Claire, Eau Claire, WI

Abstract: In humans, weight gain is a side effect of several atypical antipsychotics. The underlying mechanism behind this effect is unclear. Previous work has demonstrated that clozapine often, but not always, increases food intake in rats. Clozapine also increases rodents' motivation to acquire food under a progressive ratio schedule. The current study investigated whether clozapine would induce discriminative stimulus effects similar to "hunger". Eleven male, Sprague-Dawley rats were trained to discriminate between 22 hrs of food deprivation and 2 hrs of food deprivation in a two-lever, operant choice task. Following 2 hrs food deprivation, rats were trained to emit 15 responses (FR 15) to the right lever to earn a 45 mg food pellet. Left lever presses were punished with 8 sec of darkness under the FR 15. Training sessions lasted until subjects earned 10 food pellets or 15 min elapsed. Under 22-hrs deprivation conditions, the contingencies were reversed (left lever presses were reinforced with food delivery, and right lever presses resulted in 8 seconds of darkness). Discrimination acquisition was defined as 80% or greater condition appropriate responding for 8 out of 10 consecutive sessions. After acquiring the discrimination (mean = 76, SEM = 6 sessions), subjects were food deprived for 2 hrs and administered clozapine (1.0-5.6 mg/kg, s.c.) or vehicle (30% DMSO; 1.0 ml/kg, s.c.). The discriminative stimulus effects of food deprivation and response rates were assessed every 15 min for 2 hrs. During these 5 min test sessions, 5 food pellets could be earned and lever presses toward either lever were reinforced under the FR 15. Clozapine (1.0-3.2 mg/kg) did not alter either the discriminative stimulus effects of 2-hr deprivation or lever-pressing rates. Clozapine (5.6 mg/kg) significantly decreased lever pressing rates and significantly increased 22-hrs deprivation-appropriate responding. Approximately 50% of rats selected the lever associated with 22-hrs food deprivation following 5.6 mg/kg clozapine. These data suggest that clozapine may increase food intake by inducing "hunger-like" discriminative stimulus effects.

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Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.04

Topic: F.09. Food and Water Intake and Energy Balance

Support: Swiss National Science Foundation 310030_189110

Title: Hypothalamic orexin/hypocretin neurons mediate behavioural effects of dietary non-essential amino acids

Authors: *P. VISKAITIS[1], C. GARAU[2], M. ARNOLD[1], L. T. JENSEN[3], L. FUGGER[4], D. PELEG-RAIBSTEIN[1], D. BURDAKOV[1];
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Abstract: Dietary macronutrients can exert distinct physiological and behavioural consequences via direct or indirect effects on the brain. While a huge body of research exists detailing sensing pathways and outcomes of many nutrients, relatively little is known about such effects of non-essential amino acids

(nAAs). Hypothalamic hypocretin/orexin neurons (HONs) are prospective nAA in vivo sensors and/or mediators of nAA behavioural/physiological effects due to unique HONs' membrane properties and their roles in control of behaviour, metabolism and feeding. Specifically, it was suggested that HONs promote feeding, while their suppression by ingested calories mediates negative feedback control of feeding. However, the natural activity dynamics of HONs during intragastric nutrient absorption and metabolism remain unknown. To investigate the role of HONs in gut-brain communication, here we combined genetically-targeted neural manipulations and recordings with deep learning-assisted classification of post-ingestive behavioural effects. We show that intragastric infusions of nAAs, but not isocaloric glucose, rapidly activate HONs, suppress feeding and evoke exploratory behaviours in mice. We demonstrate that this non-canonical post-ingestive HON activation is crucial for the nAA-induced shift from feeding to exploring, because genetic ablation of HONs abolishes, while optogenetic activation of HONs recapitulates the nAA-induced behavioural switch. Collectively, these results uncover a previously unsuspected role of post-ingestive HON activation in the suppression of feeding, and identify a neural mechanism explaining behavioural differences between isocaloric nutrients.

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Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.05

Topic: F.09. Food and Water Intake and Energy Balance

Support: CSU - AAUP Faculty Research Grant

Title: The satiating benefits of low-intensity exercise on high-fat feeding behavior

Authors: *J. CORDEIRA, E. HOEGLER;
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Abstract: We previously showed that voluntary wheel running in mice for 30 minutes per day reduced weekly intake of very high-fat diet (VHFD). Here, we aimed to further characterize the benefits of voluntary exercise on high-fat feeding behavior. We provided mice with VHFD *ad libitum* and either an open or locked running wheel for 30 minutes daily. We measured food intake (amount) and meal structure (number, size, frequency and duration) during the 12-hour light (inactive) and dark (active) periods. We also assessed exercise intensity by measuring blood lactate levels before and after wheel running. Wheel running reduced VHFD intake significantly and exclusively during the light period, through reductions in meal size and duration. Meal number and inter-meal intervals were unchanged. Interestingly, these results depended on mice being fed freshly thawed VHFD daily, which stimulated overeating. Exercise had no benefit after VHFD was several days old (during weekly food replacement). Blood lactate levels before and after wheel running were not different. Altogether, results indicate that low-intensity exercise reduces overconsumption of palatable, VHFD by enhancing satiation during the inactive period. Since inactive-period feeding is especially obesogenic, understanding the mechanisms

underlying enhanced satiation from exercise may help in the treatment or prevention of diet-induced disease. Our work also identifies food quality/spoilage as a potentially confounding variable in experiments using VHFD.

Disclosures: J. Cordeira: None. **E. Hoegler:** None.

Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.06

Topic: F.09. Food and Water Intake and Energy Balance

Support: CIHR project grant # 377831

Title: Impact of the lipase alpha/beta-hydrolase domain 6 in the ventral tegmental area on feeding and reward

Authors: *D. LAU[1], L. DÉCARIE-SPAIN[2], A. ARDILOUZE-GROLEAU[1], C. HRYHORCZUK[3], D. RODAROS[4], S. MADIRAJU[5], M. PRENTKI[6], S. E. FULTON[7];
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Abstract: Endocannabinoids (eCB) are neuromodulatory lipid signalling molecules known to regulate the activity of mesolimbic dopamine neurons of the ventral tegmental area (VTA) to support reward-motivated behaviour. Alpha/beta-hydrolase domain 6 (ABHD6) is a post-synaptically localized serine hydrolase that degrades the eCB 2-arachidonoylglyerol, controlling its accumulation and signalling actions at cannabinoid type 1 receptors in a physiological range. We previously established a substantial role for ABHD6 in the nucleus accumbens (NAc) on body weight regulation and food-motivated behavior, however the contribution of VTA ABHD6 on to energy balance and the rewarding effects of food remained unknown. We assessed ABHD6 expression in the VTA using RNAscope in situ hybridization, observing expression of ABHD6 within both TH-expressing neurons and non-TH-expressing cells. To test the role of neuronal ABHD6 on feeding and metabolism, ABHD6 was conditionally deleted in neurons via adeno-associated virus microinjections to the VTA delivering Cre (or GFP control) under the control of a synapsin promotor in adult male ABHD6-LoxP mice to generate ABHD6^{VTA-KO} mice. Four weeks after surgery, mice (n=6-10/group) were subjected to a 22 hr fast with refeeding responses on chow diet, with no significant differences observed between groups. In addition, weekly body weight and cumulative food intake was measured over a 6-week period on chow diet, with a significant group main effect and group x time interaction (2-way ANOVA) showing increased food intake in ABHD6^{VTA-KO} mice. Thereafter, mice were subjected to metabolic cages for measurement of energy expenditure, respiratory exchange ratio (RER), and ambulatory locomotor activity, where

ABHD6^{VTA-KO} mice were found to have significantly reduced RER during the dark cycle. Mice were then switched to a high-fat diet (60% kcal from fat) with body weight and food intake measured weekly for 12 weeks, with no differences in body weight or food intake observed. Following this, metabolic measures were recorded via CLAMS on high-fat diet, with significantly reduced ambulatory activity during the light cycle in ABHD6^{VTA-KO} mice. To examine food-motivated behaviour, a separate group (n=8-10/group) mice were trained on an operant task to earn high-fat/high-sugar pellet food rewards. Mice were tested in a progressive ratio operant task before and after a fast, with no differences observed between genotypes. These results illuminate the influence of ABHD6 in the VTA on energy balance, and contrast with its significant impact in the NAc, a region innervated by VTA neurons, on body weight regulation and reward-directed behaviors.

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Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.07

Topic: F.09. Food and Water Intake and Energy Balance

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Title: Effects of maternal hyperglycemia associated with snack intake on offspring high-protein, high-fat and high-sugar diets preference

Authors: *G. V. SILVA[1], M. G. MARTINS[1,2], G. P. OLIVEIRA[1,2], A. G. CRUZ[1,2], L. P. RODRIGUES[1], B. C. WOODSIDE[3], A. C. I. KISS[1,2];
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Abstract: Abnormalities in maternal metabolism or nutrition can increase human and rodent offspring susceptibility to develop obesity and metabolic disorders. There is ongoing interest in the role of offspring macronutrients preference play in this scenario. Since brain circuits involved in feeding behavior starts developing during pregnancy, those conditions may impact offspring food preference. Previous studies have shown that maternal nutrition may influence offspring food preference. Additionally, maternal hyperglycemia can change offspring food intake. However, the effects of their association on offspring food preference have not been explored yet. Therefore, the present study aimed to evaluate the effects of maternal hyperglycemia associated with snack intake on offspring food preference. In order to achieve this goal, initial and sustained food preference to high-protein, high-sugar, and high-fat diet (HPD, HSD, and HFD, respectively) in infant and adult offspring from normo- or hyperglycemic dams, that received

only chow or chow plus snacks, was evaluated. Sprague-Dawley rats were mated and on pregnancy day 0 (PD0) were divided in two groups: dams fed with regular chow or regular chow plus snacks. Snacks were comprised of potato chips and 1.5% sucrose solution and were offered from PD0 until lactational day 14. On PD7, half of dams from both groups were rendered hyperglycemic by streptozotocin intraperitoneal injection (STZ, 35mg/Kg). Thus, four experimental groups were obtained: Control (n=15), Control-Snack (n=12), STZ (n=12), and STZ-Snack (n=12). Dams gave birth naturally and litters were culled to 8 pups (4 males and 4 females). HPD, HSD, and HFD preference were evaluated in female and male offspring on infancy (PND30) and adulthood (PND75). On the test day, 3 males and 3 females from each litter were housed on individual cages and fasted for 12 hours. Food preference was then evaluated by offering two different kinds of powdered diet: regular chow vs HPD, HSD, or HFD. Fasting animals were given access to both diets in the early dark phase of the cycle, and food intake was assessed 1, 12 and 36 hours later. Food preference was determined as the percentage of consumed modified diet in relation to the total amount consumed of both diets (regular chow plus modified diet). In general, infant animals exhibited a lower preference to all modified diets than adults. Offspring from hyperglycemic dams exhibited a lower preference to HSD and HFD diets, while offspring from snack-fed dams exhibited a lower preference to HPD. No effects of their association were observed. We concluded that maternal hyperglycemia and snack intake impaired offspring food preference.

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Poster

P651. Feeding and Body Weight: Pharmacological and Endogenous Regulators

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P651.08

Topic: F.09. Food and Water Intake and Energy Balance

Support: UG3 DA048353
R01 DA25267

Title: Differential Effects of Mitragynine and Morphine on Unconditioned Food and Water Intake

Authors: *J. D. ZUARTH GONZALEZ[1], F. LEON[2], M. MOTTINELLI[2], C. R. MCCURDY[2], T. HIRANITA[1], G. DE LARTIGUE[1], L. R. MCMAHON[1];
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Abstract: Amidst the current opioid public health crisis, compounds of interest have emerged in efforts to tackle the opioid epidemic. Kratom (Mitragyna Speciosa) and associated commercial products are used to self-treat a plethora of ailments including pain and opioid dependence. Among various constituents in kratom, mitragynine is the primary alkaloid. In vitro studies show that mitragynine binds to opioid receptors (e.g. Obeng et al, 2020). Studies showing in vivo opioidergic activity of mitragynine are lacking. The aim of the current study was to characterize the effects of mitragynine on unconditioned intake of food and water and compare to those of the opioid agonist, morphine. Methods: 24 male Sprague-Dawley rats received morphine or mitragynine (each, 1.78, 5.6, 17.8, 56 mg/kg, IP) while ad

libitum intake of food and water was constantly monitored using an automated system beginning at dark onset. A separate group was used to testthe pretreatment effects of opioid antagonist, naltrexone. Results: Both morphine and mitragynine showed a biphasic dose effect on food, in which low doses increased food intake, whereas higher doses decreased food intake. Both hyperphagic and hypophagic effects of morphine were reversed by naltrexone but only the hyperphagic effects of mitragynine were antagonized by naltrexone. Interestingly, morphine monotonously decreased water intake, however, the trend for mitragynine was to increase water intake. Conclusion: These data suggest that opioidergic signaling mediates the hyperphagic effects of mitragynine but hypophagia induced by the high dose of mitragynine might recruit other receptors populations. Naltrexone was ineffective reversing the adipsic effects of morphine and mitragynine, which suggests that a non-opioid mechanism is involved for fluid intake.Supported by National Institute on Drug Abuse grants UH3 DA048353 and R01 DA047855.

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Poster

P678. Motivation: Subcortical Neurocircuitry V

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P678.01

Topic: G.03. Motivation

Support: NIH NIDA IRP
NIH Center on Compulsive Behaviors Fellowship

Title: Dopamine and GABArelease from combinatorial neurons in the zona incerta play distinct but complimentary roles in threat response behavior

Authors: Z. D. BRODNIK[1], J. A. MIRANDA-BARRIENTOS[2], S. ZHANG[3], M. MORALES[4];
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Abstract: While the notion that neurons signal by releasing one unique neurotransmitter is widely accepted, we and others have provided evidence that neurons may co-release multiple neurotransmitters. Tyrosine hydroxylase (TH) positive neurons in the ventral tegmental area have been shown to release the inhibitory neurotransmitter GABA. However, in contrast to GABA neurons distributed throughout the brain, VTA TH-GABA neurons do not have the capability to synthesize GABA utilizing the enzyme glutamic acid decarboxylase (GAD) and lack the GABA vesicular transporter (VGaT). By brain mapping of cellular co-expression we identified a subpopulation of TH-GAD-VGaT neurons in the zona incerta. Based on these anatomical findings, we designed up a multidisciplinary approach to determine the role of zona incerta TH-GAD-VGaT neurons in behavior. (1) By viral based tract tracing and immuno-ultrastructural analysis, we found that axon terminals from these neurons contained both TH- and VGaT-proteins. (2) By ex vivo fast scan cyclic voltammetry and electrophysiology, we found that TH-VGaT axon terminals indeed released both dopamine and GABA. (3) By in vivo fiber photometry, we found that zona incerta TH cells preferentially respond to threatening stimuli. (4) By chemogenetics, we found that

excitation of zona incerta TH neurons suppressed threat response behaviors while their inhibition enhanced threat response behaviors. (5) By viral based CRISPR knockout strategy, we found that specific GABA signal ablation from TH-GABA neurons increased the rate of at which threat response behaviors are initiated. In contrast, specific dopamine signal ablation from TH-GABA neurons increased the duration threat response behavior bouts. In summary, we demonstrated that the zona incerta contains neurons that co-release dopamine and GABA, and provide evidence indicating that the release of these two neurotransmitters from the same neuron play distinct but complementary roles in gating the expression of active threat response behaviors.

Disclosures: Z.D. Brodnik: None. **J.A. Miranda-Barrientos:** None. **S. Zhang:** None. **M. Morales:** None.

Poster

P678. Motivation: Subcortical Neurocircuitry V

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Program #/Poster #: P678.02

Topic: G.03. Motivation

Support: This study was supported by the Intramural Research Program of the National Institute on Drug Abuse

Title: Lateral habenula topographic distribution of afferents from ventral tegmental area and entopeduncular nucleus dual glutamate-GABA neurons

Authors: *S. ZHANG[1], H.-L. WANG[2], B. LIU[3], M. F. MORALES[4];
[1]Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [2]IRP/NIDA/NIH, Baltimore, MD; [3]NIH/NIDA, Baltimore, MD; [4]Cell Neurobiol Res. Br., IRP, NIDA, NIH, Baltimore, MD

Abstract: For decades, it has been thought that glutamate and GABA neurotransmitters are released by distinct neurons. However, by immuno-electron microscopy (immuno-EM), we previously demonstrated that within the lateral habenula (LHb) about 53% of the total population of axon terminals co-express transporters for the vesicular accumulation of glutamate (VGluT2), and for the vesicular accumulation of GABA (VGaT). We had found that single $VGluT2^{+}VGaT^{+}$ axon terminals can simultaneously establish asymmetric and symmetric synapses with postsynaptic non-overlapping glutamate AMPA and $GABA_A$ receptors. By immuno-EM and immunoprecipitation analysis of confirmed LHb purified vesicles, we haven't detected coexistence of VGluT2 and VGaT at the vesicular level. From these ultrastructural and molecular findings, we had concluded that the dual $VGluT2^{+}VGaT^{+}$ terminals have two distinct pools of vesicles for accumulation and release of glutamate or GABA (for electrophysiology evidence, see Miranda-Barrientos et al., SfN 2021). We previously established that LHb $VGluT2^{+}VGaT^{+}$ axon terminals are derived from both the ventral tegmental area (VTA) and the entopeduncular nucleus (EPN). In this study, we simultaneously mapped LHb distribution of VTA-axons and EPN-axons from dual $VGluT2^{+}VGaT^{+}$ neurons. To selectively target $VGluT2^{+}VGaT^{+}$ neurons, we crossed VGluT2::Cre mice with VGaT::FlpO mice and injected INTRSECT viral vectors AAV-DJ-Cre_{ON}/Flp_{ON}-ChR2-eYFP in VTA and AAV-DJ-Cre_{ON}/Flp_{ON}-ChR2-mCherry in EPN. To validate the specificity of the mice and vectors, we

examined the expression of both VGluT2 and VGaT mRNAs in VTA-eYFP$^+$ neurons and EPN-mCherry$^+$ neurons. We detected co-expression of VGluT2 and VGaT mRNAs in 87.5 ± 2.6% of VTA-eYFP$^+$ neurons and 84.8 ± 1.8% of EPN-mCherry$^+$ neurons. At the axon level by confocal microscopy mapping, we found that while VTA-eYFP$^+$ axons and EPN-mCherry$^+$ axons had distinct LHb rostro-caudal distributions, there was some overlapping. At the axon terminal level, by quadruple immunofluorescent confocal microscopy, we established that 92.9 ± 2.5% of VTA-eYFP$^+$ axon terminals and 90.9 ± 3.0% EPN-mCherry$^+$ axons terminals co-expressed VGluT2- and VGaT-proteins. We further determined that the VTA and EPN axon terminals were segregated throughout the LHb, even in those areas in which axons from VTA and EPN overlapped, and confirmed that single axon terminals from VTA-eYFP$^+$ and EPN-mCherry$^+$ axons established each asymmetric and symmetric synapses. We concluded that glutamate and GABA release from VTA and EPN VGluT2$^+$VGaT$^+$ axons regulate the activity of distinct subpopulations of LHb neurons.

Disclosures: S. Zhang: None. **H. Wang:** None. **B. Liu:** None. **M.F. Morales:** None.

Poster

P678. Motivation: Subcortical Neurocircuitry V

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Program #/Poster #: P678.03

Topic: G.03. Motivation

Support: NIH/NIGMS 1FI2GM128622-01
NIH/NIMH 1K99MH123673-01
NIH/NIDA

Title: Neuropeptide Plasticity Underlying Cue Dependent Aversive Learning

Authors: *T. FRANCIS[1], A. BELILOS[1], C. SANDERS[1], G. SCHOENBAUM[2], M. MORALES[1]; [1]Integrative Neurosci. Res. Br., [2]Cell. and Neurocomputational Systems Br., NIH/NIDA IRP, Baltimore, MD

Abstract: Predictive environmental stimuli guide animal behavior and promote survival. Response to these stimuli require motivational brain circuits facilitated by valence and salience. The core subregion of the Nucleus Accumbens (NAc), an integration center for motivated behavior, responds to salient cues, irrespective of valence. However, the cellular and synaptic mechanisms that underlie NAc core salience processing have not been explored. Previously, we found release of substance P, a neuropeptide released by salient aversive stimuli, in the NAc core, promotes cell-type specific long-term potentiation (LTP) of excitatory transmission on dopamine 2 (D2) receptor expressing medium spiny neurons (MSNs). This LTP requires cholinergic signaling. Therefore, we aimed to test the hypothesis that NAc core substance P plasticity, via cholinergic signaling, is required for aversive learning. To test this, we used a Pavlovian fear conditioning paradigm where a cue (white noise) is paired with an aversive stimulus (footshock). In corroboration with our hypothesis, electrophysiological signatures of LTP on NAc core D2-MSNs were only observed in mice that underwent cue-footshock pairing and not the cue alone. Systemic pharmacological antagonism of the substance P receptor or conditional knockout of this receptor from

cholinergic neurons in NAc core neurons led to a strong suppression in the learned association compared to saline injected mice or mice without the knockout. These results suggest substance P release and plasticity may be facilitating aversive learning. Next, to determine the role of D2-MSN activity in this behavior, we suppressed learning by repeatedly playing the cue prior to pairing of the cue with the footshock. This procedure significantly diminished the salience of the cue and decreased expression of the activity marker c-fos selectively in NAc core D2-MSNs. Furthermore, optogenetic inhibition of D2-MSNs reversibly prevented cue recall compared to non-inhibited viral controls, suggesting D2-MSN activity is required for the recall of cues predicting shocks. Finally, using an acetylcholine sensor to monitor NAc cholinergic signaling *in vivo*, our preliminary findings indicate dynamic cholinergic signaling is required for aversive conditioning. Together, these results suggest NAc core substance P and cholinergic signaling drives plasticity that is required for learning about cues predicting aversive outcomes. This work unveils an undiscovered role for the NAc in salience processing and aversive learning which may underlie related symptoms in anxiety and mood disorders such as post-traumatic stress disorder and behavioral depression.

Disclosures: T. Francis: None. **A. Belilos:** None. **C. Sanders:** None. **G. Schoenbaum:** None. **M. Morales:** None.

Poster

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Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P678.04

Topic: G.03. Motivation

Support: NIDA Intramural Research Program

Title: Lateral habenula glutamate and GABA releasing properties from dual glutamate-GABA axon terminals

Authors: *J. MIRANDA-BARRIENTOS[1], I. CHAMBERS[2], S. ZHANG[3], B. LIU[1], H.-L. WANG[4], M. F. MORALES[5];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Natl. Inst. on Drug Abuse, baltimore, MD; [3]Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [4]IRP/NIDA/NIH, Baltimore, MD; [5]Cell Neurobiol Res. Br., IRP, NIDA, NIH, Baltimore, MD

Abstract: Neurons that utilize either glutamate or GABA as signaling molecules are widely distributed in the brain and have been studied for decades. However, we and others have recently demonstrated that the lateral habenula (LHb), a brain region activated by aversive stimuli and related to negative motivational states, contains axon terminals that release glutamate and GABA. These glutamate-GABA releasing axon terminals are originated from neurons that co-express the vesicular glutamate transporter 2 (VGluT2) and the vesicular GABA transporter (VGaT) ($VGluT2^+$ $VGaT^+$ neurons) located in both ventral tegmental area (VTA) and entopeduncular nucleus (EPN). In this study, we determined the LHb glutamate-GABA releasing properties from VTA and EPN inputs. To selectively target expression of channel-rhodopsin in $VGluT2^+$ $VGaT^+$ neurons, we crossed VGluT2::Cre mice with VGaT::FlpO mice and injected

INTRSECT viral vectors in the VTA or EPN of these dual transgenic mice. By patch-clamp electrophysiology, we found that LHb activation of VGluT2^{+} VGaT^{+} inputs, from VTA or EPN, produced monosynaptic excitatory postsynaptic currents (EPSCs) blocked by CNQX, and monosynaptic inhibitory postsynaptic currents (IPSCs) blocked by Bicuculline. By current-clamp recordings, we found that LHb activation of VGluT2^{+} VGaT^{+} inputs from VTA produced inhibition of LHb neurons due to higher amplitude of GABA mediated currents. In contrast, LHb activation of VGluT2^{+} VGaT^{+} inputs from EPN produced activation of LHb neurons due to higher amplitude of glutamate mediated currents. By stimulation of LHb VGluT2^{+} VGaT^{+} inputs from the VTA or EPN at different frequencies, we found frequency-dependent steep decline in glutamate release with a sustain release of GABA. Moreover, by pharmacological blocking of calcium channels with conotoxin, we found a 40% decrease in glutamate release without affecting GABA release, indicating that N-type calcium channels partially mediates glutamate release, but not GABA release. In summary, by the selective targeting of dual glutamate-GABA neurons, we demonstrated (1) LHb glutamate and GABA release from VGluT2^{+} VGaT^{+} inputs from both VTA and EPN neurons, (2) LHb neuronal inactivation by local activation of VTA VGluT2^{+} VGaT^{+} inputs, and LHb neuronal activation by local activation of EPN VGluT2^{+} VGaT^{+} inputs, and (3) different mechanisms for GABA and glutamate release. Collectively, these electrophysiological and pharmacological findings support the notion that glutamate and GABA are packed in independent synaptic vesicles.This study was supported by the Intramural Research Program of the National Institute on Drug Abuse.

Disclosures: J. Miranda-Barrientos: None. **I. Chambers:** None. **S. Zhang:** None. **B. Liu:** None. **H. Wang:** None. **M.F. Morales:** None.

Poster

P678. Motivation: Subcortical Neurocircuitry V

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P678.05

Topic: G.03. Motivation

Support: This study was supported by the Intramural Research Program of the National Institute on Drug Abuse

Title: Feeding behavior is modulated by an inhibitory pathway from the Substantia Nigra pars reticulata to the Dorsal Raphe

Authors: *M. F. BARBANO, H.-L. WANG, I. CHAMBERS, M. MORALES;
Natl. Inst. On Drug Abuse, Baltimore, MD

Abstract: The Dorsal Raphe nucleus (DR) is a major source of the neurotransmitter serotonin, and has been implicated in the processing of emotions, stress, anxiety, depression, and motivation. In addition to serotonin neurons, the DR has dopaminergic, GABAergic, glutamatergic and peptidergic neurons. We had previously demonstrated that DR-glutamatergic neurons expressing the vesicular glutamate transporter 3 (VGluT3) play a role in reward. However, it is currently unclear the type of neurons involved in the regulation of DR-VGluT3 neurons. To investigate the sources of monosynaptic inputs to

DR-VGluT3 neurons, we used a rabies-virus-based-*trans*-synaptic retrograde tracing strategy and identified the Substantia Nigra pars reticulata (SNr) as a major source of putative monosynaptic inputs to DR-VGluT3 neurons. Given that most neurons in the SNr are GABA neurons expressing the vesicular GABA transporter (VGaT), we used VGaT:Cre mice to express channelrhodopsin (ChR2) in the SNr. By *ex vivo* electrophysiological recordings of DR neurons, we found that GABA release from SNr neurons differentially modulate DR serotonin, VGluT3 and GABA neurons (Chambers et al., SfN 2021), indicating that SNr GABA neurons provide a major inhibitory input to different DR neuronal subpopulations. To evaluate the behavioral consequences of DR optical stimulation of SNr GABA inputs, we prepared ChR2-eYFP, Halo-eYFP and eYFP mice that we tested in two tasks: free-feeding or an instrumental task for food. We found that DR photoactivation of SNr GABA terminals elicited voracious food intake in food-sated mice, without increasing motivation for food reward. In contrast, DR photoinhibition of SNr GABA terminals did not modulate free-feeding behavior, but decreased motivation for food reward in a progressive ratio test. Collectively, these findings indicate that the modulation of feeding behavior by SNr GABA neurons projecting to DR is effort-sensitive. We next determined the extent to which DR photoactivation of SNr GABA terminals could block lithium chloride (LiCl)-induced taste devaluation. In this test, we presented mice with palatable novel food pellets and immediately after the feeding session injected them with LiCl. Next day, we measured food intake in response to DR photostimulation of SNr GABA terminals and found that food intake did not change in ChR2-eYFP mice, but significantly decreased in eYFP mice. We conclude that GABAergic neurotransmission from the SNr to DR neurons plays a role in feeding behavior, throughout a mechanism that involves the regulation of DR glutamatergic neurons.

Disclosures: M.F. Barbano: None. **H. Wang:** None. **I. Chambers:** None. **M. Morales:** None.

Poster

P678. Motivation: Subcortical Neurocircuitry V

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Program #/Poster #: P678.06

Topic: G.03. Motivation

Title: Substantia Nigra inputs to the Dorsal Raphe preferentially target glutamatergic neurons

Authors: *J. MIRANDA-BARRIENTOS, **I. O. J. CHAMBERS**, M. F. BARBANO, H.-L. WANG, S. ZHANG, B. LIU, *M. MORALES;
IRP, NIDA, NIH, Baltimore, MD

Abstract: The Dorsal Raphe (DR) is a brain structure known for containing serotonergic neurons that express Tryptophan Hydroxylase (TPH, for the synthesis of serotonin) and the Serotonin Transporter (SERT, for the uptake of serotonin). In addition to serotonin neurons, the DR has dopaminergic, glutamatergic, GABAergic and peptidergic neurons. We had previously demonstrated that both DR-glutamatergic neurons expressing the vesicular glutamate transporter 3 (VGluT3) alone or in combination with serotonergic markers (TPH or SERT) provide major glutamatergic inputs to dopamine neurons within the ventral tegmental area. In addition, by a rabies-virus-based-*trans*-synaptic retrograde tracing strategy, we identified the Substantia Nigra pars reticulata (SNr) as a major source of putative

monosynaptic inputs to DR-VGluT3 neurons (Barbano et al., SfN 2021). In this study we used *ex vivo* electrophysiological recordings to determine the connectivity between inputs from the SNr and DR-SERT, DR-VGluT3 and DR-GABAergic neurons. For the *in vivo* tagging of DR neurons, we did intra-DR injections of a Cre-dependent viral vector (AAV1-DIO-eYFP) to express enhanced yellow fluorescent protein (eYFP) into the DR of three Cre-dependent transgenic mouse lines (SERT::Cre, VGluT3::Cre and VGaT::Cre mice), and in the SNr of the same mice we injected a viral vector (AAV1-CaMKII-mCherry-ChR2) to express channelrhodopsin in SNr neurons and corresponding inputs to DR. While we detected inhibitory postsynaptic currents (IPSCs) within all DR subpopulations of tagged neurons in response to photoactivation of SNr inputs, these responses had differential properties among the DR neuronal subpopulations. We detected IPSCs in about half of the tagged SERT neurons (47.6%), about one third of tagged VGaT neurons (30.4%), and in most of the tagged VGluT3 neurons (81.0%). In addition, we found that the amplitude of IPSCs was different among each of the subpopulations of DR neurons, -5.4 pA to -95.1 pA ($\bar{x}$ = -20.22 pA) for SERT tagged neurons, -8.5 pA to -248.7 pA ($\bar{x}$ = -77.85 pA) for VGaT neurons, and -11.4 pA to -467.2 pA ($\bar{x}$ = -125.82 pA) for VGluT3 neurons. The identified diverse range of amplitude of IPSCs within each subpopulation of tagged neurons indicates further heterogeneity within DR neurons, which is likely to include neurons co-expressing more than one neurotransmitter, for instance serotonin and glutamate, serotonin and GABA, etc. We concluded that neurons from the SNr provide a major inhibitory input to the DR that preferentially synapses on glutamatergic neurons expressing VGluT3.

Disclosures: J. Miranda-Barrientos: None. **I.O.J. Chambers:** None. **M.F. Barbano:** None. **H. Wang:** None. **S. Zhang:** None. **B. Liu:** None. **M. Morales:** None.

Poster

P678. Motivation: Subcortical Neurocircuitry V

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Topic: G.03. Motivation

Support: Department of Psychiatry
Foundation of Hope
NCTraCS
NSF DGE-1650116

Title: Pnoc neurons in the extended amygdala encode and are necessary to explore anxiogenic environments

Authors: *M. M. ORTIZ-JUZA[1], R. L. UNG[1], R. A. ALGHORAZI[1], A. L. RING[1], G. VELAZQUEZ-HERNANDEZ[1], J. RODRIGUEZ-ROMAGUERA[2];
[1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. Of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Anxiety disorders are often defined by rapid and amplified arousal responses to stimuli and environments. The bed nucleus of the stria terminalis (BNST), a component of the extended amygdala, is

involved in regulating anxiety states. We recently showed that prepronociceptin-expressing neurons in the BNST (*Pnoc*^{BNST} neurons) encode arousal responses during presentation of motivationally salient stimuli (Rodriguez-Romaguera et al., 2020). The role of *Pnoc*^{BNST} neurons in encoding anxiety-like behaviors is unknown. We sought to understand how response dynamics of *Pnoc*^{BNST} neurons encode anxiogenic environments in mice. To visualize activity of *Pnoc*^{BNST} neurons we used head mountable miniature microscopes in freely moving mice exposed to the elevated plus maze (EPM). Population activity of *Pnoc*^{BNST} neurons increased when mice explored the open arms of the EPM. Further analysis on individual *Pnoc*^{BNST} neurons revealed three different types of response patterns: 1) neurons that were excited in the open arms, 2) neurons that were inhibited in open arms, and 3) neurons that did not change activity across arms. We also found that the activity of neurons that were excited in the open arms correlated with distance to the edge of the open arms, with increased activity as mice approached the edge of the open arms. Our data indicate that *Pnoc*^{BNST} neurons encode anxiogenic environments. To test if *Pnoc*^{BNST} neurons are necessary for mice to engage with anxiogenic environments, we selectively inhibited them in the EPM using optogenetics only when mice were in the open arms (real time EPM). Photoinhibition of *Pnoc*^{BNST} neurons decreased the amount of time spent in the open arms, demonstrating that *Pnoc*^{BNST} neuronal activity is necessary for mice to explore anxiogenic environments. In contrast, photoactivation of *Pnoc*^{BNST} neurons in the real time EPM did not alter time in the open arms, suggesting that *Pnoc*^{BNST} neuronal activity is not sufficient to increase exploration of anxiogenic environments. We previously showed that *Pnoc*^{BNST} neurons track arousal responses to motivationally salient stimuli, and our new findings indicate that activity of these neurons are also necessary to engage with anxiogenic environments. Taken together, our data suggest that perhaps *Pnoc*^{BNST} neurons regulate the arousal responses that are necessary for animals to explore anxiogenic environments.

Disclosures: M.M. Ortiz-Juza: None. **R.L. Ung:** None. **R.A. Alghorazi:** None. **A.L. Ring:** None. **G. Velazquez-Hernandez:** None. **J. Rodriguez-Romaguera:** None.

Poster

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Program #/Poster #: P678.08

Topic: G.03. Motivation

Support: Department of Psychiatry, UNC
Foundation of Hope
NCTraCs
NSF DGE-1650116

Title: Pnoc neurons in the extended amygdala track relative location of aversive odors

Authors: R. L. UNG[1], R. A. ALGHORAZI[3], M. M. ORTIZ-JUZA[3], R. A. GARCIA-REYES[3], G. VELAZQUEZ-HERNANDEZ[3], G. D. STUBER[4], P. ZHOU[5], H. K. KATO[2], ***J. RODRIGUEZ-ROMAGUERA**[1];
[2]Psychiatry, [1]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [3]Univ. of North Carolina at

Chapel Hill, Chapel Hill, NC; [4]Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA; [5]Shenzhen Inst. for Advanced Technologies, Shenzhen, China

Abstract: Motivational states consist of behavioral and physiological components controlled by multiple brain regions. An integral component of this neural circuitry is the bed nucleus of the stria terminalis (BNST), a part of the extended amygdala. We recently found neurons in the BNST that express the gene prepronociceptin (*Pnoc*^{BNST} neurons) modulate rapid changes in physiological arousal upon presentation of motivationally salient stimuli (Rodriguez-Romaguera et al., 2020). This was accomplished by combining pupillometric assessment in combination with *two-photon* calcium imaging in head-fixed animals, in which we observed that *Pnoc*^{BNST} neuronal responses directly correspond with rapid increases in pupillary size when mice are exposed to both aversive (TMT predator odor) and rewarding (peanut oil) odors. However, how dynamics of *Pnoc*^{BNST} neurons encode behavioral responses to the same motivationally salient stimuli remains unknown. We therefore employed calcium imaging in freely moving mice using head mountable miniature microscopes. We injected Cre-dependent calcium indicator GCaMP6s in *Pnoc*-IRES-Cre mice to visualize activity of individual *Pnoc*^{BNST} neurons when exposed to either TMT or peanut oil in their home cage. Population activity of *Pnoc*^{BNST} neurons was higher when mice were exposed to TMT, as compared to peanut oil. Furthermore, activity of individual *Pnoc*^{BNST} neurons correlated with proximity to odor source when mice were exposed to TMT, but not peanut oil. Our data suggest that *Pnoc*^{BNST} neurons preferentially encode relative location of aversive odors. Next, we tested if optogenetic manipulation of *Pnoc*^{BNST} neurons modulates time spent near TMT and peanut oil. Photoinhibition of *Pnoc*^{BNST} neurons decreased the amount of time spent in the odor zone when mice were exposed to TMT, but not peanut oil, indicating that *Pnoc*^{BNST} neuronal activity is necessary for mice to explore aversive odors. In contrast, photoactivation of *Pnoc*^{BNST} neurons did not alter time in the odor zone for either odor, suggesting that *Pnoc*^{BNST} neuronal activity is not sufficient to increase time spent near motivationally salient odors. Taken together, our data indicate that *Pnoc*^{BNST} neurons are necessary to explore aversive odors. We previously showed that *Pnoc*^{BNST} neurons encode for arousal responses to motivationally salient odors, and these new findings indicate activity of these neurons are specific to engage with aversive odors.

Disclosures: R.L. Ung: None. **R.A. Alghorazi:** None. **M.M. Ortiz-Juza:** None. **R.A. Garcia-Reyes:** None. **G. Velazquez-Hernandez:** None. **G.D. Stuber:** None. **P. Zhou:** None. **H.K. Kato:** None. **J. Rodriguez-Romaguera:** None.

Poster

P693. Cortical-Subcortical Emotional Control Circuits

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Program #/Poster #: P693.01

Topic: G.04. Emotion

Support: NSF Grant IOS 1755111

Title: Post-conditioning lesions to the perirhinal cortex impairs fear extinction to a discontinuous conditioned stimulus.

Authors: D. GONZALEZ MAGANA, N. A. VANG, R. A. K. PUREWAL, *S. C. FURTAK;
Dept. of Psychology, California State Univ. Sacramento, Sacramento, CA

Abstract: The perirhinal cortex (PER) is a medial temporal lobe structure involved in learning and memory. The PER receives both unimodal and polymodal sensory information, which make this region well positioned to associate and process stimulus information. The PER has been examined in tasks that involve processing of visual stimuli, such as delay non-match to sample, object recognition and more recently in fear memory paradigms. Studies focused on the role of the PER in fear memory specifically have tested whether the PER supports fear learning to stimuli that require unitization across modality, features or time for representation. In the current study, we assess whether excitotoxic lesions to the PER post-conditioning affect retrieval of the fear memory or extinction memory to a continuous or discontinuous white light conditioned stimulus (CS). Based on the stimulus unitization hypothesis of the PER, we predicted that the PER should be necessary for fear learning to the discontinuous CS but not the continuous CS. Male Spraque-Dawley rats (280-420 g) were assigned to one of four groups based on CS type (continuous vs discontinuous) and surgery type (lesion vs sham). The fear extinction paradigm consisted of three phases: fear acquisition, extinction training, and extinction retrieval. Animals underwent surgery three days after fear acquisition, then ten days later returned to the conditioning chamber for extinction training and extinction retrieval, which occurred on two consecutive days. Results showed that animals with damage to the PER had significant deficits, indicated by reduced freezing levels, during retrieval of the fear memory in the extinction training phase of the behavioral paradigm to both the continuous and discontinuous CS compared to their sham control groups. The next day during retrieval of the extinction memory (extinction retrieval), significant differences in freezing levels were observed between lesion and sham groups in the discontinuous CS groups but not in the continuous CS group. This study supports previous research suggesting the PER is a part of a wider system of structures engaged in fear learning and further supports a role for the PER in stimulus unitization in fear-related tasks.

Disclosures: D. Gonzalez Magana: None. **N.A. Vang:** None. **R.A.K. Purewal:** None. **S.C. Furtak:** None.

Poster

P693. Cortical-Subcortical Emotional Control Circuits

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Program #/Poster #: P693.02

Topic: G.04. Emotion

Support: NIDA Grant DA052108

Title: Dynamics of Coordinated Neural Activity in the Infralimbic Cortex - Nucleus Accumbens Shell Circuit during Conditioned Negative Affect and its Extinction

Authors: *J. E. DOUTON, M. M. BORCHLEWICZ, R. M. CARELLI;
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Abstract: The disruption in hedonic processing is associated with many psychiatric illnesses and can lead to maladaptive behaviors. For example, the prevalence of negative affect during withdrawal in substance use disorders can promote relapse. In depression, negative affect drives the aversive emotional state that can result in suicide. Thus, it is critical to understand the neural mechanisms that modulate hedonic processing, whose disruption can lead to such aversive affective states. Taste reactivity (TR) is useful to study objective hedonic behaviors. TR analyzes pleasant (positive affect) and aversive (negative affect) stereotypic oromotor expressions elicited by rats when sapid stimuli are intraorally infused, allowing to infer the affective state of the rat. Moreover, TR is used to study conditioned aversive states such as Lithium Chloride (LiCl) conditioned taste aversion (CTA). Using these methods, corticolimbic circuits have been shown to play a vital role in hedonic processing. In rats, the projections from the infralimbic cortex (IL) to the nucleus accumbens shell (NAcSh) are involved in the suppression of negative affect. The goal of this study was to characterize the role of these regions in the development and extinction of a conditioned aversive state. To this end, adult male Sprague Dawley rats (n=8) were subjected to CTA. The rats were exposed to 30 intraoral infusions (IO, 1 inf/min) of 0.15% saccharin followed by an IP injection of LiCl (0.3M). After two days of recovery, rats experienced 5 IO extinction trials with the same saccharin solution (30 inf, 1 inf/min). Finally, on the last day, rats were intraorally infused with a bitter quinine solution to study responses to a natural aversive tastant. In this experiment, in vivo electrophysiological methods that record simultaneous neural oscillations of local field potential (LFPs) allowed us to study synchronized oscillatory dynamics and assess functional connectivity between the IL and the NAcSh during the task. Preliminary data show that the development of a conditioned aversive state reduced IL-NAcSh synchronous activity, manifested as a reduction in overall coherence between these regions. Specifically, oscillations observed in the naïve state at the beta (16-20 Hz) and high gamma (80 Hz) frequency bands were affected. In addition, these changes were reverted to preconditioning levels after 3 days of extinction training. Interestingly, quinine infusion did not alter functional connectivity between the IL and NAcSh. Collectively, the data indicate that the IL-NAcSh circuit may modulate conditioned aversive states that recover in extinction, but not innate aversive states (i.e., quinine).

Disclosures: J.E. Douton: None. **M.M. Borchlewicz:** None. **R.M. Carelli:** None.

Poster

P693. Cortical-Subcortical Emotional Control Circuits

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P693.03

Topic: G.04. Emotion

Support: European Union Horizon 2020 Research and Innovation Program and Euratom research and training program 20142018 (under grant agreement No. 670118 to ML)
Deutsche Forschungsgemeinschaft (Exc 257 NeuroCure, Grant No. LA 3442/3-1 & Grant No. LA, Project number 327654276 SFB1315)
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Einstein Foundation Berlin (EVF-2017-363)
NINDS: R01NS1114702

Title: Extinction of flight and freezing responses in a simulated foraging environment

Authors: *M. RITTER[1], L. CHIRICH[1], L. SACH[1], A. HAKUS[2,3,4], R. BERGMANN[5], L. J. SCHWARZ[6], A. VOIGT[5], M. E. LARKUM[1], P. POIRAZI[7], R. N. S. SACHDEV[1];
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Abstract: Fear is a central emotion guiding the behavior of animals and people. Fight, flight or freezing are understood as reactions to threatening situations. The brain circuits related to the perception of a threat and the behavioral expression of fear have been studied extensively (Tovote, Fadok, and Lüthi 2015; Silva, Gross, and Gräff 2016; LeDoux and Brown 2017). Here we designed a behavioral apparatus that used head-fixed mice and in a controlled fashion presented an ostensibly innately threatening stimulus, a live rat, to the mouse. Mice had to decide whether to forage (lick a lick tube), flee (walk backward pushing the predator away), or freeze. During a trial, mice walked on a treadmill. The movement of the treadmill was linked to the movement of a reward tube and linked to the movement of a potential threat, a rat. Our results suggest that in a head-fixed condition where mice forage for a reward the innate expression of flight and freezing behavior is suppressed. Mice were invariably focused on obtaining the reward; they did not attend to the presence of the potential predator. We compared these results to the outcome of various behavioral tests in freely moving mice. Naïve, untrained mice with free access to water were used to examine their response to looming stimuli (Yilmaz and Meister 2013), rat odors (Murata et al. 2019), and the presence of a live rat (Yang et al. 2004). The results from these experiments showed a diverse behavioral phenotype, which included a small but significant number of mice (25-40%, tested in 12 mice) expressing fear in response to the looming stimulus, and avoidance or place preference in response to the presence or odor of a rat. Our work suggests that the expression of "innate fear" is context-dependent.

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Poster

P693. Cortical-Subcortical Emotional Control Circuits

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Program #/Poster #: P693.04

Topic: G.04. Emotion

Support: NIH Grant R01DC008983
NIH Grant RF1MH114112
NIH Grant R01EY019049

Title: Corticostriatal control of defense behavior in mice induced by auditory looming cues

Authors: *Z. LI[1], J. WEI[1], G. ZHANG[1], J. HUANG[2], B. ZINGG[3,4], X. WANG[3], H. TAO[1], L. I. ZHANG[1];
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Abstract: Animals exhibit innate defense behaviors in response to approaching threats cued by the dynamics of sensory inputs of various modalities. The underlying neural circuits have been mostly studied in the visual system, but remain unclear for other modalities. Here, by utilizing sounds with increasing (vs. decreasing) loudness to mimic looming (vs. receding) objects, we find that looming sounds elicit stereotypical sequential defensive reactions: freezing followed by flight. Both behaviors require the activity of auditory cortex, in particular the sustained type of responses, but are differentially mediated by corticostriatal projections primarily innervating D2 neurons in the tail of the striatum and corticocollicular projections to the superior colliculus, respectively. The behavioral transition from freezing to flight can be attributed to the differential temporal dynamics of the striatal and collicular neurons in their responses to looming sound stimuli. Our results reveal an essential role of the striatum in the innate defense control.

Disclosures: Z. Li: None. **J. Wei:** None. **G. Zhang:** None. **J. Huang:** None. **B. Zingg:** None. **X. Wang:** None. **H. Tao:** None. **L.I. Zhang:** None.

Poster

P693. Cortical-Subcortical Emotional Control Circuits

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Program #/Poster #: P693.05

Topic: F.04. Stress and the Brain

Support: NIH Grant R21MH114182
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PSC-CUNY Award jointly funded by the Professional Staff Congress and the City University of New York

Title: Chronic Social Defeat Stress Leads to Over-Generalized Fear: A Role for Impaired Safety Learning and Disrupted Communication Between the Amygdala and Prefrontal Cortex

Authors: *I. S. GRUNFELD[1], L. E. DENHOLTZ[2], I. NAHMOUD[3], A. V. AUBRY[6], S. HANIF[4], S. DATTA[7], S. CHATTARJI[7], N. S. BURGHARDT[4], E. LIKHTIK[5];
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Abstract: Chronic stress leads to the generalization of fear to non-threatening cues, a key symptom in numerous psychiatric disorders. We previously showed that in the absence of stress, successful discrimination of threatening and non-threatening cues is associated with suppression of the basolateral amygdala (BLA) by the medial prefrontal cortex (mPFC). In contrast, BLA activity is not under mPFC control during fear generalization. Here, we used the chronic social defeat stress (CSDS) model to investigate the contribution of the BLA and mPFC to stress-induced fear generalization in 129 Sv/Ev

mice. We found that 10 days of CSDS decreased dendritic spines in the prelimbic (n=3 mice) and infralimbic (n=4 mice) subregions of the mPFC relative to non-stressed controls (n=3 mice/group, $p<0.0001$). In contrast, CSDS enhanced consolidation of cued fear memory (n=18-19/group, $p<0.001$) and increased the expression of the immediate-early gene Arc in the BLA during fear memory retrieval ($p<0.05$), supporting differential effects of chronic stress on these brain regions. We then tested the effects of CSDS on discrimination learning using an auditory differential fear conditioning task, in which one tone was paired with a shock (CS+) and a second tone was unpaired (CS-, 2kHz and 8kHz, counterbalanced). The majority of non-stressed animals successfully discriminated between the tones (n=14/19, 73.69%), freezing at least 10% more to the CS+ than the CS-. However, the majority of stressed mice generalized their fear to the CS- (n=11/17, 64.7%), freezing similarly to the two tones. To investigate whether this might reflect an effect of stress on safety learning, mice were trained on a salient safety learning task, where the presence of a 1-sec light and a 30-sec tone signaled absence of shock. Whereas non-stressed controls reliably decreased freezing during the safe tone (n=10, $p<0.05$ compared to pre-tone), the CSDS group failed to do so (n=11, $p>0.05$). Preliminary analyses of local field potential recordings reveal that the safety cue evokes a theta (4-12 Hz) oscillation in the BLA of control mice ($p<0.05$), but not defeated mice. We conclude that chronic stress differentially impacts the mPFC and BLA and alters theta-range communication in this circuit during periods of explicit safety, potentially diminishing the ability to discriminate between threatening and non-threatening cues.

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Poster

P693. Cortical-Subcortical Emotional Control Circuits

Location: Virtual Only

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Program #/Poster #: P693.06

Topic: G.04. Emotion

Support: NIH Grant EY027713

Title: The role of claustral circuits in observational threat

Authors: *H. JUNG[1], J. HEU[1], A. D. HUBERMAN[1,2,3,4];
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Abstract: The selection of appropriate defensive strategies is essential for survival and is evolutionarily conserved among humans and animals. This process involves rapid evaluation of severity of the threat stimuli and proper decision for defensive strategies to pursue. These defensive responses are also apparent when the threat stimuli are detected through indirect experience, mainly through observation, but *how the brain links this observational threat to subsequent behaviors remains poorly understood*. Here we use a combination of behavioral, calcium imaging, and chemogenetic approaches to investigate the neural correlates underlying observational threat. First, by developing a novel visually-driven behavioral paradigm, we demonstrated that freezing is the significant responsive behavior of mice during

observational threat. Next, by analyzing neural activity of the early-immediate gene c-Fos throughout the brain, we identified that *the claustrum showed increased activity in response to observational threat*. In vivo calcium imaging also revealed that the increased activity observed in the claustrum precedes a freezing response during observational threat. Finally, by chemogenetically manipulating the claustral circuits, we demonstrated that visual information on the threat stimuli is transmitted from the basolateral amygdala (BLA) to the claustrum and that this information is critical for selecting appropriate defensive responses to observational threat. This study provides a new model for investigating the social transmission of threat and illuminates a central role of claustral circuits in visual threat perception. This novel function of the claustrum and its circuits may underlie a fundamental role in modulating defensive systems to both physical and social threats in health and disease.

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Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.01

Topic: G.05. Mood Disorders

Support: R01 MH107487

Title: Dysregulated neuronal kinase networks in major depression

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Abstract: Major depression disorder (MDD) is a chronic debilitating disorder of largely unknownetiology. Protein kinases are essential components of cellular signaling pathways. Alteredexpression and activity of a number of protein kinases have been implicated in thepathophysiology of MDD. However, less is known about how kinase-kinase interactionsare dysregulated in MDD and how perturbation of these complex kinase networks affectsdownstream biological processes. Using the Pamgene kinome peptide array platform, weexamined serine/threonine protein kinase activity in cortical excitatory neuronsdifferentiated from induced pluripotent stem cells (iPSCs) from subjects diagnosed withMDD (N=5) and corresponding controls (N=5). Neurons from an MDD patient with a 4-bpmutation in the disrupted in schizophrenia 1 (DISC1) gene and from sporadic MDD caseswere assayed. Array data was analyzed using Kinome Random Sampling Analysis(KRSA) to identify kinases with significantly altered activity. In MDD-DISC1 neurons wefound a global downregulation of kinase activity. Using KRSA analysis we identifiedkinases like extracellular signal-regulated kinases, protein kinase G, and protein kinaseA (Z score ≥±4) that were differentially represented in MDD-DISC1 neurons compared tocontrol. Conversely, there was a global upregulation of kinase activity in sporadic MDDneurons. KRSA analysis identified myotonic dystrophy protein kinase, protein kinase A,and c-Jun N-terminal kinases (Z score>=±3) as differentially represented in sporadic MDDneurons. Our data provide new insights into kinase network abnormalities in MDD.Further

exploration of kinase interaction networks and biological pathways affected by
altered kinase activity in MDD-DISC1 and MDD-sporadic neurons will also inform ourunderstanding of the dysregulated molecular mechanisms involved in cellularhomeostasis and neuronal function that could be underlie MDD pathophysiology.

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Poster

P700. Treatment and Drug Discovery: Focus on Depression

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Program #/Poster #: P700.02

Topic: G.05. Mood Disorders

Support: NIMH Grant R01MH101547
NIMH Grant R01MH111889
NIMH Grant T32MH09331502

Title: Reduction in left frontal alpha oscillations by transcranial alternating current stimulation in major depressive disorder is context-dependent

Authors: J. RIDDLE, M. L. ALEXANDER, C. E. SCHILLER, D. R. RUBINOW, F. FROHLICH; Psychiatry, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Left frontal alpha oscillations are associated with decreased approach motivation and have been proposed as a target for non-invasive brain stimulation for the treatment of depression and anhedonia. Indeed, transcranial alternating current stimulation (tACS) at the alpha frequency reduced left frontal alpha power and was associated with a higher response rate than placebo stimulation in patients with major depressive disorder (MDD) in a recent double-blind placebo controlled clinical trial. In this current study (NCT03449979), we aimed to replicate successful target engagement by delineating the effects of a single session of bifrontal tACS at the individualized alpha frequency (IAF-tACS) on alpha oscillations in patients with MDD. 84 participants were randomized to receive verum or sham IAF-tACS. Electrical brain activity was recorded during rest and while viewing emotionally-salient images before and after stimulation to investigate if the modulation of alpha oscillation by tACS exhibited specificity with regards to valence. In agreement with the previous study of tACS in MDD, we found that a single session of bifrontal IAF-tACS reduced left frontal alpha power during the resting state when compared to placebo. Furthermore, the reduction of left frontal alpha oscillation by tACS was specific for stimuli with positive valence. In contrast, these effects on left frontal alpha power were not found in healthy control participants. Together these results support an important role of tACS in reducing left frontal alpha oscillations as a future treatment for MDD.

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Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.03

Topic: G.05. Mood Disorders

Support: Funded by Ulysses Neuroscience Ltd. and Angelini Pharma S.p.A.

Title: Chronic treatment with the selective GSK-3 inhibitor SB16763 induces antidepressant-like effects in the IFN-alpha model of neuroinflammation: a behavioural and molecular study

Authors: *D. FELICE[1], A. FREEBURN[1], J. KEALY[1], B. GARRONE[2], C. MILANESE[2], F. P. DI GIORGIO[2], C. K. CALLAGHAN[1], M. BIANCHI[1];
[1]Ulysses Neuroscience, Trinity Col., Inst. of Neurosci. (TCIN), Lloyd Inst., Dublin, Ireland; [2]Global R&D External Innovation, Angelini Pharma S.p.A., Rome, Italy

Abstract: Glycogen synthase kinase-3 (GSK3) activity has recently been linked to mood disorders. The first evidence was that GSK3β is a target of the mood stabilizer lithium. Recent studies strongly support GSK3β inhibitors as potential therapeutic approaches for mood disorders. Chronic Interferon-alpha (IFN-α) administration in the rat represents a new back translational preclinical model of neuroinflammation. The model was ideated from the observation that patients undergoing IFN-α treatment often report neuropsychiatric side-effects. IFN-α is commonly used in the treatment of cancer and hepatitis. Furthermore, a subpopulation of patients with major depressive disorder (MDD) exhibit increased levels of peripheral inflammatory markers suggesting a chronic inflammation status. Here, we use the IFN-α model to investigate the effects of chronic treatment with the GSK3β inhibitor SB216763 on behaviour, adult hippocampal neurogenesis as well as BDNF and inflammatory biomarkers in hippocampus, medial-prefrontal cortex (mPFC) and plasma. The effects of treatment with SB216763 were compared to the selective serotonin reuptake inhibitor (SSRI) fluoxetine. Male Wistar rats (3mth, n=14 per group) were injected with recombinant human IFN-α (170,000 IU/kg, 3 times per week for 3 weeks) or saline (0.9%). After IFN-α, rats underwent chronic treatment (14 days) with SB216763 (2 mg/kg or 10 mg/kg; *ip*) or fluoxetine (FLX, 10 mg/kg, *po*) or vehicle. Rats were tested in the forced swim test (FST) and elevated plus maze (EPM). Following testing, hippocampal brain tissue was harvested and processed by flow cytometry for analysis of neurogenesis. Hippocampal, mPFC and plasma samples were analysed for changes in cytokines and BDNF levels by MSD assay. Data were analysed by ANOVA and Fishers LSD pairwise comparisons.SB216763 was similarly efficacious as FLX in FST and EPM, recovering IFN-α induced deficits which was associated with increased hippocampal neurogenesis. Chronic SB216763 or FLX treatment recovered IFN-α-induced decrease in mPFC BDNF levels. Only FLX treatment recovered IFN-α-induced decrease in plasma BDNF levels. Neither SB216763 or FLX treatment recovered IFN-α-induced decrease hippocampal BDNF levels. Chronic treatment with SB216763 or FLX rescues IFN-α induced increase in IL-6 levels in the mPFC and plasma, and recovered IFN-α induced increased TNFα in the hippocampus and mPFC. These data validate IFN-α treatment in the rat as a back translational model of neuroinflammation and depression and demonstrates the antidepressant-like effects of SB216763.
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Disclosures: D. Felice: A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **A. Freeburn:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **J. Kealy:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **B. Garrone:** A. Employment/Salary (full or part-time):; Angelini Pharma. **C. Milanese:** A. Employment/Salary (full or part-time):; Angelini Pharma. **F.P. Di Giorgio:** A. Employment/Salary (full or part-time):; Angelini Pharma. **C.K. Callaghan:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **M. Bianchi:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience.

Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.04

Topic: G.05. Mood Disorders

Support: Sage Therapeutics
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Title: The endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP, allopregnanolone) moderates toll-like receptor (TLR) inflammatory signaling with sex differences and relevance to postpartum depression (PPD)

Authors: *I. BALAN[1], R. MEEKER[2], G. BOERO[3], R. PATTERSON[4], H. KROHN[4], S. MELTZER-BRODY[4], T. K. O'BUCKLEY[3], A. L. MORROW[1];
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Abstract: Depression is associated with activation of both TLR4 and TLR7 inflammatory pathways and their downstream inflammatory mediators. We recently discovered that 3α,5α-THP inhibits MyD88-dependent but not TRIF-dependent TLR pro-inflammatory signal activation and the production of cytokines/chemokines through its ability to block TLR-MyD88 binding in the alcohol-preferring (P) rat brain and the mouse macrophage RAW264.7 cell line. Here, we examine the effect of 3α,5α-THP on cultured human macrophages, derived from both males and females and examine whether Brexanolone (Brex; a proprietary form of 3α,5α-THP) treatment of postpartum depression (PPD) involves the inhibition of TLR4 and TLR7 activation. Human macrophages cultured from peripheral blood mononuclear cells of male and female healthy subjects (3-5/group) were treated with lipopolysaccharide (LPS, 1 μg/ml, 24h) or imiquimod (IMQ; 30 μg/ml, 24 h) alone or with 3α,5α-THP (1 μM) and examined for TLR pathway activation as defined by the expression of cytokines/chemokines and activated (phosphorylated) transcription factors. 3α,5α-THP inhibits the LPS-activated TLR4 signaling pathway assessed by elevations of TNF-α (30%/males and 60%/females), MCP-1 (50%/males and 100%/females) and pCREB (70%/males and 100%/females) in the cells derived from both males and females ($p<0.05$, Two-way ANOVA). In contrast, 3α,5α-THP, inhibited the IMQ-activated TLR7 signal assessed by elevations of IL-6 (100%), IL-1β (80%) and pIRF7 (70%) in macrophages cultured from female ($p<0.05$, Two-way ANOVA), but not male ($p>0.05$, Two-way ANOVA) subjects. In patients with PPD, whole

blood collected before and after (60 h) Brex infusion was treated with LPS (10 µg/ml, 4h) or IMQ (30 µg/ml, 4 h) and cell lysates were examined for levels of TNF-α, IL-6 and IL-1β. Both LPS and IMQ caused a significant ($p<0.05$, Two-way ANOVA) increase in the levels of TNF-α (24%/IMQ and 23%/LPS), IL-6 (85%/IMQ and 94%/LPS) and IL-1β (60%/IMQ and 80%/LPS) in blood cells collected before Brex infusion. Blood cells collected after Brex infusion were completely insensitive to LPS and less sensitive to IMQ as defined by the levels of TNF-α, IL-6 and IL-1β ($p<0.05$, Two-way ANOVA) when compared with cells collected before Brex infusion. The data indicate a strong inhibition of inflammatory signaling following Brex infusion. Furthermore, the therapeutic potential of 3α,5α-THP is more promising in female than male subjects and involves modulation of pro-inflammatory MyD88-dependent TLR signaling pathways resulting in diminished TLR signal activation in human immune cells. This mechanism likely contributes to the therapeutic effects of Brex in PPD patients.

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Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.05

Topic: G.05. Mood Disorders

Title: PIPE-307, a brain penetrant M1 selective antagonist, exhibits scopolamine-like antidepressive effects

Authors: *M. M. POON[1], A. R. BROADHEAD[1], K. J. STEBBINS[1], A. CHEN[2], J. M. BACCEI[2], D. S. LORRAIN[1];
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Abstract: A recent CDC report suggests that 30.2% of adults aged >18 years report experiencing some type of depressive disorder (Vahratian et al., 2021). While treatments for major depressive disorder (MDD) alleviate symptoms, these are often impeded by factors such as unwanted side effects, time needed to generate a therapeutic response (weeks to months), as well as forms of depression that are treatment resistant (TRD). By contrast, fast-acting antidepressants, such as scopolamine or ketamine, act on the order of hours to days and are effective in patients with TRD (Jaffe et al., 2013 and Krystal JH, 2007). Although scopolamine is a non-selective muscarinic acetylcholine receptor (mAChR) antagonist, its antidepressive effects are mediated by the M1 receptor isoform (M1) as evidenced by knockout and pharmacological data (Witkin et al., 2014). Scopolamine (and ketamine) act on layer 5 pyramidal neurons in the medial prefrontal cortex (mPFC), antagonizing inhibitory neurons, resulting in enhanced excitatory, transmission. Concomitantly, BDNF release and spine density are also enhanced. Together, these effects likely contribute to scopolamine's antidepressive effect (Wohleb et al 2017). Because scopolamine does not selectively target the M1 receptor, clinical dosing is associated with adverse events common to all non-selective muscarinic antagonists. We have identified and characterized an M1 selective, brain penetrant, small molecule antagonist, PIPE-307. Similar to scopolamine, we show that PIPE-307: 1) shows efficacy in the forced swim test, 2) increases mEPSC amplitude in pyramidal neurons in the

mPFC, 3) increases dendritic spine density, and 4) enhances BDNF levels. We further show that M1 protein is present on GABAergic interneurons. Together, these data suggest that (like scopolamine) PIPE-307 may be beneficial as a fast-acting antidepressant, but with an improved tolerability profile.

Disclosures: M.M. Poon: A. Employment/Salary (full or part-time):; Pipeline Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics. **A.R. Broadhead:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics. **K.J. Stebbins:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics. **A. Chen:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics. **J.M. Baccei:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics. **D.S. Lorrain:** A. Employment/Salary (full or part-time):; Pipeline Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pipeline Therapeutics.

Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.06

Topic: G.05. Mood Disorders

Support: RO1 MH107487

Title: Hippocampal Transcript Expression of Extracellular Adenosine Generating Pathway Genes in Major Depression

Authors: *D. SINCLAIR[1], S. ASAH[2], H. PANTAZOPOULOS[4], R. E. MCCULLUMSMITH[2], S. M. O'DONOVAN[3];
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Abstract: Major depressive disorder (MDD) is a debilitating disease that is characterized by low mood, anhedonia, impaired cognitive function, sleep difficulties and appetite disturbances. It is a serious neuropsychiatric illness that affects approximately 20% of the population over the course of a lifetime. Efforts to develop new treatments are stymied by our limited understanding of the pathophysiology of depression. Epidemiological, clinical and animal model data suggests significant perturbation of the adenosine system in MDD. However, the pathways that regulate extracellular adenosine availability have yet to be studied in the human brain in this disorder. We used qPCR to assay transcript expression of adenosine metabolism pathway genes (GFAP, ADORA1, ADORA2A, ENTPD1, ENTPD2, ENTPD3, ENT1 and ADA) in the hippocampus from subjects diagnosed with MDD, MDD and substance use

disorder (SUD), SUD and a non-psychiatrically ill control group (n=20/group). Since SUD is highly comorbid with MDD, analyzing both groups will offer insight regarding MDD specific changes in adenosine generating pathways. Subjects were matched for age, sex and postmortem interval (PMI). Relative concentrations of the transcripts of interest are calculated with comparison to a standard curve made with dilutions of cDNA from a pooled sampling of all the subjects. Values for the transcripts of interest are normalized to the geometric mean of B2M, β-actin, GAPDH and PPIA. We hypothesize that the expression of targets involved in pathways that generate extracellular adenosine and the expression of adenosine receptors will be dysregulated in the hippocampus in MDD. These findings will improve our understanding of adenosine system dysfunction in MDD and offer novel insight into the pathophysiology of this serious mental illness.

Disclosures: D. Sinclair: None. **S. Asah:** None. **H. Pantazopoulos:** None. **R.E. McCullumsmith:** None. **S.M. O'Donovan:** None.

Poster

P700. Treatment and Drug Discovery: Focus on Depression

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P700.07

Topic: G.05. Mood Disorders

Title: Connectivity based identification of candidate repurposable drugs in Major Depression using DrugFindR

Authors: *E. A. BATES, A. S. IMAMI, X. ZHANG, R. MCCULLUMSMITH, S. O'DONOVAN; Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: Major depressive disorder (MDD) is a serious mental health disorder that affects millions of people in the United States. Many patients who experience MDD are resistant to available antidepressant treatments and there is a pressing need to develop novel therapies for this debilitating disorder. DrugFindR is an R Shiny application created to identify candidate repurposable drugs from the Library of Integrated Network-Based Cellular Signatures (LINCS). Extensive MDD transcriptome data is available on public databases, making entirely computational analyses more accessible and reliable. Here, we utilize DrugFindR to identify potential candidate repurposable drugs for the treatment of MDD. For this analysis, gene signatures are obtained from publicly available RNAseq datasets (GSE102556) generated from postmortem brain tissue from male and female subjects with MDD and non-psychiatrically ill controls. Following a standardized RNAseq analysis pipeline, a quantile approach is used to determine the optimal log fold change threshold for gene expression for each brain region (DLPFC, NAC, VMPFC) in the dataset. Simultaneously, LINCS signatures for known antidepressants (fluoxetine, escitalopram, sertraline, venlafaxine, moclobemide, amitriptyline) are identified and grouped based on mechanism of action (SSRI, SNRI, MAOI-A, tricyclic). Finally, using signature-based connectivity analysis, DrugFindR identifies chemical perturbagens that are highly discordant (<-0.321) with the disease gene signatures (i.e. reverse the MDD gene signatures) and highly concordant (>0.321) with known antidepressant signatures. The identified candidate repurposable drugs have significant discordant signatures across multiple different cell lines in LINCS and are FDA approved. This study utilizes the extensive repository of

chemical perturbagen signatures available in LINCS to identify novel candidate drugs that may be explored for the treatment of MDD in male and female subjects. This study addresses a pressing need in neuropsychiatric research and provides a computational basis for future clinical applications. Future studies will examine the utility of the identified drugs in vivo.

Disclosures: E.A. Bates: None. **A.S. Imami:** None. **X. Zhang:** None. **R. McCullumsmith:** None. **S. O'Donovan:** None.

Poster

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Program #/Poster #: P700.08

Topic: G.05. Mood Disorders

Support: R01 MH121509
Florida State University Team Science for Translational Research Seed Grant

Title: Manipulating reward sensitivity using reward circuit-targeted transcranial magnetic stimulation

Authors: *J. RYAN[1], J. J. POULIOT[2], G. HAJCAK[2,1], D. E. NEE[2];
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Abstract: The mesolimbic reward circuit is important for learning and motivation, and dysregulations of the reward circuit are prominent in anhedonic depression. Specifically, depression has been linked to diminished activation to rewarding stimuli and follows animal studies relating dopaminergic reductions in the reward circuit to reduced reward motivation. Non-invasive interventions that can selectively target the reward circuit may hold promise for the treatment of anhedonia, a core symptom of many individuals who exhibit treatment resistant depression. Modern transcranial magnetic stimulation (TMS) interventions have not directly targeted reward circuitry, and have shown mixed results for long-term treatment of anhedonic depression. Thus, we utilized a novel TMS intervention for modulating the reward circuit. 34 healthy individuals participated in a cross-over controlled study targeting the reward circuit or a control site (M1 or S1) with intermittent theta-burst stimulation (iTBS), an excitatory form of TMS. Individual reward circuit targets were defined based upon fMRI functional connectivity with the ventral striatum (VS), yielding targets in the rostromedial prefrontal cortex (rmPFC). The rmPFC is a novel site for TMS depression treatment, but has shown strong connectivity with the VS, an area that is otherwise unable to stimulate directly with TMS. This methodology follows previous TMS literature showing the ability to alter downstream activation through stimulation of cortical areas exhibiting high co-activation with subcortical targets. Reward circuit functioning was assessed at baseline using fMRI, and reward circuit modulation was assessed using an event-related potential referred to as the reward positivity (RewP), which has been shown to reliably track reward sensitivity, and depression risk and course. A well-established gambling paradigm was used to determine reward circuit functioning and to elicit the RewP following iTBS. Relative to control-iTBS, rmPFC-iTBS enhanced the RewP. These effects were most pronounced in individuals with reduced VS fMRI activation at baseline. These data provide promising evidence that that the reward circuit can be modulated by rmPFC-iTBS and amenability to such

modulations are most effective on individuals with reduced reward circuit function. This provides the first step towards a novel non-invasive treatment of anhedonic symptomology commonly seen in depression and other disorders of the reward circuit.

Disclosures: J. Ryan: None. **J.J. Pouliot:** None. **G. Hajcak:** None. **D.E. Nee:** None.

Poster

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Topic: G.05. Mood Disorders

Support: NIH UH3 NS103550
Hope for Depression Grant
Medtronic (Devices)

Title: Differential acute and chronic effects of subcallosal cingulate cortex deep brain stimulation for treatment-resistant depression

Authors: S. ALAGAPAN[1], S. HEISIG[2], A. C. WATERS[2], A. VEERAKUMAR[3], M. OBATUSIN[2], T. J. NAUVEL[2], A. CROWELL[3], P. RIVA POSSE[3], R. J. BUTERA[1], H. S. MAYBERG[2], C. ROZELL[1]; [1]Georgia Inst. of Technol., Atlanta, GA; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Emory Univ., Atlanta, GA

Abstract: Subcallosal cingulate deep brain stimulation (SCC DBS) has shown effectiveness in treating patients with treatment-resistant depression (TRD). However, inter-individual variability in recovery trajectory as well as intra-individual variability in clinical symptoms hinders systematic adjustment of stimulation parameters. To overcome this limitation, we aim to identify electrophysiological markers of symptom recovery as well as response to stimulation from longitudinally collected local field potential (LFP) recordings. LFPs were acquired weekly during the first 6 months of therapeutic SCC stimulation using implanted pulse generators with data acquisition capabilities (Medtronic Activa PC+S). We used a neural network classifier to differentiate the beginning and the end of the 6-month period using spectral features extracted from LFPs. We used a novel tool, generative causal explainer (GCE), to identify 'spectral discriminative factors (SDCs)' that identified the feature changes that explained the classifier performance. We used separate classifiers to differentiate facial features extracted from videos of clinical interviews taken concurrently. The classifier based on LFP was able to differentiate the early and late stages of DBS treatment (Area under ROC curve: 0.91 ± 0.05, accuracy: 0.78 ± 0.09). GCE analysis revealed increases in alpha, beta and gamma band power contributed to the classifier performance. However, beta band power exhibited a decrease initially. Using the SDCs decoded from GCE in the intermediate period between the beginning and end of the 6 months, we identified distinct transitions which coincided with, or preceded transitions identified from individualized facial features (Kendall tau = 0.89, p = 0.04). In addition, SDCs responded to changes in stimulation dose. The results suggest long-term effect of stimulation that accompanies clinical recovery is distinct from acute effect of stimulation.

In addition, SDCs may serve as biomarkers to augment clinical decision-making and as potential control signals in closed-loop DBS.

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Poster

P700. Treatment and Drug Discovery: Focus on Depression

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Program #/Poster #: P700.10

Topic: G.05. Mood Disorders

Support: CIHR

Title: Sex-specific profiles of m6A RNA methylation in the brain of individuals with Major Depressive Disorder

Authors: *H. MITSUHASHI[1], Z. AOUABED[3], P. DANTHI[3], C. NAGY[2,3], G. TURECKI[1,3];
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Abstract: Introduction: Major Depressive Disorder (MDD) is twice as prevalent in females than males, and mounting evidence suggests that it may be driven by sex-specific molecular mechanisms. Recent gene expression studies have revealed a small overlap between differentially expressed genes (DEG) in male and female MDD. Moreover, these DEGs are enriched in synaptic regulation in males, whereas they are enriched in immune response in females, suggesting a sex-specific mechanism in MDD. However, little is known about how molecular mechanisms lead to sex differences in MDD. Epigenetic mechanisms, which are altered in response to environmental factors, are known to be involved in the pathophysiology of MDD. Similar to these epigenetic modifications, RNA modifications have emerged as a dynamic and crucial mechanism in the post-transcriptional regulation of gene expression in recent years. Among the 150 known RNA modifications, N6-methyladenosine (m6A) is the most abundant and reversible RNA modification in mammalian messenger RNA (mRNA). Emerging evidence suggests that m6A plays an important role in the brain, including neurogenesis, and memory and learning. Moreover, recent studies have linked m6A to molecular and behavioral responses to stress, making it an important candidate regulator of stress-related psychiatric disorders, including MDD. This project aims to investigate the landscape of m6A in the human brain and to identify changes that may occur in the context of MDD. **Methods:** We optimized a low-input m6A-seq method for human postmortem brain tissue and showed that the m6a-peaks are enriched in the known m6A GRACH motif and near 3'UTR and stop codon as suggested by the previous study. The ventromedial prefrontal cortex was obtained from male and female MDD and healthy control subjects to investigate the role of m6A in MDD. We performed m6A-seq and RNA-seq to investigate m6A at transcripts levels and the impact of m6A on gene expression. **Results:** We identified ~25,000 m6A peaks in the human brain, and these peaks were enriched in genes related to neuronal and synaptic regulation. Moreover, our results show a distinct m6A

profile in MDD and control, with a little overlap between males and females. **Conclusion:** Our results show sex-specific transcriptional profiles in MDD as suggested by the previous studies, and how epitranscriptomic regulation could regulate these different molecular mechanisms. Our research will help us understand the role of m6A in psychiatric disorders and will serve as a much-needed example of sex-specific analysis in MDD.

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Poster

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Support: Swedish Research Council (2016- 01439, 2020-01801)
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Title: Symptom improvement is not associated with white matter changes in women with premenstrual dysphoric disorder under selective progesterone receptor modulator treatment.

Authors: *E. KALTSOUNI[1], X. GU[1], E. COMASCO[1], I. SUNDSTRÖM POROMAA[2];
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Abstract: Approximately 5-8% of reproductive women suffer from premenstrual dysphoric disorder (PMDD) which is characterized by severe cyclic mood symptoms emerging in the luteal phase of the menstrual cycle. Impaired cortico-limbic function is related to the affective symptoms experienced in the luteal phase in PMDD, likely due to maladaptive neural response to ordinary hormonal fluctuations. The aim of this study is to employ tract-based spatial statistics (TBSS) to evaluate the microstructural integrity changes of white matter (WM) tracts in women with PMDD after selective progesterone receptor modulator (SPRM) treatment compared with placebo. Diffusion tensor imaging (DTI) data were acquired from 35 women that underwent brain scanning during the luteal phase of the menstrual cycle, before and after a three-month treatment with SPRM or placebo. Reporting of PMDD symptoms severity was done through self-reports using the Daily Record of Severity of Problems, while liquid chromatography - tandem mass spectrometry was used for the measurement of gonadal hormone levels. Whole brain and region of interest TBSS analyses were performed to assess time by treatment interaction effects on WM microstructure by integrating multiple DTI metrics including fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. No significant treatment effects emerged from the permutation-based non-parametric analyses. Analyses on the relationship between hormonal level over time and changes in white matter are ongoing. Additionally, ongoing correlation analyses are being performed to further investigate the relationships between changes in DTI metrics over time and symptom improvement. These preliminary results suggest that white matter alterations may not contribute to the

improvement of mental symptoms observed after selective progesterone receptor modulator treatment in women with PMDD.

Disclosures: E. Kaltsouni: None. **X. Gu:** None. **E. Comasco:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Swedish Research Council (2015-00495), EU FP7-People-Cofund (INCA 600398). Other; Marie Skłodowska Curie fellow. **I. Sundström Poromaa:** None.

Poster

P794. Prefrontal Mechanisms: Rodents and Learning

Location: Virtual Only

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Program #/Poster #: P794.01

Topic: H.04. Executive Functions

Support: 1R01AA025652-01

Title: Glutamatergic and GABAerigc modulation of cognitive flexibility during rodent touchscreen reversal

Authors: *J. CHANDRASEKARAN[1], D. N. LINSENBARDT[3], J. L. BRIGMAN[2];
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Abstract: Executive functions, such as behavioral flexibility, allow an individual to adapt to an ever-changing environment. Impaired flexibility has been associated with multiple neuropsychiatric and neurodevelopmental disorders and understanding the mechanisms of flexibility is critical for developing effective treatment. Preclinical studies have demonstrated that the lateral orbitofrontal cortex (OFC) tracks and updates changing reward values during reversal, a well-validated cross-species task of flexibility. NMDARs are known to globally mediate learning and the ratio of NMDAR subunits GluN2A and GluN2B have been suggested to act as a gate for synaptic plasticity during learning. Loss of forebrain GluN2A impairs learning while loss of cortical GluN2B is sufficient to impair flexibility and alter coherence with the dorsal striatum (DS). It is still unknown if the 2A/2B ratio varies during stages of learning and reversal. In addition, AMPARs also play a critical role in synaptic plasticity. The membrane insertion of AMPAR depends on NMDAR activation which is essential for learning, yet the role of AMPAR subunits in reversal learning is still unknown. In addition to evidence showing the OFC tracks reward value via intra-region coherence of glutamatergic neurons, GABAergic interneurons also play a role in reversal learning. However, the role of E/I balance during reversal learning is unknown. In order to test if NMDAR and AMPAR subunit expression is critical for gating plasticity during reversal, we tested C57BL/6J male mice (n=20/group) to stages associated with learning and flexible choice. 2 hours following the beginning of the session mice were sacrificed, brains removed and immunoblotting performed to quantify the levels of NMDAR and AMPAR subunits in the synaptic fraction. To examine E/I balance during reversal, C57BL/6J mice were implanted with drivable 64 channel shank electrode (Cambridge neurotech) following discrimination. Single unit firing activity of putative pyramidal and

fast-spiking interneurons was recorded during early reversal sessions 1-4 and chance reversal (50% correct choice). Our results show a pattern of increased GluN2B expression in the DS during learning, and a subsequent increase in the subunit in the OFC during early reversal when flexibility was required. Analysis of glutamatergic and GABAergic activity in vivo revealed dynamic alteration in E/I balance during reversal. Together, these results further our understanding of the mechanisms mediating flexibility, and provide a strong foundation to develop better treatment strategies for neuropsychiatric disorders presenting with maladaptive perseveration.

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Poster

P794. Prefrontal Mechanisms: Rodents and Learning

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Program #/Poster #: P794.02

Topic: H.04. Executive Functions

Support: NIH T32 NS082145
NIMH R01 MH053851

Title: Increased activation of the lateral orbitofrontal cortex impairs reversal learning

Authors: *K. M. TUITE, M. GIROTTI, D. A. MORILAK;
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Abstract: Stress-related psychiatric disorders, such as major depressive disorder and anxiety disorders, have cognitive symptoms that are not well-treated by classical antidepressants and cause major detriments to patients' quality of life. Reversal learning, a form of cognitive flexibility necessary to adapt to a changing environment, is disrupted in stress-related psychiatric disorders. The orbitofrontal cortex (OFC) is involved in reversal learning, and hyperactivity in the OFC is associated with psychiatric disorders in humans. Reversal learning in rodents is evaluated using the first three stages of the attentional set-shifting test (AST). We have previously reported that chronic stress impairs reversal learning and that inducing long-term depression (LTD) in the mediodorsal thalamus to OFC projection reverses these deficits. This indicates reducing OFC activity following stress restores reversal learning to control levels. However, we have yet to investigate OFC activity in reversal learning under baseline conditions. To address this, animals went through either the compound discrimination or reversal learning stages of AST and brains were processed for Fos immunohistochemistry. In lateral OFC, Fos induction significantly decreased following reversal learning compared to compound discrimination. Additionally, Fos expression was increased after reversal learning in the central medial thalamus (CM), an afferent to the OFC, that has yet to be implicated in reversal learning. We next tested the hypothesis that a decrease in OFC activity is necessary for successful reversal learning. We used an adeno-associated virus to deliver an excitatory (Gq) DREADD or control GFP construct into the lateral OFC under the control of the CaMKII promoter to increase activity specifically of glutamatergic neurons. Animals received injections of DREADD agonist 21 (1 mg/kg, i.p.) 20 minutes preceding reversal learning. Activating the Gq DREADD significantly impaired reversal learning, increasing trials to criterion during reversal learning as well as

regressive errors. These results suggest that preventing inhibition in the OFC during reversal learning impairs performance. Future experiments will investigate circuit-level activity in the OFC and its efferent targets and determine the potential role of the excitatory CM thalamic afferent to the OFC in reversal learning and in the effects of stress.

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Poster

P794. Prefrontal Mechanisms: Rodents and Learning

Location: Virtual Only

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Program #/Poster #: P794.03

Topic: H.04. Executive Functions

Support: MSCA-IF

Title: Population dynamics of individual neurons in prelimbic and infralimbic cortices of rats in a behavioral paradigm requiring action control.

Authors: *A. PARTHASARATHY[1,2], B. J. G. VAN DEN BOOM[1,2], F. VEEN[1], N. YEE[1], I. WILLUHN[1,2];
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Abstract: Several psychiatric conditions, classified as impulsivity disorders, are associated with impaired inhibitory control of behavior. Such an inability to inhibit unwanted behavior is often linked to dysfunctional expression or suppression of appetitive behavior. A number of studies suggest that prelimbic (PL) and infralimbic (IL) cortices play dichotomized roles in the expression and suppression (respectively) of reward-driven actions, drug seeking, or fear conditioning. However, the neural encoding of appetitive behavior in PL and IL in the context of such behaviors is understood insufficiently. Thus, we investigated how populations of neurons within PL and IL are coordinated and collaboratively establish appetitive behavior. We recorded calcium transients from PL and IL neurons by imaging GCaMP6s activity with implantable, miniaturized fluorescence microscopes (miniscopes) in rats that performed a reward-driven go/nogo task. We observed that similar proportions of neurons in PL and IL encoded task relevant information during go (expression) and nogo (suppression) trials. To investigate the role of population activity in PL and IL, we used a dimensionality-reduction approach to compute the (neural) activity space that contains information about the animal's task-related behavior and studied the temporal dynamics within this activity space. Using this computational approach, we detected significant information about the two trial types in both PL and IL neuron populations on a trial-by-trial basis, prior to the trial-relevant behavioral response of the trial. In addition, PL and IL population activity played a role in encoding individual behavioral events, such as lever presses (the operant action in go trials). Such extraction of task-relevant information at a single-trial level provides a strong behavioral correlate that is difficult to detect using traditional population activity representations such as single-cell averaging.

Furthermore, our population-activity data demonstrate that go and nogo trials are encoded differently in PL and IL. Overall, we showed that population activity in PL and IL exhibits task-relevant information about the animal's behavior on a trial-by-trial basis. Based on these findings, we can now focus on investigating which subpopulations of neurons in PL and IL encode the aforementioned neural activity during go and nogo trials. In the long run, this line of research will help us understand how PL and IL neurons contribute to expression (go) and suppression (nogo) of action under both normal and psychiatric conditions, to which impaired inhibitory behavioral control is central.

Disclosures: A. Parthasarathy: None. **B.J.G. van den Boom:** None. **F. Veen:** None. **N. Yee:** None. **I. Willuhn:** None.

Poster

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Topic: H.04. Executive Functions

Support: NIH Grant NS108259

Title: Differential projections from the five divisions of the orbital cortex to the thalamus in the rat

Authors: R. P. VERTES, S. B. LINLEY, A. K. P. ROJAS, W. B. HOOVER;
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Abstract: Using the anterograde tracer, PHA-L, we examined projections from the orbital cortex (ORB) to the thalamus in the rat; that is, from the medial orbital (MO), ventral orbital (VO), ventrolateral orbital (VLO), lateral orbital (LO) and dorsolateral orbital (DLO) cortices to the thalamus. Overall, projections from the ORB to the thalamus were essentially restricted to central/medial regions of the thalamus, with a lack of projections to principal (or relay) nuclei of the thalamus. Although differentially innervated by each subdivision, the main thalamic targets of the ORB were: the paratenial nucleus (PT), nucleus reuniens (RE), medial and central divisions of the mediodorsal nucleus (MD), intermediodorsal nucleus (IMD), the submedial nucleus (SMT) and the rostral intralaminar nuclei (ILt). MO distributed heavily to the PT, RE and medial MD and lightly to IMD. Similar to MO, VO distributed heavily to PT and RE but unlike MO to the central rather than to the medial division of MD. VO heavily targeted ventrolateral parts of RE, including the lateral wings of RE. The projections of VLO significantly differed from those of MO and VO. There was an absence of VLO projections to the rostral thalamus including to PT and RE; the main VLO targets were SMT, central MD, anterior medial (AM) nucleus and the rostral ILt -- central medial (CEM), paracentral (PC) and central lateral (CL) nuclei. LO distributed heavily to the central MD, moderately to IMD and SMT, and lightly to PT and the rhomboid (RH) nucleus. DLO distributed heavily to PT and medial MD and moderately to IMD, RH and SMT. In summary, (1) all ORB divisions projected to MD, with notable differences across medial and central divisions of MD; (2) with the exception of VLO, all ORB divisions projected to PT; (3) projections to RE mainly arose from MO and VO; (4) projections to the intralaminar nuclei mainly arose from VLO; and (5) interestingly, there was a general absence of ORB projections to the paraventricular nucleus, and with some exceptions, to the

anterior nuclei of the thalamus. In the absence of direct projections from medial prefrontal cortex (mPFC) to the hippocampus (HF), we previously showed that RE is an important anatomical link between the mPFC and the HF (Vertes et al., 2007). In the same manner, RE appears to critically link the ORB (MO and VO) with the HF, possibly involved in relaying information on reward contingencies or behavioral adaptations from the ORB to the HF. The foregoing indicates that each of the subdivisions of the ORB exhibit a unique pattern of projections to the thalamus in the rat, which suggests that individual divisions of ORB may exert unique functional effects on thalamic or thalamocortical systems.

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Poster

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Topic: H.04. Executive Functions

Support: McKnight Endowment Fund for Neuroscience (VSS)

Title: Gamma-frequency auditory stimulation improves rule shifting in Dlx5/6$^{+/-}$ mice

Authors: *J. SHI, A. J. PHENSY, V. S. SOHAL;
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Abstract: Cognitive flexibility is critical for organisms to adapt to changing environments. Deficits in this ability are associated with neuropsychiatric disorders such as schizophrenia. We have previously shown that synchronized gamma-frequency oscillations generated by parvalbumin (PV) interneurons in the medial prefrontal cortex (mPFC) play a key role in cognitive flexibility (Cho et al. 2015, 2020), and that optogenetically enhancing this gamma-frequency synchronization in mutant mice with abnormal PV interneuron development can rescue their deficits in cognitive flexibility, measured using a rule shifting task (Cho et al., 2015, 2020). Recently, multiple studies have demonstrated the effectiveness of using gamma-frequency trains of visual and/or auditory stimuli to entrain higher-order brain regions including the mPFC and ameliorate cognitive deficits in mouse models of Alzheimer's disease (Martorell et al. 2019, Adaikkan et al. 2019). Here, we investigated the effect of gamma-frequency (40 Hz) auditory stimulation on *Dlx5/6*$^{+/-}$ mice during a rule shifting task. In this task, mice form an initial association between one cue (an odor or a textured digging medium) and the location of a hidden food reward. Upon successful learning, the association is shifted to a familiar (but previously task-irrelevant) cue belonging to the other modality (odor or texture). Gamma-frequency auditory stimulation rescued the performance of *Dlx5/6*$^{+/-}$ mice in this rule shifting task, significantly reducing the numbers of trials needed to reach a learning criterion and of preservative errors to near wild-type levels. Unlike the pro-cognitive effects of gamma-frequency optogenetic stimulation (Cho et al., 2015), these effects did not persist in the absence of additional stimulation on subsequent days of testing. We also recorded signals from genetically encoded voltage indicators expressed in mPFC PV interneurons to measure gamma-frequency synchronization. We are currently analyzing these data to identify possible circuit changes elicited by gamma-frequency auditory stimulation.

Disclosures: J. Shi: None. **A.J. Phensy:** None. **V.S. Sohal:** None.

Poster

P794. Prefrontal Mechanisms: Rodents and Learning

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Program #/Poster #: P794.06

Topic: H.04. Executive Functions

Title: Activity of Drd2-expressing neurons in the mouse medial prefrontal cortex (mPFC) during social decision making

Authors: *M. TURNER, V. SOHAL;
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Abstract: The medial prefrontal cortex (mPFC) is a hub for many forms of cognition and decision making, and is also important for normal social behavior. Dopaminergic modulation of mPFC activity is critical for these functions, and is believed to be altered in many psychiatric conditions. Of particular interest are dopamine D2 receptors (D2Rs), which have been shown to be important for normal working memory and set-shifting in rodents, and are thought to play key roles in the pathology of schizophrenia and bipolar disorder in humans. Published work from our lab using fiber photometry showed that D2R-expressing neurons in the mPFC are preferentially recruited during social interaction in mice. Which behavioral variables these neurons might encode during social interaction, and how D2Rs contributes to this activity, remains unknown. Here, we use in vivo calcium imaging and head-mounted miniature microscopes to examine the activity of D2R+ neurons in the mPFC during the three-chamber test, which is commonly used to assay social preference and social novelty preference. To image D2R+ neurons under normal conditions (D2R-WT), Drd2-Cre+/- mice were injected with AAV2-hSyn-DIO-GCaMP6m (n = 7 mice [4M, 3F], n = 362 neurons). To explore the role of the D2R in socially recruited activity, we used a separate strategy to image D2R+ neurons and knockout the receptor (D2R-KO): Drd2f/f mice were co-injected with AAV2-EF1a-DIO-GCaMP6m and AAV8-D2sp-Cre, which expresses Cre recombinase from a D2R-specific promoter (n = 6 mice [3M, 3F], n = 345 neurons). As a comparison, a separate cohort of Drd2-Cre+/- mice were injected with AAV2-hSyn-GCaMP7f to label all neurons of the mPFC (mPFC-WT) (n = 5 mice[2M, 3F], n = 355 neurons). Interestingly, we found that the largest fraction of D2R-WT neurons had significantly increased activity specifically within the center chamber (19.43% ± 7.54% per mouse, based on comparison to shuffled datasets). Notably, , a significantly smaller proportion of D2R-KO (10.41% ± 3.51%; $p = 0.023$) and of mPFC-WT (9.88% ± 2.98%; $p = 0.022$) neurons significantly increased activity within the center chamber (One-way ANOVA [$F(2,15) = 6.294$, $p = 0.0104$] with Tukey's post-hoc). These results indicate that the D2R+ population of the mPFC is preferentially recruited in the center of the three-chamber apparatus, and that this recruitment depends on D2Rs. Given that the center chamber represents a decision point in the task, this work potentially opens new doors into the study of the cells and circuits that underlie social decision-making in mice.

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Poster

P794. Prefrontal Mechanisms: Rodents and Learning

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Title: Prefrontal long-range inhibition exerts top-down control over hippocampal signal-to-noise and exploratory behavior

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Abstract: The prefrontal cortex (PFC) plays a crucial role in top-down executive control of brain activity and behavior. It is postulated that PFC communicates with several cortical and subcortical brain regions, monitoring and gating their ongoing activity, in order to exert top-down control over innate and learned behaviors. One brain region that is known to interact with the PFC is the hippocampus (HPC), a key brain region for processing spatial information, and using spatial representations to guide exploratory behavior. Multiple lines of evidence in humans, non-human primates, and rodents have suggested that PFC exerts top-down control over information processing in the HPC, particularly during exploratory behaviors. However, the circuit mechanisms mediating prefrontal top-down control remain unclear, and it is not known whether the PFC acts by transmitting specific information to the HPC or by modulating the network state and emergent circuit function. Our study addresses this major gap by revealing a novel anatomical substrate mediating prefrontal top-down control. Specifically, we have identified monosynaptic long-range GABAergic (LRG) projections from the PFC to the dorsal HPC, and have elucidated how these projections regulate exploratory behavior via actions on hippocampal neurons, microcircuits, network dynamics, and information processing. We found that PFC-HPC LRG projections preferentially inhibit vasoactive intestinal polypeptide expressing interneurons, which are known to disinhibit hippocampal microcircuits, thus representing a novel ‘doubly disinhibitory’ long-range circuit motif. Due to this specific targeting, stimulation of LRG projections increases hippocampal feedforward inhibition and reduces hippocampal activity in vivo. The net effect of these actions is to specifically enhance the signal-to-noise ratio for hippocampal representations of objects. Correspondingly, both stimulation and inhibition of PFC-HPC LRG projections affect object exploration behavior. Together, these results outline a new top-down pathway in which prefrontal LRG projections target hippocampal disinhibitory microcircuits, thereby enhancing signals and network dynamics underlying exploratory behavior.

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Poster

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Title: Amphetamine use and withdrawal impairs interval timing in mice

Authors: *H. R. STUTT[1], M. A. WEBER[2], N. S. NARAYANAN[3];
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Abstract: Amphetamine dependence and withdrawal is associated with high incidences of relapse, stress hypersensitivity, and anxiety. Cognitive dysfunctions such as impaired working memory, attention, and temporal control of action may underlie these factors to drive the cycle of addiction. Further, amphetamine-related hospitalizations and overdoses are increasing, and only a few treatment options are available. Therefore, it is critical to elucidate how amphetamine abuse affects cognitive function. Interval timing, i.e. the temporal control of action, is ideally suited to investigate amphetamine-induced cognitive dysfunction as it requires processes such as working memory and attention and is dependent on dopamine in both the dorsomedial striatum and frontal cortex. Here, we investigated how amphetamine use and withdrawal in rodents impacts interval timing behavior using an operant-based timing task. This task requires the rodent to make a decision to "switch" from one response port to another based on their perception of how much time has passed. Following training, half the subjects received daily amphetamine injections (2.5 mg/kg ip.) for 14 days while the other half received equivalent volumes of saline. We observed that acute exposure to amphetamine resulted in both earlier and greater variability of switch times on average. In addition, following a 14 day period of forced withdrawal, subjects previously exposed to amphetamine were more variable on average. These results suggest that amphetamine exposure can produce changes in time perception immediately following exposure and well into withdrawal. We hypothesize that this acute and prolonged deficit in interval timing is the result of altered dopamine function in the dorsomedial striatum and frontal cortex. We will test this hypothesis using dLight, an in vivo dopamine sensor, and fiber photometry recordings before, during, and after chronic amphetamine administration. Together, these findings will provide detailed mechanistic understanding of how amphetamine use and withdrawal can negatively impact cognitive function, and may guide future studies exploring brain stimulation and pharmacological interventions for cognitive dysfunctions associated with amphetamine use and withdrawal.

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Topic: H.04. Executive Functions

Support: The Charles E. Kubly Mental Health Research Center at Marquette University

Title: Sex Differences in the Effects of Chronic Stress and Prefrontal Cortical REDD1 Overexpression on Pavlovian Autoshaping Behavior in Rats

Authors: B. KURTOGLU[1], D. WHEELER[2], B. WINDSOR[1], M. SPRING[3], J. EVANS[1], D. NOWAK[1], M. MANTYCH[1], P. LAMBERTON[2], R. WHEELER[2], *J. MANTSCH[1];
[1]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [2]Biomed. Sci., Marquette Univ., Milwaukee, WI; [3]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Sign tracking and goal tracking have been linked to human disease states including substance use disorders and depression. The prefrontal cortex (PFC) is important for regulating Pavlovian autoshaping behavior and chronic stress is known to produce structural and functional changes in PFC that might also contribute to disease states. In this task, a cue (the presentation of a lever) is associated with the subsequent delivery of a reward (a sucrose pellet). Rats can express the acquisition of this association by approaching the cue (sign tracking), or by anticipatory approach to the reward (goal tracking). In contrast to prior studies, chronic unpredictable stress (CUS) promoted a CS+ responding in male rats consistent with the shift to a sign tracking phenotype. In contrast, in females rats CUS produced a shift towards a goal directed behavior. Previous studies have shown that the protein REDD1 (regulated in development and DNA damage responses-1) is increased in post-mortem PFC tissue from individuals diagnosed with depression. Recently, we observed that, there is an increase in REDD1 expression and a decrease in Raptor phosphorylation, one of the key elements of the mTORC1 complex, in rat PFC after CUS, suggesting disrupted mTORC1 function. This effect was transient as it was not observed at a later time point after CUS. To determine if REDD1 overexpression is sufficient to produce changes in Pavlovian autoshaping, we used a viral vector to overexpress REDD1 in the PFC of male rats before training them in a Pavlovian autoshaping task. Similar to CUS, REDD1 overexpression produced a phenotype that was consistent with sign tracking behavior in male rats. Relative to control rats, REDD1 rats showed reduced anticipatory approach to the food (goal tracking), but enhanced approach to the cue (sign tracking). The observation that CUS and REDD1 overexpression produce sign tracking phenotypes in male rats likely has relevance for understanding a number of stress related disorders. Future research will determine whether female rats are similarly affected by REDD1 overexpression, and examine the time course of REDD1, necessity of disrupted mTORC1 for stress effects and reconcile the differences between our current and past findings.

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Poster

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Support: U.S. Department of Veterans Affairs Biomedical Laboratory Research and Development Program Merit Award 1I01BX003512
William and Ella Owens Medical Research Foundation

Title: Extinction learning promotes neuroplasticity in the medial prefrontal cortex of chronically stressed rats

Authors: *S. E. BULIN, J. LIU, D. A. MORILAK;
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Abstract: Posttraumatic stress disorder (PTSD) is a serious mental disorder that affects 7-8% of the population in the USA. Our lab has established a model of cognitive behavioral intervention in rats, namely extinction therapy, which resembles prolonged exposure therapy for PTSD. Our animal model of extinction therapy ameliorates stress-induced deficits in cognitive flexibility and active coping behavior and these therapeutic effects are blocked by inhibition of the pyramidal neurons in the medial prefrontal cortex (mPFC). In this current study, we investigate mechanisms underlying the efficacy of extinction therapy involving alterations in synaptic and structural plasticity of the mPFC in chronically stressed rats. To test for changes in neuroplasticity in the mediodorsal thalamus (MDT) to mPFC pathway, previously shown to be less responsive after stress, rats were injected with the viral vector AAV5-CAMKII-ChETA-YFP in the MDT to achieve pathway specificity. 3-4 weeks after virus injections, rats underwent chronic unpredictable stress (CUS) or control treatment. Extinction or control treatment was applied 24 hrs after the end of CUS, and 24 hrs later, rats were anesthetized to record local field potentials evoked in the mPFC by stimulating in the MDT. A current-response curve was collected prior to applying optogenetic laser stimulation to induce long-term potentiation (opto-LTP). Responses were then recorded at an intensity that generated 50% maximal response at baseline for 90 minutes after opto-LTP induction. In male rats, extinction rescued stress-induced deficits in the afferent-evoked response and increased potentiation after opto-LTP ($p<0.001$). However, in stressed female rats, extinction learning had no effect on mPFC responsivity, but rescued stress-induced deficits in opto-LTP ($p<0.01$). In a separate experiment, changes in structural plasticity was examined. CUS and nonstressed rats were sacrificed 24 hr after extinction learning or tone exposure to examine changes in spine density and neuronal morphology. Images of pyramidal cells in layer II/III and layer V of the mPFC were acquired and spine density and morphology in both apical and basal dendrites were measured. 10 µm segments were analyzed every 50 µm from the soma. Quantification is ongoing.

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Poster

P797. Subcortical-Cortical Interactions: Circuitry and Complex Behavior

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Topic: H.04. Executive Functions

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Title: Putamen inhibition enhances flexibility in action selection in rhesus monkeys

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Abstract: The activity of parallel cortico-basal ganglia circuits are responsible for action selection. The associative cortico-basal ganglia circuit, that includes the striatal caudate nucleus, is critical for flexible behaviors that adapt in response to changing contingencies. In contrast, inflexible or habitual behaviors rely primarily on the sensorimotor cortico-basal ganglia circuit that includes the striatal putamen. Here we test the hypothesis that decreasing the output of the sensorimotor circuit, will bias towards the use of the associative circuit in action selection, therefore increasing behavioral flexibility. To this end, the impact of reversible putamen inhibition on performance of an attentional set-shifting task (ASST) was tested in 12 rhesus monkeys (6 females) in which Gi-DREADDs were virally expressed in the pre-commissural putamen under the human synapsin 1 promoter. The ASST was based on solving a sequence of up to 8 visual-discrimination "sets" of two geometric shapes and colors, that increased in difficulty across sets. Touching the "correct" stimuli resulted in reinforcement while touching the "incorrect" stimuli resulted in a 10-s delay to the next trial and no reinforcement. Advancing through sets was self-pacing and occurred with 12 of 15 correct trials. Sessions ended when all 8 sets were completed or 45 minutes elapsed. All monkeys were housed in the same room and given 37 daily ASST sessions simultaneously within their housing cages (task acquisition). The DREADD actuator, deschloroclozapine (DCZ, 300mg/kg) or saline was given 30 minutes prior to ASST sessions. Neither DCZ or saline injection altered performance on the well-trained ASST performance (activation was tested following 5 baseline sessions). However, following an ASST session that incorporated a sensorimotor challenge (SMC), where the visual stimuli was reduced in size to assess action selection flexibility (Shnitko et al., 2020), animals that received DCZ performed better than those that were treated with saline. Activation of Gi-DREADDs within the putamen led to animals completing more sets (DCZ = 8 sets, saline = 3 sets) as well as decreased the number of errors made (DCZ = 25±4 errors, saline = 42±10 errors). Thus, study revealed that disruption within the sensorimotor neurocircuit via putamen inhibition enhances flexibility in action selection when subjects presented with a novel aspect of a well-learned visual discrimination.

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Poster

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Support: NIH P40OD010996
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Title: Segregated Output Channels from Cerebellar Cortex to Prefrontal Cortex

Authors: *A. C. BOSTAN[1], R. P. DUM[2], P. L. STRICK[3];
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Abstract: There is a growing recognition that the cerebellum is not only concerned with the control of movement, but also is involved in cognitive function. Indeed, it is now clear that a substantial portion of the output from the cerebellum is directed at nonmotor areas of the cerebral cortex in the frontal lobe. These same areas of the prefrontal cortex are a major source of signals back to the cerebellar cortex. We have begun to explore the mapping principles that define this cerebro-cerebellar circuitry. To do this, we injected the CVS-N2C strain of the rabies virus with the mCherry marker gene (RV-MC) into area 9L of the prefrontal cortex in a Cebus monkey. In the same animal, we injected the CVS-N2C strain with the GFP marker gene (RV-GFP) into an adjacent region of the prefrontal cortex, the PrePMd. We set the survival time to allow transport of both virus strains to infect first-order neurons in regions of the thalamus, second-order neurons in the cerebellar nuclei, and then third-order neurons (Purkinje cells [P-cells]) in the cerebellar cortex. Virus transport from either injection site infected P-cells located laterally in the posterior lobe of the cerebellum, within regions of Crus I, Crus IIa, and Crus IIp. However, the densest labeling following transport from the PrePMd injection of RV-GFP and that following transport from the area 9L injection of RV-MC displayed limited overlap. Three regions of the cerebellar cortex contained infected RV-GFP and RV-MC P-Cells: (1) the posterior bank of the cerebellar cortex in the fissure between Crus I and Crus IIa; (2) the posterior bank of cerebellar cortex in the fissure between Crus IIa and IIp; and (3) the surface of Crus IIp. Even at these sites, patches of P-cells infected by virus transport from PrePMd were interleaved with patches of P-cells infected by virus transport from area 9L. Our estimate is that the overlap in the two types of patches is less than 6%. These results along with others indicate that a relatively large region of the cerebellar cortex in the hemisphere is interconnected with areas of the prefrontal cortex. However, within this region, separate channels exist that are focused on specific prefrontal areas.

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Poster

P797. Subcortical-Cortical Interactions: Circuitry and Complex Behavior

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Topic: H.04. Executive Functions

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Title: Internal states guiding instrumental behaviour engage the anterior insular cortex in rats

Authors: *M. PUAUD, D. JOSHI, A. WRIGHT, V. HO, M. FOUYSSAC, D. BELIN;
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Abstract: Interoceptive mechanisms contribute to both, subjective states but also to guide behaviour and control executive functions. fMRI studies in humans have revealed that the posterior insula (PI) is

involved in the integration of emotional states triggered by peripherally-generated interoceptive cues, such as the increased heart rate induced by the peripherally-acting β-adrenoreceptor agonist, isoproterenol. In contrast, the anterior insula (AI) seems to mediate the utilisation of interoceptive states to make predictions about the environment and thereby to guide behaviour. We tested two hypotheses in 42 male Sprague Dawley rats (i) that rats can equally utilise peripherally- and centrally-generated interoceptive states to guide their behaviour in a drug discrimination task (DDT), and (ii) that the utilisation of interoceptive states to guide behaviour is specifically associated with functional activation of the AI. Rats were trained to discriminate between (i) different exteroceptive cues, (ii) saline and the centrally-acting $GABA_A$ receptor antagonist pentylenetetrazol (PTZ) or (iii) saline and isoproterenol. The reliance on the different cues to guide behaviour was measured and compared over a 12 min challenge session under extinction conditions. Transcriptomic correlates of PTZ discrimination were assessed by qPCR from cDNA libraries of the amygdala, the AI, PI and motor cortex M1. Discrimination was acquired at the same rate across interoceptive and exteroceptive cues, suggesting that interoceptive states are at least equally potent at guiding behaviour as salient exteroceptive stimuli. At the neurobiological level, administration of PTZ in non-trained animals resulted in an increase in mRNA levels of the cellular plasticity marker zif268 in the PI and the central (CeN), but not the basolateral, amygdala. No changes in zif268 mRNA levels were observed in the AI. In contrast, administration of PTZ in animals subsequently tested in the DDT resulted in an increase in zif268 mRNA levels in the AI alongside the PI and CeN. No changes in cellular plasticity were observed in the Motor cortex M1, thereby ruling out non-specific effect of PTZ on the activity of the brain. Together, these results show that a PI-CeN neural system is involved in the integration of the interoceptive effects of PTZ whereas plasticity in the AI is specifically recruited when animals utilise these interoceptive states to guide their behaviour.

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Poster

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Title: The direct and indirect pathways of the basal ganglia modulate dorsal cortical activity and future perceptual decisions

Authors: *E. H. VAN BEEST[1], M. A. O. ABDELWAHAB[1], J. L. CAZEMIER[2], C. BALTIRA[1], M. C. MAES[1], B. D. PERI[1], M. W. SELF[1], I. WILLUHN[3,4], P. R. ROELFSEMA[1,4,5];
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Abstract: The striatum, the major input structure of the basal ganglia, receives topographically organized neural projections from the cortex. Two complementary pathways emerge from the striatum: the direct pathway, primarily expressing dopamine D1 receptors, and the indirect pathway, primarily expressing dopamine D2 receptors. The direct pathway disinhibits the thalamus, thereby promoting activity in the thalamocortical circuit. Conversely, the indirect pathway suppresses this circuit. Here we asked how this organization modulates persistent activity related to perceptual decisions in the cortex. We unilaterally injected a virus to express an excitatory opsin in either pathway and measured behavioral responses and neural activity across the dorsal cortex in adult mice using widefield imaging. The mice had been trained to report the location of a grating stimulus with a left or right licking response. Photo-stimulating the direct pathway in “resting state” evoked activity across the dorsal cortex, specifically in visual and motor regions relevant for the task. Photo-stimulation of the indirect pathway had little effect during “resting state”. Stimulation of the direct pathway during the visual detection task evoked extra cortical activity globally and increased the number of lick-responses to the contralateral side. Stimulation of the indirect pathway evoked more ipsilateral lick-responses and a local decrease in activity in visual areas. We also included a condition in which the decision had to be postponed by 1500ms to measure persistent activity. Persistent activity, which is a neural correlate of working memory, has been observed in many different regions including cortical areas and nuclei of the basal ganglia, which may suggest that working memories are coded in a distributed manner. We tested the influence of the complementary pathways on persistent activity and found that stimulating the direct pathway before or during the delay evoked similar neuronal activity as to when a contralateral grating was presented, and promoted future contralateral lick responses. The opposite effect occurred when stimulating the indirect pathway before or during the memory delay. In conclusion, the direct and indirect pathway enable flexible modulation of cortical activity, biasing both current and future perceptual decisions. These findings support a gating function for the basal ganglia in perceptual decisions, in which cortical inputs can be reverberated by the direct pathway or terminated by the indirect pathway. Dopaminergic inputs to the striatum could play a role in balancing the decision such that rewards are optimized.

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Poster

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F32AA026774

Title: Chronic intermittent ethanol exposure alters the excitability of dorsal medial striatum-projecting orbitofrontal cortex and basolateral amygdala neurons

Authors: S. NIMITVILAI-ROBERTS, D. GIOIA, J. J. WOODWARD;
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Abstract: Alcohol addiction is associated with dysfunction of brain circuitry including areas of the orbitofrontal cortex (OFC) and the basolateral sub-region of the amygdala (BLA). The OFC sends strong unidirectional glutamatergic inputs into the areas of the dorsal striatum (DS), in which the medial DS (DMS) is involved in goal-directed actions while the lateral DS (DLS) is important in gating habit-like behaviors. In addition to the OFC that provides top-down control of the DS, the BLA also projects glutamatergic inputs to the DS and is reciprocally interacted with neurons in the OFC. Several studies including ours reported that chronic ethanol exposure (CIE) induces changes in electrophysiological properties of neurons within the OFC, BLA and DS. However, no studies have examined whether CIE alters the function of OFC and BLA neurons that selectively project to the DS. In this study, we injected fluorescent retrobeads into the DMS of adult mice and recorded changes in current-evoked spiking of OFC and BLA neurons from the same animals following four weekly cycles of air or CIE treatment. Consistent with our previous findings, 3-day and 7-day withdrawal from CIE exposure enhanced excitability of DMS-projecting OFC neurons, and this increase was accompanied by a reduction in the after-hyperpolarization amplitude. In contrast, neuronal spiking varied in DMS-projecting BLA neurons with a decrease in evoked firing at 3-day withdrawal followed by an increase in firing at 7-day withdrawal from CIE treatment. An enhanced excitability of DMS-projecting BLA neurons in 7-day withdrawal CIE group was accompanied by a significant increase in the action potential width, suggesting a downregulation of voltage-gated potassium channels, possibly Kv1.1. Overall, these results suggest that chronic exposure to ethanol alters neuronal excitability of DMS-projecting OFC and DMS-projecting BLA neurons in distinct ways and on a different time scale that may contribute to the impairment of emotional processing and flexible behavior observed in alcohol-dependent individuals. Supported by P50AA010761.

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Poster

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Topic: H.04. Executive Functions

Support: F32MH115550
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Title: Top down regulation of dopamine activity affects cognitive flexibility in a sex-specific manner when behaviors are well-learned

Authors: *D. BORTZ, C. FEISTRITZER, A. A. GRACE;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cognitive flexibility is the act of adjusting behavior in response to changing reward contingencies. Deficits in cognitive flexibility are pervasive and represent core, predictive features in disorders such as depression, bipolar, addiction, and schizophrenia. For example, cognitive flexibility deficit severity predicts mood symptom onset and severity in depression and bipolar. The circuitry that

regulates cognitive flexibility has been well-studied, highlighting the necessity of dopamine (DA) release and receptor activation in prefrontal cortex and striatum. These studies, however, typically measure flexibility 1-2 sessions after the initial discrimination was learned, but not after overtraining. This gap in knowledge is important because rewarded behaviors that are repeated eventually become outcome-insensitive, stereotyped habits, which coincides with a shift in related DA release patterns from ventral to dorsolateral striatum. This suggests that the circuitry underlying cognitive flexibility, particularly with regard to the regulation of DA activity, may be different as behaviors become well-learned.
Previous studies have indicated a role for the medial septum (MS) and its bidirectional regulation of ventral tegmental area (VTA) and substantia nigra (SNc) DA activity in cognitive flexibility; however, the extent of its role, particularly following overtraining, is unclear. To investigate this, we activated the MS or prelimbic cortex to MS pathway of male and female rats using DREADDs and measured their performance on an operant-based set-shifting task, following 1, 10, or 15 days of discrimination training. Rats tested following 1 day of training showed no effect of MS activation. Following 10 days of training, however, activation of the MS or the prelimbic to MS pathway significantly improved set-shifting performance, but only in female rats. Following 15 days of training, MS activation improved performance in both male and female rats. These effects were mediated by the MS's regulation of VTA and SNc DA activity, but to differing degrees based on sex. The difference in MS activation efficacy in male and female rats may be explained by learning rate during training. Female rats reached an average of >92% correct performance during discrimination training in fewer days than males, and more days at this performance criteria predicted worse performance in controls and better performance following MS activation. These data suggest that MS activation may be more effective as training increases and that this region may be a critical relay from prelimbic cortex to midbrain by which flexibility is reinstated once behaviors are well-learned.

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Poster

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Title: Physiology of thalamic nucleus reuniens projections to the medial prefrontal cortex in mice

Authors: *G. VANTOMME[1], G. DEVIENNE[1], A. LUTHI[2], J. R. HUGUENARD[1];
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Abstract: The hippocampus, along with the medial prefrontal cortex (mPFC) and the nucleus Reuniens of the thalamus (Re) form a neuronal circuit that is essential for memory, learning and executive functions. A critical gap exists between known anatomical and behavioral aspects of this network compared to the paucity of knowledge regarding functional connectivity as governed by synaptic properties, neurotransmitter receptor content, plasticity profile and synaptic integration. This project aims to fill this knowledge gap and to study the synaptic dysfunction within the Hippocampus-Re-mPFC circuit in executive function disorders. Initial ex-vivo electrophysiological recordings showed that optogenetic activation of Re afferents in mice induced excitatory postsynaptic currents in deep layer mPFC neurons. Evoked responses showed a strong short-term depression, consistent with high release probability as observed with other higher order thalamocortical neurons. Interestingly, Re synapses on mPFC neurons showed a low NMDA/AMPA ratio and a high GluN2B and GluN2C subunit content. GluN2C-NMDARs are rarely expressed in CNS synapse, and so far mostly described in cerebellar granule cells and in thalamic relay neurons. Optogenetic activation of Re afferents also induced feedforward inhibition in mPFC neurons, and train stimulation in current-clamp induced a persistent depolarization. Altogether, these data showed that Re synapses in the mPFC of mice have the plasticity profile of driver inputs and set the foundations to study synaptic dysfunctions in the Hippocampus-Re-mPFC circuit in mouse model of executive function disorders.

Disclosures: G. Vantomme: None. **G. Devienne:** None. **A. Luthi:** None. **J.R. Huguenard:** None.

Poster

P797. Subcortical-Cortical Interactions: Circuitry and Complex Behavior

Location: Virtual Only

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Program #/Poster #: P797.08

Topic: H.04. Executive Functions

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CIHR grant PJT152879
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CIHR

Title: Fmri study of alterations of cortico-cortical connectivity in a case with damage to the medial dorsal thalamus

Authors: *K. GEIER[1,2], L. YU[2], A. KACOLLJA[2], D. MCQUIGGAN[2], J. RYAN[2,1], B. R. BUCHSBAUM[2,1], R. K. OLSEN[2,1];
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Abstract: Introduction: The medial dorsal thalamic nuclei (MDN) are key contributors to executive processes, attention, cognitive control, working memory and components of long term memory. The MDN may act as modulators of cortical activity, coordinating regions within the prefrontal cortex (PFC), in support of these different cognitive processes. Anatomically, MDN neurons project to multiple cortical

areas so they are ideally suited to modulate communication within the cortex. Computationally, feedback within a thalamocortical network can improve the efficiency of the network.
The primary empirical evidence for a role of the MDN in cortical modulation comes from optogenetic control of the MDN in rodents which shows a causal relationship between MDN activity and contralateral PFC to PFC signaling. It is crucially important to follow up on these findings with human research as PFC development is substantially different between species.
To investigate this question in humans, we examined potential differences in cortico-cortical connectivity in an amnesia case with MDN damage due to perinatal stroke.
Methods: To assess alterations in cortical connectivity we examined background functional magnetic resonance imaging (fMRI) activity for case NC, who has a lesion affecting his left and right MDN, and for 50 healthy age-matched controls. We measured background connectivity by generating correlation matrices of activity time series based on a coarser full cortex parcellation (100 regions) and a finer grained parcellation restricted to the left and right PFC. We used univariate and multivariate (principal components analysis) techniques.
Results: Univariate results showed 5 pairs of cortical regions which showed lower background functional connectivity in case NC than healthy controls using an adjusted Crawford t-test and with false discovery rate (FDR) correction. These regions included the dorsal and medial PFC, the posterior cingulate, and precuneus which are regions known to be strongly structurally and functionally connected to the MDN. Univariate analysis for the finer grained PFC regions did not show any significant results after multiple comparisons correction.
Multivariate results revealed that there was a significant difference in the pattern of background connectivity within the PFC with lesions to the MDN, confirming the importance of the MDN in humans for PFC modulation.
Conclusion: Reductions in background connectivity in NC is consistent with findings from the rodent literature. Disorders that show MDN alterations, such as schizophrenia, may be caused in part by alterations in thalamic modulation of cortico-cortical connectivity.

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Poster

P797. Subcortical-Cortical Interactions: Circuitry and Complex Behavior

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Program #/Poster #: P797.09

Topic: H.04. Executive Functions

Support: National Institute of Health (NS116883)

Title: Subcortical Contributions to Arithmetic Procedures

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Abstract: Humans exhibit complex arithmetic skills, often attributed to the exceptional enlargement of neocortical regions during evolution. However, the past 30 years have provided ample evidence that the functional domain of the basal ganglia (BG) and cerebellum, two ancient subcortical regions extend beyond the motor domain. Using a neuropsychological approach, we explored the contributions of these two subcortical regions to processes involved in a symbolic arithmetic operation, addition. To this end, we compared the performance of three groups of participants: Individuals with either spinocerebellar ataxia (SCA), Parkinson's disease (PD, our model of BG), and matched controls. In Experiment 1, we utilized a verification task, in which participants were required to indicate if an addition problem of three, non-identical, operands (e.g., 5+6+8=19) was true or false. We examined the practice benefits for repeated items and practice benefits for non-repeated items. For the former, we assumed the benefits would reflect the operation of memory-based processes; for the latter, we assumed the benefits would reflect facilitation in the use of algorithmic procedures required for doing arithmetic. Although the SCA and PD groups were slower than the controls, all three groups showed a similar practice benefit on the repeated items, pointing to intact memory-based learning. However, the SCA group showed attenuated practice benefit compared to the other two groups for the non-repeated items, suggesting a selective impairment in algorithm-based learning. In Experiment 2, we examined two possible components of requisite algorithmic operations, execution of the counting operation and the number of required operations. To evaluate the former, we manipulated the magnitude of the calculated sum (small vs. large); for the latter, we compared equations involving the addition of two or three single digits. The SCA group showed a selective impairment on the magnitude manipulation, exhibiting a larger slope for the function relating RT to the sum of the digits. In contrast, the PD group showed a bigger cost compared to the other two groups when adding three digits relative to two digits. This pattern of results points to a double dissociation between two procedures that are involved in symbolic arithmetic, and the involvement of two subcortical areas in these algorithmic procedures.

Disclosures: W. Saban: None. **P. Pinheiro-Chagas:** None. **S. Piantadosi:** None. **R. Ivry:** None.

Poster

P837. Hippocampal Interactions V

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Program #/Poster #: P837.01

Topic: H.08. Learning and Memory

Support: New York University Dean's Undergraduate Research Fund

Title: Influence of anatomical variability on neural decoding strategies by target regions of the hippocampus

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Abstract: The hippocampus plays a vital role in an animal's spatial navigation, where place cells encode positional information through spiking activity. The precise spiking patterns of different place cells vary

based on their anatomical position along the septotemporal axis of the hippocampus. From the septal pole to the temporal pole of the hippocampus, the phase of local theta oscillations shifts one half cycle as the wave travels along the axis, meanwhile, the size of place fields is reported to increase. Such variability in anatomical organization may impact the information decoded by downstream readers in distal regions. To investigate where and how such impact occurs, we simulate spiking in populations of place cells with the position-theta-phase (PTP) model previously published (McClain et al. 2019). We utilize two types of decoders to quantify positional information contained in spiking activity: a canonical Bayesian firing-rate decoder and a novel Bayesian theta-phase decoder. We then compare accuracy when decoding from place cells with anatomically inspired differences in theta phase and place field width. Results suggest that the phase shift across anatomically distributed place cells does not have a significant influence on firing rate decoding accuracy, while the inclusion of larger place fields leads to reduced firing rate decoding accuracy. Additionally, theta-phase decoding is generally more accurate than firing rate decoding within equivalent populations of place cells. Further characterization of these interactions between population encoding properties and spatial information content is ongoing. By assessing and comparing different strategies for decoding from different anatomical distributions of place cells, we can find out which mechanisms are more efficient for the brain and why downstream regions may utilize one specific decoding strategy over the other. Understanding the decoding strategy of downstream regions may shed important light on the mechanisms for information transfer from the hippocampus that are necessary for spatial navigation and memory consolidation, as well as the fundamental question of what is the purpose of the existence of such anatomical variability and why does it occur during evolution.

Disclosures: Y. Jin: None. **K. McClain:** None. **G. Buzsaki:** None.

Poster

P837. Hippocampal Interactions V

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Program #/Poster #: P837.02

Topic: H.08. Learning and Memory

Support: DFG NI 2057/1-1

Title: Brain wide modulation of spiking activity by hippocampal ripples

Authors: *N. NITZAN[1], R. A. SWANSON[2], G. BUZSAKI[3];
[1]New York Univ., Brooklyn, NY; [2]Neurosci., New York Univ., New York, NY; [3]New York University, Sch. of Med., New York, NY

Abstract: Sharp wave ripples (SPW-Rs) are bouts of high frequency oscillations reflecting the highest levels of synchronized activity of hippocampal pyramidal cells and interneurons. Although SPW-Rs are intrinsically generated in the hippocampus, their occurrence is known to be biased by brain-state changes and by various slower brain rhythms. In return, SPW-Rs can transiently affect the ongoing activity at numerous brain regions and this bidirectional communication has been hypothesized to play an important role in the consolidation of new memory traces. However, while numerous studies addressed the effects of SPW-Rs of individual brain areas, the brain-wide coupling to events has been difficult to study at high

temporal and spatial resolution. Here, we leveraged on publically available datasets using multiple high-density Neuropixel electrodes covering numerous cortical and subcortical brain areas as well as multiple hippocampal subdivisions to study this question (Siegle et al., 2021; Steinmetz et al 2019). We found that the majority of brain areas are differentially modulated by SPW-Rs of different anatomical origin. Moreover, we report that the timing, sign and magnitude of responses to SPW-Rs are related to the magnitude of SPW-Rs. Finally, we show that the magnitude of SPW-Rs is strongly correlated with various indicators of brain-state, suggesting brain-wide coordination of activity on multiple scales. Our findings expand on previous results from functional magnetic resonance imaging studies and suggest that SPW-R triggered responses of a given brain area are not a simple function of anatomical connectivity.

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Poster

P837. Hippocampal Interactions V

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Topic: H.08. Learning and Memory

Support: U19 NS107616
U19 NS104590

Title: Birthdate and rate of neurogenesis affect functional properties of adult hippocampal neurons

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Abstract: The hippocampus can be conceived as a uniform large single unit, in contrast to the modularly organized neocortex. In the neocortex, radially migrating excitatory neurons derived from the same progenitors form vertically organized functional columns (Angevine and Sidman, 1961; Li et al., 2012). In contrast, hippocampal neurons migrate radial-tangentially in a zigzag manner and assume the form of horizontal clusters (Kitazawa et al., 2012, Xu et al., 2014). Despite this organization, 'place cells' (O'Keefe and Nadel, 1978) representing the same or different parts of the environment are thought to be randomly distributed in the hippocampus (Redish et al. 2001). Yet, distinct anatomical and functional groups have been noted radially even within the thin hippocampal pyramidal layer (Soltesz, Losonczy 2018; Valero, de la Prida 2018), and it remains to be clarified how these functional groups relate to developmental lineage (Cavalieri et al., 2021). To address how intrauterine development affects future hippocampal function, we birthdated CA1 pyramidal neurons with in-utero electroporation over a wide range of embryonic ages, and compared their functional features in freely moving, adult mice. Neurons of the same birthdate displayed distinct connectivity, and strong coactivity during theta waves and sharp-wave ripples. Birthdated neurons joined into cell assemblies whose rate of expression scaled with the pool size of neurons that were born together. Anatomically clustered (<500μm) same-day born neurons displayed overlapping spatial representations. Overall, the wiring and functional features of CA1 pyramidal neurons reflected a combination of birthdate and the rate of neurogenesis. These observations

demonstrate that sequential neurogenesis in embryonic development shapes the preconfigured forms (Dragoi, Tonegawa 2011; Grosmark et al., 2015; McKenzie et al., 2021) of adult network dynamics.

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Poster

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Topic: H.08. Learning and Memory

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U19NS107616

Title: A metabolic function of the hippocampal sharp wave-ripple

Authors: D. TINGLEY[1], K. MCCLAIN[2], E. KAYA[2], J. N. CARPENTER[2], G. BUZSAKI[3]; [1]Neurosci., NYU Neurosci. Inst., New York, NY; [2]NYU, New York, NY; [3]New York University, Sch. of Med., New York, NY

Abstract: The hippocampus has been implicated in both cognitive and endocrine functions. To identify an activity pattern which may link such disparate functions, we simultaneously measured electrophysiological activity from the hippocampus and interstitial glucose concentrations in the body of freely behaving rats. We report that clusters of sharp wave-ripples (SPW-Rs) recorded from the hippocampus reliably predicted a decrease in peripheral glucose concentrations within ~10 minutes. This correlation was not dependent on circadian, ultradian, or meal-triggered fluctuations, it could be mimicked with optogenetically induced ripples in the hippocampus, but not in the parietal cortex, and was attenuated to chance levels by pharmacogenetically suppressing activity of the lateral septum (LS), the major conduit between the hippocampus and hypothalamus. Our findings demonstrate that a novel function of the SPW-R is to modulate peripheral glucose homeostasis and offer a mechanism for the link between sleep disruption and blood glucose dysregulation in type 2 diabetes.

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Poster

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Title: Toward monosynaptic inference by dissecting causal relationships in pairwise spike trains

Authors: *Z. SACCOMANO[1], J. PLATKIEWICZ[2], S. A. MCKENZIE[3], D. F. ENGLISH[4], A. AMARASINGHAM[5];
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Abstract: Can we study synapses simply by observing spike trains? Very precise (under 1 millisecond), short-latency peaks in the cross-correlogram between extracellularly-recorded spike trains are widely observed in cortex and a recent experiment used optogenetic and juxtacellular stimulation of pyramidal neurons in vivo to verify this feature as primarily monosynaptic in origin. We studied this large-scale dataset and developed biophysical models of paired neurons driven by common, nonstationary inputs that can quantitatively reproduce the observed spiking dynamics between monosynaptically-connected neurons in these data. In parallel, we developed statistical inference methods to assess monosynaptic connectivity. These methods exploit a principle of conditional inference in order to be robust to nonstationarity in the underlying dynamics, and were motivated by the causal inference question: how would fine-timescale correlations change - in a connected pair - if the monosynapse did not exist in otherwise identical statistical conditions? The methods were tested on the biophysical models and the robustness of the inference technique was examined over a large range of biophysical parameters. We found that an unbiased estimator for the monosynaptic cause, derived theoretically, works precisely in the biophysical simulations, where ground truth is available, and regardless of the specific mechanisms underlying the statistical behavior of the biophysical models. Finally, we explore how to combine spontaneous and perturbation data to develop an effective parameterization of 'causal synaptic weight,' as it relates to the probabilistic theory of necessary and sufficient causation developed in the causal inference literature.

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Poster

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Title: A cyclic diterpenoid has a neuroprotective effect against Gulf War Illness involved neurotoxicants

Authors: J. L. MARRERO-VALENTIN[1], S. VÁZQUEZ-ALICIA[1,2], F. G. RIVERA-MOCTEZUMA[1,3], D. PEREZ[1], P. A. FERCHMIN[4], ***N. S. SABEVA**[1];
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Abstract: Organophosphate (OP) compounds have been widely used as agricultural and household pesticides, jet engine lubricants, and warfare nerve agents. Therefore, the general population and military personnel could be exposed to OPs not only during combat or terroristic attacks but also during routine military, industrial or private activities. Delayed neuronal damage of OP intoxication is thought to contribute to neuronal death and various neurological illnesses. Gulf War Illness (GWI) is one of them. GWI is a currently untreatable multi-symptom disorder experienced by more than 250,000 veterans from the Persian Gulf War (1990-1991). The distinctive hallmark of GWI includes chronic fatigue, migraine, muscle and joint pain, gastrointestinal problems, and cognitive disturbances such as depression and anxiety. Various studies have consistently linked these symptoms to exposure to pyridostigmine, DEET, permethrin, and traces of sarin (the most commonly used nerve agent). There is no effective cure for the GWI or the chronic effect of other neurotoxicants. Our group demonstrated *ex vivo* that exposure to diisopropylfluorophosphate (DFP, a surrogate of sarin) and the above-mentioned neurotoxicants reduce the number of functionally active neurons in hippocampal slices. This loss of neuronal functionality can be reversed by the application of a 4R-cembranotrienes-diol (4R), a cyclic diterpenoid with anti-inflammatory and anti-apoptotic properties. The cembranoid is not toxic and reaches higher concentrations in the brain than plasma. We took advantage of *our ex vivo* GWI model (rat hippocampal slices) to investigate whether 4R has a protective effect on synaptic integrity and neuronal survival in the presence of DFP. We combined electrophysiological recordings with molecular analysis on acute hippocampal slices. Our results suggest that 4R protects neuronal functionality and activates AKT/PI3K cell survival pathway. Thus, this cembranoid is a promising compound to protect the nervous system against neurotoxicants.

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Poster

P837. Hippocampal Interactions V

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Program #/Poster #: P837.07

Topic: H.08. Learning and Memory

Title: Can Transcranial Radio Frequency Stimulation Modulate Ongoing Brain Activity?

Authors: *O. YAGHMAZADEH[1], G. BUZSAKI[2];
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Abstract: Affecting brain activity by means of external stimuli provides various possibilities for research and clinical applications. In this context, non-invasive neuromodulation techniques sit in a unique position due to their potential low level of side effects. Here we report examination of a novel non-invasive contact-less neuromodulation technique based on Radio Frequency (RF) waves searching for potential entrainment of neuronal activity, at single-cell and neural network levels, in rodent models. We apply RF stimulation at around 1GHz using commercially available patch or custom-made stub antennas. Activity of neurons in the CA1 region of mice hippocampus is recorded by the means of a miniature head-mounted 1-photon imaging system (UCLA Miniscope). This recording system permits us to collect data in a metal-implant-free manner thus avoid RF interference on the collected data. In addition, the miniscope's LED circuit is replaced by a fiber-coupled far-away LED light source to avoid additional RF-induced artifacts. Animals are head-fixed at ~4cm from the center of a patch antenna and their head is exposed to continuous-wave RF radiation at 950MHz. The RF exposure is applied in a 3s-ON 3s-OFF paradigm to avoid unsafe brain and body temperature increases. Our results, comparing stimulated and sham conditions, demonstrate that RF exposure (up to 40W of power fed into the antenna) does not affect the ongoing activity of CA1 neurons in a statistically significant manner (n = 5 mice). Nevertheless, we show that by adjusting parameters of the RF stimulation (e.g. power and duty cycle) we are able to increase the brain temperature in a controlled manner. Our MR thermometry experiments show that RF-induced temperature increase is lower at the peripheral sites than in the brain which favors for less-invasive exposure. We observed that our RF paradigm, over a period of 30 minutes, induces ~1°C increase in the brain temperature (without exceeding the physiological range). It is well established that temperature changes can affect the activity of neurons in different brain regions. Hence, we suggest that Transcranial RF Stimulation can be used (and further studied) as a novel neuromodulation technique and help expanding the spectrum of non-invasive tools for brain stimulation.

Disclosures: O. Yaghmazadeh: None. **G. Buzsaki:** None.

Poster

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Topic: H.08. Learning and Memory

Support: NIH Grant

Title: State-dependent neocortical dynamics surrounding hippocampal ripples

Authors: *R. SWANSON, N. MOUSAVI, N. NITZAN, R. DE LA TORRE, J. BASU, G. BUZSAKI; New York Univ., New York, NY

Abstract: Hippocampal sharp-wave ripple (SPW-R) coupled modulation of neural activity is observed throughout the neocortex during periods of quiescence and non-REM sleep (Buzsaki 2015; Logothetis 2012), and is thought to mediate systems consolidation of multi-modal memories. However, how this dynamic coupling is spontaneously achieved across regions, and thus across spatial and temporal scales in the absence of coordinating sensory input, is unknown. Taking advantage of the high spatial and temporal

resolution of widefield calcium imaging, we develop a preparation that allows simultaneous imaging of dorsal neocortex with high-density chronic ipsilateral silicon probe recordings of the hippocampus and retrosplenial cortex, allowing us to monitor mesoscale neocortical activity during sleep surrounding hippocampal SPW-Rs. In alignment with previous studies, hippocampal SPW-Rs are robustly correlated with increased fluorescence in mouse visual and association cortices, or mouse default mode network. Taking this work further, our preparation allowed us to i. deconvolve the widefield calcium signal into putative population rate across dorsal neocortex, and ii. sleep state score mice in the head-fixed preparation with respect to natural sleep in the homecage. With this additional information, we find the majority of SPW-Rs are preceded by increased excitation in neocortex followed by a DOWN state, matching a model of neocortical NREM sleep whereby neocortex is in an excitableUP regime that exhibits noise or input-driven transient cessations of spiking activity (Levenstein 2019). Leveraging the spatial resolution of widefield imaging, we find that the depth of NREM sleep corresponds to both the degree of excitation preceding the SPW-R and degree to which the evoked DOWN state spreads along the cortical hierarchy from retrosplenial cortex to visual areas. We further find that the magnitude and spatial extent of preceding neocortical excitation is correlated with the depth of coincident sharp wave in CA1, likely reflecting the magnitude of excitatory drive from neocortex to the hippocampus. This suggests the depth of NREM sleep corresponds to more or less excitable regimes, governing the extent to which transient transitions remain local, possibly serving a homeostatic rescaling function, or propagate across the brain, providing a substrate for multi-modal reactivation.

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Poster

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Topic: H.08. Learning and Memory

Support: NIH Grant T90DA043219

Title: Distinct ground state and activated state spiking modes in forebrain neurons

Authors: *D. LEVENSTEIN[1], R. HUSZAR[3], J. GORNET[4], G. GIRARDEAU[5], A. D. GROSMARK[6], A. PEYRACHE[2], Y. SENZAI[7], B. O. WATSON[8], J. M. RINZEL[9], G. BUZSAKI[10];
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Abstract: The spatiotemporal variety of neuronal firing patterns has no agreed upon answers or theory. Using a combined experimental and modeling approach, we show that neuronal spiking can be described by discrete modes of activity with distinct temporal properties and functional implications. We

investigated spike interval statistics of excitatory neurons from six forebrain regions and found that the majority of spikes can be attributed a neuronal "ground state" (GS) mode, characterized by irregular spiking at a cell-specific low rate (~0.1-5Hz). GS rate is lognormally-distributed and conserved across wake and sleep states. In addition to the GS mode, each neuron has a repertoire of "activated state" (AS) modes, with spiking at specific higher-rate timescales and regularity, which are common among neurons in a given region/state. AS modes correspond to temporal coordination by network and/or intrinsic cellular mechanisms and are evoked by relevant inputs. Supporting this view, we find that a probabilistic modal model of stimulus encoding better accounts for spiking in thalamic head direction cells and hippocampal place cells than a model in which neurons encode stimulus features with smoothly-varying rate. We then show that GS/AS activity is readily produced in a self-balancing network of spiking neurons, in which GS rate reflects the balance of excitation and inhibition, while AS modes reflect cellular coupling to network-specific activation patterns. We hypothesize that GS spiking reflects a default mode of balanced activity that serves to maintain a persistent backbone of neuronal dynamic, from which neurons can depart and switch transiently to a communication mode of AS spiking.

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Poster

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Title: Probing subthreshold dynamics of hippocampal neurons by pulsed optogenetics

Authors: *M. VALERO, G. BUZSÁKI;
NYU Neurosci. Inst., New York, NY

Abstract: The fundamental computation a single neuron performs is to integrate incoming excitatory and inhibitory inputs to decide whether to fire an action potential and feedback its activity into the network. Investigation of this synaptic computation requires access to the neuron subthreshold dynamics, whose state-of-art methodologies have remained unaltered for decades and are unrealistic for cell assemblies and behaving animals.
Here, instead of intracellular recording, we probed the membrane polarization with short depolarizing

pulses optogenetically. Using chronically implanted µLED probes (4 shanks with 3 µLED on each shank), we recorded and probed large numbers of neurons simultaneously in freely moving CamKIIα-Cre::Ai32 mice. Weak blue light pulses (20 ms), inducing firing in only a handful of nearby neurons, were delivered to each µLED in a random manner so that each site was stimulated at ~0.6 s intervals. The short duration of pulses and their sparse recurrence did not perturb the properties of the neurons. Light-sensitive neurons responded to one or more µLEDs and the spike numbers were used as a proxy for estimating relative changes of the membrane potential dynamics. Strikingly, induced spike responses gain sharply increased several-folds inside the preferred position (place fields) of the responsive pyramidal cells. These results are compatible with a tuning curve model in the CA1 pyramidal cells where excitation and the inhibition display a concerted and reciprocal relationship. When optogenetic stimulation was probed on non-place cells, majority of the putative non-place cells showed place-related activity (>65%). Both place cells and non-place cells gained information rate during optogenetic stimulation, but this gain was stronger for non-place cells. Finally, to reveal whether the CA1 network is guided by a single or multiple operation modes, we optically probed neurons around hippocampal sharp wave ripples (SPW-Rs) events. In the short time window of SPW-R, excitatory and inhibitory neurons increased in parallel. As expected, optogenetic probing of the CA1 networks showed that, in contrast to the large gain within place fields, responsivity of pyramidal cells showed a robust decrease during SPW-Rs.
We have developed a method for studying subthreshold dynamics of individual cells in chronic recordings using novel high-resolution optical stimulation as a proxy for the membrane polarization. These experiments disclosed a reciprocal interaction between inhibition and excitation along the place fields of CA1 and demonstrated that the same exact perturbation can bring about opposite responses during exploration and transient SPW-Rs.

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Poster

P837. Hippocampal Interactions V

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P837.11

Topic: H.08. Learning and Memory

Support: R00MH118423

Title: Estimation of neural coupling with time varying synaptic conductance and background statistics

Authors: Y. ZHANG[1], R. HUSZAR[2], Z. SACCOMANO[3], T. DONALDSON[4], A. AMARASINGHAM[5], H. G. ROTSTEIN[6], G. BUZSAKI[7], *S. MCKENZIE[8];
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Abstract: Synaptic communication lies at the heart of neural computation and changes in synaptic strength are thought to be the neural substrate for memory. Synaptic strength is usually equated to

changes in membrane conductance caused by the binding of transmitters released at the presynaptic terminal. Necessarily, such changes in conductance interact with other dynamical properties of the postsynaptic neuron to determine how the presynaptic spike affects the probability of postsynaptic firing. Several statistical methods have been developed to measure effective neural coupling, and these are usually benchmarked *in silico* to show convergence between the estimate and the modeled effect of the synapse on membrane conductance. Despite the growing use of these methods to characterize real synaptic interactions, it is unknown how the postsynaptic state interacts with presynaptic input to skew the statistical estimation of synaptic coupling strength. To explore these issues, we studied spike transmission in the leaky integrate and fire (LIF) neuron and developed a method to track changes in spike transmission probability over time. We modeled the postsynaptic firing rate as the sum of a leak current, synaptic input, and Gaussian noise. Synaptic input was modeled as an instantaneous increase and exponential decay in postsynaptic conductance. The maximal synaptic conductance and the standard deviation of the "background" noise varied across modeled neurons and over time. We then designed a generalized linear model (GLM) to track changes in the synaptic contribution to the postsynaptic firing rate. The model assumed a separation in time scales between rapid rate fluctuations driven by the synapse and slower fluctuations driven by an unknown and unspecified "background". As previously shown, background noise strongly diminished the spike transmission between pre- and postsynaptic neurons. This change was well captured by the GLM, as were changes in conductance between neurons and over time. We next applied the GLM to ensembles of pyramidal cell to interneuron synapses recorded in the mouse CA1 region. We found that synaptic coupling strength was dynamic with "synapsembles" or groups of synapses from different neurons whose connection strength rose and fell together. The synaptic state was strongly modulated sleep/wake state and changes in spike transmission were related to changes in the postsynaptic spike-timing coefficient of variation, which also differed across sleep state. Our findings show that modulation of postsynaptic firing rate variability could be an important control point in gating the flow of information from pre- to postsynaptic neuron.

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Poster

P837. Hippocampal Interactions V

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MH118423
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U19 NS107616
U19 NS104590

Title: Jump the gap: action-driven remapping of the hippocampal population code

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Abstract: The current dominant view of the hippocampus is that it is a navigation 'device', guided by environmental inputs. Yet, a critical aspect of navigation is a series of pre-planned coordinated actions. We examined the role of action in the neuronal organization of the hippocampus by training rats to jump a gap on a linear track. Recording local field potentials and ensembles of single units in the hippocampus, we found that when rats jumped a small gap on a running track, it produced a stereotypical behavior associated with consistent electrophysiological patterns, including phase reset of theta oscillations, predictable global firing rate changes and population vector shifts of hippocampal neurons. A subset of neurons ('jump cells') were systematically affected by the act of jumping, yet were influenced by distant environmental cues. Novel place fields emerged and others were either boosted or attenuated by jumping. Thus, jumping involves an entirely different action plan for the animal to traverse the same route as without jumping, which is faithfully tracked by hippocampal neuronal activity.

Disclosures: L. Green: None. **D. Tingley:** None. **J.M. Rinzel:** None. **G. Buzsaki:** None.

Poster

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Support: Leon Levy Neuroscience Fellowship
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Title: Extrinsic control and autonomous computation in the hippocampal CA1 circuit

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Abstract: In understanding circuit operations, a key issue is the extent to which neuronal spiking reflects local computation or responses to upstream inputs. We addressed this issue in the hippocampus by performing combined optogenetic and pharmogenetic deafferentation and local silencing. Silencing the medial entorhinal cortex (mEC) largely abolished extracellular theta and gamma currents in CA1, without affecting firing rates. In contrast, CA3 and local CA1 silencing strongly decreased firing of CA1 neurons without affecting theta currents. Each perturbation reconfigured the CA1 spatial map. Yet, the ability of the CA1 circuit to support place field activity persisted , maintaining the same fraction of place fields, spatial information and spike theta phase relationship as in the intact mouse. Thus, the CA1 network can

support autonomous computation to support coordinated place cell assemblies without reliance on its inputs, yet these inputs can effectively reconfigure and assist in maintaining stability of the CA1 map.

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Poster

P837. Hippocampal Interactions V

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Program #/Poster #: P837.14

Topic: H.08. Learning and Memory

Support: SFB 779

Title: Phase locking of CA3 neurons to distal CA1 theta oscillations predicts nonspatial memory performance

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Abstract: Cumulative evidence in rodents has suggested a crucial role of hippocampal theta oscillations in memory function, especially in tasks involving spatial information. Much less is known about their role in non-spatial memory, even though studies in humans indicate a crucial role within this frame. Electrophysiological and immediate-early-gene imaging evidence for a robust proximodistal functional segregation of the hippocampal subfield CA1 and CA3 has recently accumulated and suggested the existence of non-spatial and spatial subnetworks segregated along this axis: the proximal CA3 (close to the dentate gyrus)- distal CA1 (close to the subiculum) and the distal CA3-proximal CA1 subnetworks, respectively (Henriksen et al, Neuron, 2011;Nakamura et al, 2013; Beer and Vavra et al, 2018). However, the mechanisms subserving information processing within these subnetworks is still not known. Here, we focus on characterizing CA3-CA1 interactions during non-spatial memory retrieval by studying CA3 spikes phase locking to theta oscillations along the proximodistal axis of CA1 using *in-vivo* electrophysiological recordings. Rats were trained on a human to rat translational high memory demand task using odors as stimuli (Nakamura et al, 2013) upon which they were chronically implanted with tetrodes along the proximodistal axis of hippocampal CA1 and CA3 to record single cell firing and LFP. In this task, the memory for odors presented during a study phase is tested after a delay (20min) by presenting the same odors (‘old’ odors) intermixed with ‘new’ odors during a retrieval phase. Overall, theta power was enhanced during retrieval when compared to any other phases of the task and selectively enhanced in distal CA1 as opposed to proximal CA1 in trained rats but not in naïve animals, indicative of a preferential role of distal CA1 theta in non-spatial information processing. In addition, population analyses of the preferred angles of CA3 spikes showed a selective phase-locking to the peak of distal CA1 theta (not proximal CA1) for the retrieval of the ‘old’ odors. Furthermore, support vector machine analyses revealed that the classification performance of CA3 neurons phase locked to distal CA1 theta was the only one predicting performance comparable to behavioral performance. In contrast, local phase-

locking in CA1 or CA3 did not. Altogether our results show that theta oscillations might play an important role in non-spatial memory as is the case for memory based on spatial information and suggest a prominent role of the coordination of electrophysiological signals between CA3 and distal CA1 (as opposed to proximal CA1) in non-spatial memory retrieval.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

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Title: Age Differences in Dorsolateral Prefrontal Cortex Activity During a Novel Task Manipulating Memory Load and Logic Load

Authors: *E. STURM[1], M. MUSICH[2], D. THORNTON[2], A. S. MENDEZ COLMENARES[2], J. DUFFY[2], A. Z. BURZYNSKA[2], M. L. THOMAS[2];
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Abstract: Studies have found that older adults show increased activity in the dorsolateral prefrontal cortex (DLPFC) at higher memory loads in comparison to younger adults. This age-associated increase in activity could be interpreted as compensation for decreasing neural efficiency. However, competing theories have also been proposed (e.g., dedifferentiation and alternative strategy use). We propose that manipulating memory (concrete) load and rule (abstract) load, which engage different sub-regions of the DLPFC, can help us better interpret the meaning of changes in functional brain activity with age. To better understand these relationships, we developed a novel version of the classic Sternberg paradigm wherein we manipulated working memory load and logic load. Memory load was manipulated by parametrically increasing the number of letters to be remembered. Boolean logic complexity load was manipulated by presenting a colored test letter (i.e., blue or red), allowing disjunction (e.g., repeated or red), conjunction (e.g., repeated and red), and disjunction of two rules (e.g., repeated and red -or- new and blue). The purpose of this study was to provide initial evidence that logic load manipulations are related to differential brain activity with age. We hypothesized that older-adults will show increased activity in the DLPFC at high logic load levels Data were acquired from 29 healthy adults (M=52.9 years, SD = 23.6 years, range = 28-85, 48% female), using a Siemens 3-Tesla Skyra Magnetom system. Images were sensitive to the Blood-Oxygenation-Level-Dependent (BOLD) response using T2* weighting. Region of interest-based data were analyzed using linear regression and linear mixed-effects models. We found a significant negative association between accuracy and age on the Sternberg task ($b = -.003$; $p < .05$).

Logic load had a significant effect on activity in the right (b = .02, $p < .05$) and left (b = .02, $p < .05$) DLPFC. BOLD signal increased in both the right (b = .002; $p < .05$) and left DLPFC (b = .002; $p < .05$) with age at high logic load levels. These results suggest a promising avenue for insight into brain activity associated with healthy aging. The DLPFC showed increased activity in older adults at higher load levels in our novel task, similar to traditional working memory tasks. These results suggest a promising avenue for insight into brain activity associated with healthy aging and logic load. Further research will aim to determine whether logic load manipulations engage unique regions of the DLPFC, and where these changes reflect compensatory brain activity.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

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Topic: H.12. Aging and Development

Support: BMBF 01GQ1421B
Max Planck Society

Title: A novel approach to measure exercise-induced changes in latent structural integrity of the brain in sedentary healthy older adults

Authors: S. E. POLK, *E. WENGER, M. M. KLEEMEYER, Y. KÖHNCKE, A. M. BRANDMAIER, U. LINDENBERGER, S. DÜZEL;
Max Planck Inst. For Human Develop., Berlin, Germany

Abstract: Studies investigating the effects of aerobic exercise on the aging brain have found that frontal areas, such as the anterior cingulate cortex (ACC), and temporal areas, such as the hippocampus, show more positive changes in gray matter volume in exercisers versus controls over the course of a longitudinal aerobic exercise intervention. However, use of single indicators (e.g., volume), rather than a latent factor comprising multiple indicators, is more susceptible to unreliability due to measurement error. In this study, we adopted recently developed multi-modal methods using structural equation modeling to compute a latent factor including both macro- and microstructural characteristics of gray matter to capture a more reliable, global measure of gray matter structural integrity. Estimations from three different imaging modalities were used as indicators: gray matter probability (i.e., volume), magnetization transfer saturation (i.e., demyelination), and mean diffusivity (i.e., density), in order to capture the shared variance of different imaging modalities. In this way, we modeled latent change in integrity during a six-month exercise intervention in brain regions of interest previously reported in studies using volumetric approaches. Seventy-five healthy, previously sedentary older adults (63-76 years old) completed an at-home intervention study either in an exercise group ($n = 40$) or in an active control group ($n = 35$). Exercisers showed gains in cardiovascular fitness over controls, measured pre- and post-intervention using maximal oxygen uptake (VO_2max), $\Delta\chi^2_{(df = 1)} = 5.37$, $p = .010$. We successfully established reliable

latent change score models of structural integrity with three time points (pre-, mid-, and post-intervention); notably, the right ACC showed significant inter-individual differences in change, as well as significant group differences in mean change with controls decreasing and exercisers maintaining integrity in the first three months of the intervention, $\Delta\chi^2_{(df = 1)} = 4.069$, $p = .022$. Finally, change in VO_2max was positively correlated with change in rACC integrity overall and within the exercise group in the first three months, $Z = 2.296$, $p = .011$, but not within the active control group, $Z = 1.165$, $p > .050$; this difference between groups was significantly greater than zero, $\Delta\chi^2_{(df = 1)} = 4.67$, $p = .015$. In summary, the exercise group benefited from aerobic exercise in terms of cardiovascular fitness and gray matter structural integrity in the rACC, a region that has previously shown exercise-related volumetric changes. Furthermore, those exercisers who showed greater change in VO_2max also decreased less in rACC integrity.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

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Program #/Poster #: P892.03

Topic: H.12. Aging and Development

Support: R01AG050523

Title: Thicker cortex is more strongly associated with motor function than cognition in older adults

Authors: *A. M. HAMLIN, S. MITTAL, E. C. NELSON, T. A. POLK;
Psychology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Previous research has found that cortical thickness declines with age. While some studies have found age-related cortical thinning primarily in the frontal, temporal, and parietal association cortices, others have noted similar or greater cortical thinning in sensory and motor regions. Furthermore, individual differences in cortical thickness have been associated with both cognitive measures (e.g., fluid and crystallized intelligence, memory, and processing speed) and measures of strength and motor function. Here we examine age-related differences in cortical thickness as well as the ability of cortical thickness to predict both cognitive and motor measures in a large sample of younger (*N*=58, 18 to 29 years old) and older (*N*=81, 65+ years) adults. A high-resolution T1-weighted structural image was obtained for each participant and estimates of cortical thickness were calculated using the FreeSurfer Cortical Parcellation technique. Behavioral data included the NIH toolbox Cognition Battery, Rivermead Behavioral Memory Story Test, NIH 2-minute Endurance Walk, NIH Grip Strength Test, and a Cortical Metrics vibrotactile somatosensory task. We first performed exploratory factor analyses (EFA) on the cognitive measures and identified latent factors associated with fluid and crystallized cognition, memory, and processing speed. Likewise, we performed EFA on the sensorimotor measures and identified factors related to gross motor, fine motor, and tactile ability. Finally, we performed EFA on the regional cortical thickness measures and identified three latent factors in both the left (dorsolateral frontal, cingulate

temporal, and posterior cortex) and right hemispheres (lateral frontal, medial occipital, and posterior cortex). Associations between these cortical thickness factors and age were examined through linear regressions. We found evidence of age-related cortical thinning in all three thickness factors in both hemispheres (Bs ≥ 0.01, ps ≤ 0.013). Furthermore, within older adults almost all of the cortical thickness factors were also positively associated with gross motor function after controlling for both age and sex (Bs ≥ 0.15, ps ≤ 0.035). The positive association with strength was not region specific but was observed in frontal, parietal and occipital regions in both left and right hemispheres. In contrast, we found no significant associations between cortical thickness and any of the cognitive factors. Establishing patterns of decline in cortical thickness and their relation to behavior could help identify those at risk for age-related impairments and facilitate early intervention.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

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Title: Age-related differences in white matter structure-function associations, relation to bold modulation and cognitive control

Authors: T.-C. LUNG, D. A. HOAGEY, K. M. RODRIGUE, *K. M. KENNEDY;
The Univ. of Texas at Dallas, Dallas, TX

Abstract: Age-related alterations to the structure and function of the human brain are widely reported. However, the associations among brain structure, function and cognitive performance during aging remain unclear. The current study used functional clusters from a parametric difficulty modulation contrast to functionally define ROIs for diffusion-based tractography to isolate tracts connecting regions of gray matter demonstrating difficulty-related up-modulation (positive modulation, POSMOD) and down-modulation (negative modulation, NEGMOD) to spatial distance judgments. We explored the association between age-related BOLD modulation and white matter tract fractional anisotropy (FA) and examined how this association relates to executive function performance across the adult lifespan (N=161 adults (age 20-94). Deterministic tractography was conducted between all in 9 functional ROIs, including regions associated with the frontal-parietal and multiple demand networks (from POSMOD) and regions overlapping with default mode network (from NEGMOD). Tractography between these functionally-defined ROIs generated 8 tracts connecting ROIs among significant age-related POSMOD (5 tracts), NEGMOD (1 tract), and cross-connecting POS-NEG modulation regions (2 tracts). Three tracts showed significant age-related decrease in FA, one POSMOD (inferior frontal-insula U-fiber), one NEGMOD (cingulum and genu of CC), and 1 CROSS-MOD (cingulum). We next tested for structure-function

associations predicting BOLD modulation using tract FA, age, and their interactions, controlling for whole-brain FA. Among these three tracts, the NEGMOD tract (cingulum and CCgenu connecting medial orbitofrontal and precuneus) FA interacted with Age to predict negative BOLD modulation, where older adults demonstrated a weaker structure-function association. Further, an Age by FA by NEGMOD interaction was found on task-switching ability, driven by older adults with lower FA and weaker negative modulation demonstrating poorer task switching performance. The present findings highlight the importance of cingulum/CCgenu tracts in the modulation of deactivations as task difficulty increased. Further, older adults with poorer white matter anisotropy in the cingulum/CCgenu and less deactivation to difficulty exhibited poorer cognitive control than their counterparts. In this visuospatial task under increasing working memory loads, the deactivation of medial orbital frontal cortex and precuneus, and the white matter integrity of the cingulum connecting these two areas influence cognitive control in later life.

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Poster

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Title: White matter complexity and entropy change with age, are driven by changes in crossing fibers, and predict cognitive performance

Authors: *A. R. BENDER[1], J. PLASS[2], M. MEIRING[1], J. SATOW[1], S. DÜZEL[3], U. LINDENBERGER[3], T. A. POLK[2], S. KÜHN[3];
[1]Michigan State Univ., East Lansing, MI; [2]Univ. of Michigan, Ann Arbor, MI; [3]Max Planck Inst. For Human Develop., Berlin, Germany

Abstract: Age-related changes in white matter microstructure observed via diffusion magnetic resonance imaging (dMRI) are commonly thought to reflect a loss of white matter integrity. However, recent findings show that much of the reported age-related differences in white matter are due to alterations in crossing fiber complexity. Histological evidence suggests smaller-diameter axons are preferentially sensitive to the effects of enrichment, aging and pathology. Thus, it appears that variable effects of aging on differently oriented intra-voxel fiber populations may drive concomitant changes in the spatial entropy or complexity of the diffusion signal. We hypothesized that within- and between-person variation in measures of white matter complexity and entropy (CXE) reflect the differential contributions of individual fiber populations, and that these may provide a more sensitive marker of cognitive aging. The present analyses utilized data from cognitive testing and dMRI acquired in a sample of 420 younger and older adults recruited from the Berlin Aging Study-II. We processed and analyzed dMRI data (b=1000

s/mm^2; 60 directions) using the MRtrix3 single-shell fixel-based analysis (FBA) pipeline. Using this framework, we estimated fixel measures of fiber density (FD) and fiber cross-section (FC) and voxelwise parameters of CXE, transformed to a sample-specific template. Voxelwise regressions of CXE on age, corrected for multiple comparisons, revealed widespread bilateral patterns of significant positive and negative age effects. Analysis of CXE in age-sensitive regions on demographic and cognitive measures showed strong relationships with fluid and crystalized intelligence, speeded processing, and education, even controlling for differences in age. Next, we extended the FBA pipeline to output image data for FD and FC, separately for each of the three most prominent crossing fiber populations. Using this approach, we demonstrate that differential alterations of FD and FC in crossing fiber populations drive age-associated differences in CXE, and are sensitive to differences in cognition. These findings reveal the complementary capacity of non-tensor dMRI approaches for studying relationships between white matter microstructure, cognition, and lifespan development. Moreover, the present results emphasize the need for an updated framework for analyzing and interpreting dMRI data in cognitive aging that includes measures of white matter entropy.

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Poster

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Program #/Poster #: P892.06

Topic: H.12. Aging and Development

Support: NIH Grant AG068149

Title: Age-related reductions in network segregation are larger in active cognitive tasks compared to rest

Authors: L. E. HARMON, *J. D. KOEN;
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Abstract: Older adults exhibit a decrease in the distinctiveness of neural networks and their functional specialization, a phenomenon more broadly referred to as age-related neural dedifferentiation. Previous studies have analyzed resting-state fMRI data to describe age-related differences in functional connectivity of brain networks and found that increased age is associated with decreased segregation of neural networks. Here, we leverage data from the Cam-CAN cohort to investigate if age-related reductions in large-scale network segregation differ between rest and 'active' tasks. The Cam-CAN dataset provides resting state fMRI data (n=652; eyes closed) as well as fMRI data from two 'active' tasks in which participants watch a movie (n=649) and complete a sensorimotor reaction task (n=651) for healthy adults from across the lifespan (aged 18-88 years). Using the Power et al. (2011) parcellation, we measured network segregation following the procedure of Chan and colleagues (2014) in which segregation is defined by contrasting within-network from between-network connectivity. We used a linear mixed effects model to examine how network segregation differed between the rest, movie, and sensorimotor tasks and with age (linear and quadratic terms). First, the results replicated prior findings

showing that network segregation decreased with age. This relationship was nonlinear with the rate of decrease accelerating with increasing age. Critically, we also found that the relationship between age and network segregation differed between rest and the two 'active' tasks. Specifically, age-related reductions were significantly more negative for the sensorimotor and movie tasks compared to networks derived from the (eyes-closed) rest data. This appeared to be mainly in the quadratic age term of the model, suggesting that network segregation connectivity measures derived from 'active' tasks might reveal stronger nonlinear age-trends. These analyses provide a more comprehensive view of age-related network desegregation by accounting for differing cognitive states.

Disclosures: L.E. Harmon: None. **J.D. Koen:** None.

Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

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Topic: H.12. Aging and Development

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R01AG047972

Title: Age-related changes in neural-vascular coupling modulate load-induced parametric effects among younger and older adults in visual and cognitive tasks

Authors: *Y. ZHAO[1], D. H. ABDELKARIM[4], M. P. TURNER[4], J. HUTCHISON[5], D. SIVAKOLUNDU[6,7], K. WEST[2], B. P. THOMAS[8], P. LIU[9], J. SPENCE[5], H. LU[9], B. P. RYPMA[3]; [1]Univ. of Texas At Dallas, Addison, TX; [2]Ctr. for BrainHealth, [3]Behavioral & Brain Sci., Univ. of Texas At Dallas, Dallas, TX; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX; [5]Univ. of Texas at Dallas, Richardson, TX; [6]Dept. of Biol. Sci., Univ. of Texas at Dallas, Dallas, TX; [7]Yale Sch. of Med., New Haven, CT; [8]Advanced Imaging Res. Ctr., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [9]Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Age-related decline in the modulation of neural recruitment with increasing task demand has been observed in many studies using blood-oxygen-level-dependent signal (BOLD). We measured demand-dependent age-changes in physiological factors underlying BOLD while participants performed an in-scanner visual task and two cognitive tasks (digit-symbol-verification task; DSVT and Sternberg working memory task; SWMT). In all tasks, we parametrically increased the visual or cognitive demand. In the visual tasks, participants viewed a checkerboard that flickered at 2, 4, or 8 Hz. In DSVT, participants judged if a probe pair matched one from a key of either 1, 3, or 9 digit-symbol pairings. In SWMT, participants judged if a probe letter matched one from a previously encoded memory set of either 2, 4, or 6 letters. BOLD and cerebral blood flow (CBF) were simultaneously measured using a dual-echo sequence. Hypercapnia enabled modeling of cerebral metabolic rate of oxygen ($CMRO_2$) and the neurovascular coupling ratio (NVC). In the visual task, older adults demonstrated reduced BOLD, CBF, and NVC but equivalent $CMRO_2$ at higher load conditions, compared to younger adults. In both cognitive tasks, significant reaction time differences were observed between age groups. While younger adults

demonstrated load-dependent increases in BOLD, CBF and $CMRO_2$, older adults showed discrepancies between these measures. These results suggest that age-related decreases in NVC limit older adults' capacity to modulate neural resources in response to variations in task demand.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P892.08

Topic: H.12. Aging and Development

Support: Oticon Foundation

Title: Neurophysiological effects of longitudinal hearing aid use on auditory entrainment and speech in noise perception in older adults with age related hearing loss

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Abstract: Age-related hearing loss (ARHL) is a common feature of human aging, has been strongly linked to accelerated cognitive decline in older individuals and is the largest modifiable risk factor of developing dementia. These impairments are preceded by the maladaptive re-organization of the auditory cortex, which is thought to occur as a compensatory response to degraded auditory input. The current study posited that this remodeling profoundly hinders the dynamics of brain systems and affects the temporal synchronization of neural circuits to the rhythmic fluctuations of speech that demarcate phoneme and syllable transitions. Speech-brain entrainment is related to speech intelligibility: individuals with ARHL exhibit poor speech comprehension and reduced neural entrainment to speech audio in noisy environments. Hearing aids (HA) are often considered in interventions for preventing, attenuating or delaying the onset of cognitive decline seen in ARHL. Yet, most research has reported correlational effects, with limited insight into the causal benefits of HA. In particular, whether HA can help maintain or recover auditory entrainment remains poorly investigated. The current study aimed to delineate the longitudinal neurophysiological effects of HA on auditory entrainment and speech intelligibility. MEG recordings were acquired from a group of (N=12) older adults with ARHL before and after 3-months of HA use during a speech-in-noise detection task. Subjects were presented with sentences embedded in varying levels of background noise and asked to repeat the words they heard. Our data indicate that the HA intervention modulated the magnitude of activity in left language areas associated with speech articulation, comprehension and verbal working memory, as well as right dorsolateral prefrontal cortex

and bilateral primary auditory and premotor regions involved in attentional and inhibitory control, and acoustic processing. Moreover, these areas appeared to be differentially recruited based on behavioural task performance. Collectively, these results clarify the neurophysiological mechanisms of how HA contributes to increasing speech intelligibility in aging and open new perspectives in terms of optimizing and personalizing HA interventions based on brain signal markers.

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Poster

P892. Cognitive Natural Aging: Neural Mechanisms: Structure and Function

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P892.09

Topic: C.01. Brain Wellness and Aging

Support: NIH 1RF1AG039103

Title: Structural and functional correlates of longitudinal memory change in a sample of cognitively healthy older adults

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Abstract: Structural and functional variability in the medial temporal lobe have been proposed to correlate with individual differences in episodic memory and longitudinal memory change in cognitively healthy older adults. The entorhinal cortex in particular has been reported to be sensitive to early cortical tau accumulation and reductions in its structural integrity have been reported to be associated with memory decline. The current study implemented detailed manual tracing of the entorhinal cortex following established protocols to obtain volumetric measures from its anterolateral and posterior-medial divisions. The study cohort comprised 67 older (ages 63 - 76 yrs. at baseline), cognitively healthy adults. Participants were administered a battery of neuropsychological tests on three occasions: the second occasion one month after the first test session, and a third session three years after the first one. Structural and functional MRI data were acquired between the first two sessions. Memory component scores were derived from a principal components analysis of the neuropsychological test scores. To reduce retest effects, mean memory scores across sessions 1 and 2 served as a baseline for assessing change in memory performance at session 3. Fifty-five participants, all of whom had remained cognitively healthy, returned for the session 3 tests. None of the volumetric measures derived from the entorhinal cortex demonstrated a statistically significant relationship either with baseline memory performance or longitudinal memory change. By contrast, volume of the posterior hippocampus (which was also traced manually) correlated negatively with memory decline, as did functional activity in the anterior hippocampus obtained during an

in-scanner experimental memory test. These findings suggest that structural integrity of the entorhinal cortex does not appear to be a sensitive predictor of memory performance or longitudinal memory change in older adults at low risk of prodromal Alzheimer's Disease.

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Poster

P915. Genomic and Transcriptomic Techniques II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: The Lieber Institute for Brain Development
10x Genomics

Title: Transcriptomic analysis of Aβ-tau synergy in the inferior temporal cortex of the human brain in Alzheimer's disease

Authors: *S. KWON[1], M. TIPPANI[2], A. SPANGLER[2], H. DIVECHA[2], K. MONTGOMERY[2], C. BRUCE[3], S. WILLIAMS[3], M. MAK[3], G. YU[3], J. AVALOS-GRACIA[3], T. M. HYDE[2], S. C. PAGE[2], S. C. HICKS[4], L. COLLADO-TORRES[2], K. MARTINOWICH[1,2], K. R. MAYNARD[1,2];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by senile plaques of β-amyloid (Aβ) and neurofibrillary tangles of phosphorylated tau (pTau). Accumulating evidence suggests that Aβ and tau act in concert to orchestrate complex pathobiological events underlying AD, but their additive effect remains poorly understood. Our experiments investigate Aβ-tau synergy at the level of gene expression in inferior temporal cortex (ITC) of individuals with AD. We employed 10x Genomics Visium Spatial Transcriptomics (ST) coupled with immunofluorescence (Visium-IF) to generate a proteomic-based, spatially-resolved, transcriptomic-scale map of the human ITC in AD. Visium-IF is a next-generation ST platform in which IF staining is paired with on-slide cDNA synthesis using barcoded arrays (5000 gene expression spots/array) to retain spatial X-Y coordinates of transcript expression. For this study, brain blocks were dissected to include ITC from 3 brain donors with late-onset AD (Amyloid C/Braak III) and 1 age-matched neurotypical donor. We validated laminar patterning in each block using RNAscope in situ hybridization with Layer I and VI marker genes (*RELN* and *NR4A2*). Cryosections from each block were collected in triplicate on Visium arrays and immunostained for Aβ, pTau, MAP2 and GFAP to visualize plaques, tangles, neurites, and astroglial processes. Each section was scanned using multispectral imaging and sequenced (whole-genome and targeted gene expression using the 10X Genomics human neuroscience panel). We are executing two analysis strategies with these data to identify molecular, cellular, and morphological associations with spatially-localized Aβ and tau pathology. The first compares AD patients with the neurotypical control to identify differentially expressed genes (DEGs) between diseased and normal-aging states. The second within-subject analysis examines the local effect of plaques and tangles in the same tissue section of the AD-donors. Specifically,

after clustering by staining patterns, we compare gene expression in Visium spots with 1) no pathology, 2) Aβ only, 3) tau only, 4) Aβ/tau, using a t-distributed stochastic neighbor embedding algorithm. Gene ontology analysis defines common disease pathways associated with the identified DEGs, and spot deconvolution analysis by cellular staining helps identify cell types associated with the DEGs. With enhanced spatial and cellular resolution, our novel approach can disentangle regional heterogeneity in gene expression and refine annotation of genes and cell types that are functionally linked to AD.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Support from Lieber Institute for Brain Development

Title: Single-molecule cartography of adult neurogenesis in the human dentate gyrus

Authors: *A. D. RAMNAUTH[1,4], S. C. PAGE[4], E. A. PATTIE[4], M. TIPPANI[4], T. M. HYDE[4,2,3], K. MARTINOWICH[4,1,2];
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Abstract: Hippocampal (HPC) neurogenesis in the dentate gyrus (DG) has been reliably documented to occur across the lifespan of many mammals, including nonhuman primates, at a high rate early in life then dropping substantially lower but still present in later life. Subsequent research has linked differential rates of adult HPC neurogenesis in these model organisms with changes to plasticity, behavior, and brain disorders. Despite decades of research, indisputable evidence of adult HPC neurogenesis in humans remains elusive and the persistence of neurogenesis throughout the entire lifespan in the human DG remains controversial. The vast majority of past studies on human brain tissue have relied primarily on antibody-based methods, such as immunohistochemistry and western blotting, which are highly sensitive to variability in post-mortem tissue processing. Another limitation of these studies is the limited age range of brain donors that were used. To circumvent these technical limitations, we are employing single-molecule RNA-based methods to probe for neurogenesis in human DG cryosections throughout the entire lifespan. Specifically, we are using the Advanced Cell Diagnostics RNAscope Multiplex Fluorescent V2 Assay to probe for candidate markers of neurogenesis at various cell development stages, ranging from stem cells to immature granule cells, in the DG of fresh frozen HPC from neurotypical donors ranging in age from infant to 70+ years. We then quantify the density of expressing nuclei, as well as co-expression

and degree of expression of neurogenesis markers in nuclei in the granule cell layer of human DG using our MATLAB package dotdotdot for nuclei and transcript segmentation. Our preliminary results show that nuclei co-expressing common markers of neurogenesis such as doublecortin (DCX), sex determining region Y - box transcription factor 2 (SOX2), and nestin (NES) are abundant in the infant DG and drop dramatically with age, but remain at detectable levels, suggesting the continuation of neurogenesis throughout the entire human lifespan. In addition, we are starting to adapt our previously used workflow of the 10x Genomics Visium Spatial Gene Expression platform to define the spatial topography of the human HPC across the lifespan. We will use the resulting dataset to explore the spatial architecture of adult neurogenesis in the human DG. The resulting analyses will be useful to describe the degree to which neurogenesis persists across the lifespan and correlated changes to the neighboring tissue.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Identifying Spatial Patterns of Gene Expression and Cell-type Specificity in Human Lateral Septum

Authors: *E. A. PATTIE[1], L. A. RODRIGUEZ[1,2], T. M. HYDE[1,3,4], S. C. PAGE[1], K. MARTINOWICH[1,2,3];
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Abstract: The lateral septum (LS) plays a regulatory role in the processing of sensory stimuli and affective information to modulate movement, fear response, and social behavior. The LS is densely interconnected with multiple brain regions related to mood and motivation including the hippocampus, ventral tegmental area, hypothalamus, and amygdala. In rodents, septal lesions modulate anxiety-related behaviors and influence activity levels, reactivity, and behavioral disinhibition. The rodent LS is predominantly composed of GABAergic cells which abundantly express TrkB, the cognate receptor for the neurotrophin, brain-derived neurotrophic factor (BDNF). However, BDNF is supplied to the LS via projections from other BDNF-rich brain regions as LS neurons do not synthesize BDNF themselves. Dopaminergic projections from the ventral tegmental area to the LS play a regulatory role on LS neural activity, and are implicated in psychotic spectrum disorders including schizophrenia. However, the degree to which circuitry, neurochemistry, and cellular composition of the LS is conserved between rodents and humans remains unclear. To address this gap, we investigated cell-type specific and spatial patterns of gene expression in the post-mortem human LS to address convergence and divergence between humans and rodents. First, we obtained fresh frozen brain blocks, and collected cryosections from n=4 neurotypical human brain donors. Then, we used multiplexed single molecule fluorescence in situ hybridization to quantify the spatial expression patterns of *BDNF* and *NTRK2*, interneuron markers (including *GAD1*, *CALB1*, *CALB2*, and *PVALB*), and dopamine receptors in the LS. Based on *GAD1*

expression patterns, we determined that neurons in the human LS are predominantly GABAergic, as seen in rodents. We also observed an abundance of *NTRK2* expression in LS neurons, and exclusion of *BDNF* transcripts. Collectively, these results indicate many similarities in the cellular composition between the rodent and human LS. Understanding the conservation of LS circuity and cell types cross-species will allow us to more effectively translate preclinical research findings in the rodent LS to understanding human neurobiology and disease.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Lieber Institute for Brian Development

Title: Spatial landscape of gene expression in the human locus coeruleus

Authors: *H. R. DIVECHA[1], L. WEBER[2], S. KWON[1], A. SPANGLER[1], T. M. HYDE[1], L. COLLADO-TORRES[1], K. MAYNARD[1], S. C. HICKS[2], K. MARTINOWICH[1];
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Abstract: The locus coeruleus (LC), a brainstem pontine nucleus, is the primary site for noradrenaline (NA) production in the mammalian brain. NA-producing cells in the LC project widely to central nervous system areas with highly divergent functions. The LC-NA system plays important roles in regulating arousal and mood, and serves an integral role in several higher cognitive functions ranging from attention to motivation to working memory. Importantly, LC cell loss is a prominent hallmark of the two most prevalent neurodegenerative disorders, Alzheimer's disease and Parkinson's disease. It is hypothesized that the ability of the LC to achieve such widely divergent function-specific neuromodulation is achieved by the existence of molecularly distinct neuronal subpopulations that retain unique anatomical and functional connectivity. While several studies have examined the molecular profile of LC-NA neurons in the rodent, gene expression signatures of cell populations in the human LC are not yet available. To address this gap, we generated a spatial map of gene expression in the postmortem human LC using the transcriptome-scale 10x Genomics Visium platform. We first localized the LC in tissue sections by using RNAscope single-molecule fluorescent in-situ hybridization for NA-expressing neuron markers including SLC6A and TH. We then applied the Visium assay to tissue sections from n=4 neurotypical control brain donors (n=2 LC sections/donor). We evaluated conservation of gene expression patterns in LC-NA neurons between mouse and human LC, using data-driven approaches to identify spatially variable genes across the LC, and investigated enrichment of genes associated with Alzheimer's and Parkinson's disease in LC cell populations. In summary, we created a spatial gene expression map for the human LC, and identified molecular profiles for LC-NA neurons in the human brain.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Knut and Alice Wallenberg Foundation

Title: An extended transcriptomic analysis of more than 200 regions of the human brain with a focus on protein-coding genes

Authors: *N. MITSIOS[1], W. ZHONG[2], S. BARDE[1], M. KARLSSON[2], P. OKSVOLD[2], L. FAGERBERG[2], C. ZHANG[2], T. ZHENG[1], K. VON FEILITZEN[2], C. LINDSKOG[3], E. SJOSTEDT[1], V. YANG SWARTZ[4], Y. LUO[4], E. RENNER[5], M. PALKOVITS[5], T. HOKFELT[1], M. UHLEN[2], J. MULDER[1];
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Abstract: The Human Protein Atlas (HPA; www.proteinatlas.org) is a public online database that provides an integrated overview of protein expression and distribution in all major human tissue types, including brain. The current version (HPA20) provides a comprehensive overview of gene and protein expression in the main anatomical structures of the mouse, pig, and human brain, by combining in-house generated and publicly available transcriptomic data. However, there is an incomplete coverage of the human brain, and several regions with key roles in brain physiology and pathophysiology have not been included. To fill this gap, a more extended analysis of these areas in a greater anatomical detail was performed. In HPA21, planned to be released in November 2021, we have included additional in-house generated RNA sequencing data, based on regional and subregional protein expression in nearly 1400 samples from more than 200 (209) human brain regions microdissected in the Human Brain Tissue Bank, Budapest. These include 11 samples from different basal ganglia, 16 thalamic and 9 from the hypothalamic nuclei, 9 samples from the hippocampal complex, 5 from the amygdala, over 70 brainstem (midbrain, pons, medulla) and from 5 cerebellar cortical and nuclear samples. From the cerebral cortex 86 areas, gyri and subregions have been studied. The HPA brain section provides gene-centric pages that give an extensive and integrated overview on protein expression across regions and subregions of the brain and allow comparison between species. Furthermore, we classify all protein coding genes based on regional distribution and co-expression, thus providing lists of genes associated to brain regions and functions. All data presented are freely accessible based on the FAIR Data Principles.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Program #/Poster #: P915.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Expression quantitative trait loci (eQTL) of the human spinal cord

Authors: S. SINGH[1], P. MOHAMMADI[2], D. DAS[1,2], ***N. GAVVA**[1];
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Abstract: INTRODUCTION: Tissue specific expression quantitative trait loci (eQTL) has emerged as a great tool in fine mapping to identify causal genes underlying GWAS loci for neurodegenerative diseases. The challenge however has been the lack of tissue specific eQTL data. For diseases like Amyotrophic lateral sclerosis (ALS) with spinal cord (SC) involvement wherein the single available GTEx SC eQTL dataset only captures the c-1 level of SC. We thus set out to create a rich SC eQTL dataset capturing the thoracic and lumbar regions. **METHODS:** We extracted high quality DNA and RNA from thoracic and lumbar regions of SC from 93 donors and performed whole genome sequencing to capture SNP and RNA-seq to capture mRNA expression. Stringent quality control and eQTL analysis was performed according to the Broad/GTEx eQTL pipeline. Genetic data from WGS was used for principal component (PC) analysis for ancestry. PEER factors were calculated from gene expression data to account for unknown covariates. Fast-QTL was used for analyzing cis-eQTLs (< 1Mb from TSS) and Matrix-QTL was used for analyzing trans-eQTLs (>1Mb from TSS). Both the analyses were adjusted for sex, age, 10 PCs and 30 PEER factors. Allelic log fold change (aFC) a measure for cis-eQTL effect size for the lead variant in eGenes (Genes with at least one significant eQTL) was also calculated. The aFC for overlapping eQTLs from our SC eQTL dataset was compared with that of multiple tissues from GTEx including c1-SC, cerebellum and whole blood using non-parametric Spearman Rank Correlation test. **RESULTS AND CONCLUSION:** Post QC, we retained all the 93 samples for eQTL analysis. We identified 198133 cis-eQTLs and 2248 trans-eQTLs to be significantly associated with gene expression. Of the more than 24000 expressed genes in our dataset, we identified 2345 eGenes with at least one significant eQTLs. On comparison with GTEx for overlapping eQTLs we found the spearman correlation coefficient (rho) to be 0.63, 0.49 and 0.45 with c1-SC, cerebellum and whole blood tissue respectively. The differences in correlation between tissues is indicative of the stark differences in the tissue specificity of eQTLs and further highlights the need of interrogation of tissue specific eQTLs to understand the underlying role of genetics of gene expression in diseases. In conclusion, we herein generated a rich resource of SC eQTLs which will prove to be a great resource and provide impetus in drug discovery efforts by identifying underlying mechanisms and causal genes for neurodegenerative diseases like ALS.

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Poster

P915. Genomic and Transcriptomic Techniques II

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Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: R01-MH120227
R01HD100022
3R01HD100022-02S2

Title: Cellular models of fetal neurodevelopment in maternal viral infection

Authors: *R. M. DE GUZMAN, S. D. SHERIDAN, L. T. MCCREA, J. M. THANOS, J. E. HORNG, T. FU, C. M. SELLGREN, R. H. PERLIS, A. G. EDLOW;
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Abstract: Background: Maternal immune activation may have deleterious effects on fetal brainmacrophages (microglia). Microglia play a key role in modulating synaptic pruning,neurogenesis, and regulation of synaptic plasticity. They also are critical mediators ofneurodevelopmental morbidity in maternal immune activation. Microglia areinaccessible during fetal life and early development and there are no surrogatebiomarkers or cellular models for *in utero* microglial priming and function that can aidin identifying neonates and children most vulnerable to neurodevelopmentalmorbidity. Two candidate cell types that could serve as a proxy for fetal brain microgliainclude fetal placental macrophages (Hofbauer cells), which share a common originwith microglia in the fetal yolk sac; and cord blood monocytes, which also may carrythe imprint of *in utero* exposures. We have previously demonstrated that clusters offetal placental macrophages share a highly conserved single cell signature with fetalbrain microglia in a mouse model.Methods: The MGH COVID-19 Pregnancy Biorepository includes banked placental cellisolates and umbilical cord blood mononuclear cells (CB-MNCs) from >500 pregnantwomen positive for SARS-CoV-2, and contemporaneous SARS-CoV-2-negativecontrols. We used our previously-validated cellular models of reprogrammed inducedmicroglial-like cells (iMGs) and synaptosome phagocytosis assay to determinewhether: (1) umbilical cord blood mononuclear cell-derived iMGs (CB-iMGs) and (2)placental villous macrophage-derived iMGs (Pl-iMGs) from SARS-CoV-2-exposed casesand matched SARS-CoV-2-negative controls can be used to model the impact ofmaternal COVID-19 on fetal brain microglia. We evaluated expression of classicmicroglial markers, iMG morphology, and function using the synaptosomephagocytosis assay.Results: We demonstrated that both CB-MNCs and placental macrophages can besuccessfully reprogrammed to create iMGs that express classic microglial markers andexhibit ramified and ameboid microglial morphology. Both CB-iMGs and Pl-iMGsphagocytosed synaptosomes *in vitro*.Conclusions: These results demonstrate the potential for both CB-MNCs and placentalvillous macrophages to serve as proxy cell types that can model the impact of *in utero*exposures on fetal brain microglia. If these cellular models correlate with

neurodevelopmental phenotypes in long-term follow-up, they could be used at birthto identify at-risk neonates exposed to varied maternal environmental or infectiousexposures, during a key developmental window when intervention may improveoutcomes.

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Poster

P915. Genomic and Transcriptomic Techniques II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.08

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Allen Institute for Brain Science
NIH Grant U01 MH114812-02

Title: Characterizing regional specializations of cell types across the human cortex with single nucleus transcriptomics

Authors: *N. JORSTAD[1], T. BAKKEN[1], R. D. HODGE[1], A. YANNY[1], K. SMITH[1], D. BERTAGNOLLI[1], J. GOLDY[1], C. RIMORIN[1], M. TIEU[1], D. MCMILLEN[1], T. PHAM[1], A. TORKELSON[1], K. WARD[1], K. LATHIA[1], S.-L. DING[1], N. DEE[1], T. CASPER[1], D. HIRSCHSTEIN[1], N. SHAPOVALOVA[1], E. BARKAN[1], M. KROLL[1], K. SILETTI[2], L. HU[2], P. LONNERBERG[2], S. LINNARSSON[2], E. LEIN[1];
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Abstract: Single nucleus transcriptomics is a powerful tool to understand cortical cellular diversity and areal variation that underlie functional parcellation. In this study we explored regional variation across the human cortex, analyzing graded and discrete variation between areas and differences in cellular makeup of sensorimotor versus association cortices. Specifically, we analyzed over 1.2 million nuclei from 8 different cortical regions (A1, ACC, ANG, DLPFC, M1, MTG, S1, and V1) collected from 7 postmortem adult donors of both sexes. Dissociated nuclei were stained for the neuronal marker NeuN and FACS-purified to enrich for neurons and a minority of non-neuronal cells. Broad sampling across all cortical layers and regions was performed with 10x Chromium V3, with ~100,000 nuclei per region passing quality control (QC). To enrich for the sparse but distinctive and disease-relevant layer 5 extratelencephalic-projecting (L5 ET) neurons, we also generated a micro-dissected layer 5 dataset from six of the brain regions with 10x Chromium V3, with ~30,000 nuclei per region passing QC. Finally, a layer-dissected SMART-seq V4 datasets was generated for each brain region, with ~10,000 nuclei per region passing QC. Together, these three datasets provide broad cell type coverage, enrichment of rare and interesting layer 5 neuron types, and the ability to annotate cell types by their laminar distribution within the cortical column. In analyzing this rich dataset we find evidence for regional specializations of specific cell populations, especially for glutamatergic types in primary visual cortex. We also report differences in neuronal cell type proportions and explore conserved signatures of cell types across brain regions. As a result of analyzing such a large and complex dataset, we also provide a computational

framework for assessing quality control, integrating datasets across donors/modalities, and clustering/curating the datasets into cross-cortical cell type taxonomies. Analysis was performed in R with significant use of normalization, integration, and clustering functions from Seurat 3.2.2.

Disclosures: N. Jorstad: None. **T. Bakken:** None. **R.D. Hodge:** None. **A. Yanny:** None. **K. Smith:** None. **D. Bertagnolli:** None. **J. Goldy:** None. **C. Rimorin:** None. **M. Tieu:** None. **D. McMillen:** None. **T. Pham:** None. **A. Torkelson:** None. **K. Ward:** None. **K. Lathia:** None. **S. Ding:** None. **N. Dee:** None. **T. Casper:** None. **D. Hirschstein:** None. **N. Shapovalova:** None. **E. Barkan:** None. **M. Kroll:** None. **K. Siletti:** None. **L. Hu:** None. **P. Lonnerberg:** None. **S. Linnarsson:** None. **E. Lein:** None.

Poster

P915. Genomic and Transcriptomic Techniques II

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Program #/Poster #: P915.09

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant U01MH114812

Title: Analysis of primary motor cortex across diverse mammalian species reveals divergent cell type features

Authors: A. YANNY[1], N. JORSTAD[1], T. BAKKEN[1], *R. HODGE[3], K. SMITH[1], J. GOLDY[1], N. GUILFORD[1], J. GUZMAN[1], T. PHAM[1], A. TORKELSON[1], R. CHAKRABARTY[1], D. HIRSCHSTEIN[1], N. SHAPOVALOVA[1], S. BARLOW[1], T. YELLOWHAIR[4], T. BARRETT[4], M. ENGLUND[5], L. KRUBITZER[5], J. J. PADBERG[6], C. STIMPSON[7], C. SHERWOOD[7], A. GOROPASHNAYA[8], V. FEDOROV[8], K. DREW[8], G. WILKERSON[9], E. LEIN[2];
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Abstract: Model organisms have been studied for generations to explore the cellular components and functions of different brain regions. But how comparable are mammalian model organisms to the human brain? What are the common features of organization, and how have specific brain regions, cell types and gene expression patterns changed in different lineages throughout evolution? We explored these questions by sampling primary motor cortex (M1) from the brains of multiple (n>10) mammalian species, spanning diversity that represents more than 100 million years of mammalian evolution. Using single nucleus RNA-sequencing, we compiled species-specific transcriptomic cell type taxonomies and a cross-species taxonomy of conserved cell types. Marker gene expression was well conserved across species. For example, extra-telencephalic projecting layer 5 (L5 ET) pyramidal neurons, a major source of information output in the mammalian cortex, were reliably marked by expression of *POU3F1* in every species. While marker genes were conserved across species, M1 cell type proportions diverged. For example, L5 ET neurons were less abundant in humans and great apes compared to rodents. Notably, the ratio of excitatory to inhibitory neurons in M1 across species was higher in the rodent clade compared to other

mammals, suggesting that the balance of inhibition and excitation is functionally different in the rodent cortex compared to the other species examined in this study. Brain samples were collected from adult animals of each species (at least n=2 animals per species). Nuclei were stained for NeuN and captured with fluorescence-activated cell sorting (FACS) to enrich for neurons (NeuN+) while also capturing a minority of non-neuronal (NeuN-) cells. Single nucleus libraries were generated with the 10x Chromium 3' Single Cell kit (v3.1 chemistry), and ~100,000 nuclei per species passed quality control. Datasets were analyzed in R using Seurat 3.2.2. *In situ* validation was performed with RNAScope multiplex fluorescent *in situ* hybridization and immunohistochemistry.

Disclosures: A. Yanny: None. **N. Jorstad:** None. **T. Bakken:** None. **R. Hodge:** None. **K. Smith:** None. **J. Goldy:** None. **N. Guilford:** None. **J. Guzman:** None. **T. Pham:** None. **A. Torkelson:** None. **R. Chakrabarty:** None. **D. Hirschstein:** None. **N. Shapovalova:** None. **S. Barlow:** None. **T. Yellowhair:** None. **T. Barrett:** None. **M. Englund:** None. **L. Krubitzer:** None. **J.J. Padberg:** None. **C. Stimpson:** None. **C. Sherwood:** None. **A. Goropashnaya:** None. **V. Fedorov:** None. **K. Drew:** None. **G. Wilkerson:** None. **E. Lein:** None.

Poster

P915. Genomic and Transcriptomic Techniques II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P915.10

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: U19AG060909

Title: Tools for optimizing multiplexed single-nucleus sequencing experiments

Authors: *J. MAHONEY[1], A. YANNY[3], B. P. LEVI[1], J. K. MICH[1], Y. DING[3], J. A. MILLER[3], A. TORKELSON[3], K. SMITH[3], D. HIRSCHSTEIN[3], S. BARLOW[3], N. SHAPOVALOVA[3], E. LEIN[4], R. D. HODGE[2];
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Abstract: The rise of highly multiplexed single cell sequencing technologies has significantly accelerated the rate and lowered the cost of generating large sequencing datasets. However, as with every new technology, a fresh set of challenges has arisen. Here we demonstrate how class-identifying antibody panels and cholesterol modified oligo (CMO) nuclei barcoding can aid researchers in collecting more useful and meaningful data from human postmortem fresh frozen brain tissue.
Non-neuronal oligodendrocytes, although interesting, have an outsized presence in single nucleus sequencing experiments due to their relative abundance throughout the human brain, particularly in subcortical regions. Therefore, investigating the diversity of cell types within the brain can be difficult when rare cell types are overwhelmed in sequencing datasets by more populous cell classes. Many research experiments use the neuronal nuclear marker NeuN and fluorescence-activated cell sorting (FACS) to deplete non-neuronal nuclei during tissue collection. Here we demonstrate how staining with NeuN, OLIG2, and SOX2 nuclear markers can identify astrocytes, inhibitory neurons, excitatory neurons,

microglia, oligodendrocyte precursor cells, and oligodendrocyte populations. For example, using a BD FACSaria Flow Cytometer and 10x Chromium 3' Single Cell kit (v3.1 chemistry), a NeuN(+) Olig2(-) Sox2(+) FACS population is shown to be ~90% inhibitory neurons. This enrichment strategy can be incredibly powerful in applications such as generating atlases or investigating rare cell types.
One drawback to highly multiplexed sequencing platforms is the large amount of tissue required as input. CMO barcodes, commonly used for overloading 10x Chromium 3' chips, can also be used to tag and pool sparse populations of nuclei. We demonstrate how CMO barcoding facilitates snRNA-seq for samples with as few as 2,000 sorted nuclei on the 10x 3' platform.

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Poster

P918. Single-Cell Techniques III

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Program #/Poster #: P918.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant U01MH114812

Title: Morphoelectric characterization of transcriptomic cell types in layer 1 of human neocortex

Authors: *T. CHARTRAND[1], B. E. KALMBACH[2], R. DALLEY[1], G. MOLNÁR[3], N. GORIOUNOVA[4], N. L. JORSTAD[1], J. T. TING[2], J. A. MILLER[5], B. R. LEE[5], T. BAKKEN[1], K. SMITH[1], N. MIHUT[3], N. W. GOUWENS[1], V. OMSTEAD[1], M. TIEU[1], A. L. KO[8], J. G. OJEMANN[9], C. COBBS[11], R. P. GWINN[11], C. KEENE[10], A. P. PATEL[8], D. L. SILBERGELD[8], R. G. ELLENBOGEN[8], S. A. SORENSEN[5], H. ZENG[6], C. P. J. DE KOCK[12], I. SEGEV[13], G. TAMAS[3], H. MANSVELDER[14], E. LEIN[7];
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Abstract: The outermost layer of the neocortex, layer 1 exclusively contains inhibitory neuron cell bodies as well as axons and dendrites from deeper layer pyramidal neurons and axons from other brain areas. Through synapses onto pyramidal apical dendrites and volume transmission of inhibition, these neurons are thought to play a critical role in modulation of the cortical circuit according to behavioral state. Although primarily made up of neurogliaform (NDNF+) cells, the distinct "canopy" type within that population and other distinct rarer cell types have both been identified in recent work in rodent cortex. L1 cell types in human and non-human primate have been less well characterized, although two recent studies have characterized L1 electrophysiology and morphology and identified a highly specialized type,

the “rosehip” cell. To better characterize the diversity of types in human L1, we present a comprehensive dataset of >250 neurons characterized by Patch-seq in neurosurgically resected human tissue (available at biccn.org/data). Combining transcriptomics with electrophysiology and morphology, these data allowed mapping of each neuron onto a transcriptomic cell type taxonomy. Through broad sampling of cells across L1 and adjacent layers, we characterize the morphoelectric properties of each of these L1 “t-types”, including types that maintain a distinct identity across layer boundaries.
Most L1 t-types have distinct properties, while certain transcriptomically similar types show overlap in their phenotypes. We characterized rare cell types (PAX6+) with distinctive intrinsic bursting electrophysiology, and further characterize the transcriptomic identity of the previously identified rosehip type. We also present comparisons to mouse L1 cells characterized by the same platform, according to a cross-species homology of transcriptomic types. Both mouse and human have significant physiological and transcriptomic diversity in L1, and much of this diversity is aligned across species by the homology. However, we also find distinctive t-types that break from this pattern, evidence for species specialization: the stuttering rosehip and bursting PAX6 types in human, and strongly adapting VIP types that span L1 and L2/3 in mouse. Finally, we explored potential causal factors for cross-type and cross-species differences in electrophysiology by correlations to gene expression and morphological features. Together, these results leverage advantages of the Patch-seq method to deeply characterize L1 neuronal diversity across species, demonstrating species specialization within distinct cell subclasses in human and mouse.

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Poster

P918. Single-Cell Techniques III

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Program #/Poster #: P918.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 5U19MH114830

Title: Multiple modality classification of long-range projecting glutamatergic neurons in mouse visual cortex

Authors: *S. SORENSEN[1], N. W. GOUWENS[4], F. BAFTIZADEH[4], Y. WANG[7], A. BUDZILLO[2], R. DALLEY[4], B. R. LEE[1], R. MANN[1], C. LEE[5], O. GLIKO[4], M. MALLORY[1], A. MUKORA[1], G. WILLIAMS[1], L. ALFILER[1], H. KUO[7], P. LESNAR[1], E. SHEN[1], W. XU[1], X. KUANG[8], Y. LI[8], Y. YU[4], L. NG[1], U. SÜMBÜL[4], Z. YAO[1], B. TASIC[6], H. ZENG[3];
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Abstract: Mouse excitatory cortical neurons are well-understood to be organized into layers and have distinctlong-range, inter-areal projections. Each of these layers contains a variety of cell types with differentmorphology, electrophysiology and/or molecular properties. However, it is still unknown how these celltypes integrate together to form complex cortical circuits.Recent studies have described over 30 transcriptomically-defined types (t-types) among the excitatoryneurons of mouse visual cortex. These t-types correspond to previously described cell types based ontheir gene expression, laminar location, and long-range projection subclass (determined by retrogradelabeling studies; Tasic et al., 2018). Yet the diversity of the transcriptomic types exceeds the observeddiversity of those properties.The Patch-seq method measures morphological (m), electrophysiological (e) and transcriptomic (t)properties from the same cells. Here we apply that method to describe the t- and e-properties andprecise anatomical location of >1500 cells mapped to previously defined excitatory transcriptomic types.We also describe the morphological properties of >800 of those neurons from which morphologiescould be reconstructed. With these data, we relate many t-types to well-known neuron types for thisbrain region (e.g., L2/3 intratelencephalic (IT) wide branching, L5 IT slim-tufted, L5 extratelencephalicthick-tufted (TT), and L6 corticothalamic tall, narrow neurons). We also observe less well-describedtypes, such as inverted *Car3*+ L5/6 neurons and TT *Chrna6*+ L5 neurons, each of which are associatedwith a single t-type. The *Chrna6*+ neurons had different electrophysiological properties from other TTneurons. Using all three modalities together, we define a set of integrated, morpho-electric-transcriptomic (met)-types with congruent properties.In addition, to relate long-range axonal projections to met-types and t-types, we reconstruct ~170 wholebrain morphologies of visual cortical neurons. We describe the relationship between local and long-range morphological properties, and we use morphological classifiers to integrate cell type assignmentsacross the data sets using local morphology. Finally, we validate these mappings with full morphologydata collected from neurons labeled with cell type specific transgenic tools. Together, these results helpestablish a comprehensive, integrated characterization of multimodal excitatory cell types in mousevisual cortex.

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Poster

P918. Single-Cell Techniques III

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Program #/Poster #: P918.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH P51OD010425
NIH UL1TR000423
NIH U01 MH114812-02

Title: A combinatorial approach using viral genetic labeling and multimodal Patch-seq for targeted analysis of human neocortical interneuron subclasses and types.

Authors: *B. R. LEE[1], L. NG[2], K. HADLEY[1], K. BAKER[1], L. KIM[1], R. MANN[1], R. RAJANBABU[1], J. TRINH[1], S. VARGAS[1], N. WEED[2], R. DALLEY[2], N. DEE[2], T. JARSKY[2], B. E. KALMBACH[5], K. SMITH[2], J. BERG[6], S. A. SORENSEN[2], H. ZENG[3], E. LEIN[4], J. T. TING[5];
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Abstract: A bottom-up approach to understanding neocortical function is to start with identifying the constituent cell types and characterize their defining properties across multiple modalities. While much progress has been made in the mouse model in this context, exploration of human brain cell types has been more challenging and hindered by the lack of tools and mature brain tissue platforms to support targeted analysis. The *ex vivo* adult human neocortical slice culture paradigm provides an opportunity to extend the use of human neurosurgically-derived acute brain slices over days to weeks, thereby enabling application of viral genetic tools. We used rapid onset AAV vectors with cell class specific enhancers to prospectively label and then target human neocortical interneurons for multimodal Patch-seq analysis. Mapping recorded neurons to a human temporal cortex taxonomy based on transcriptomic profiles confirmed the high specificity of the viral approach for marking human neocortical GABAergic neurons. Additionally, this multimodal approach allowed us to evaluate the impact of the use of genetic tools and the culture paradigm has on electrophysiological, transcriptomic and morphological features. Upon examination of specific electrophysiological features, when comparing acute versus culture paradigm, we found subtle shifts in selected features; however, when reducing these features down to 2-dimensional representation, the two datasets displayed a high degree of overlap with similar structure. We have found that there are gene expression signatures from the culture paradigm (e.g. immediate early genes, stress response genes); however, these do not preclude the ability to identify canonical cell subclass and types. Lastly, close examination into specific morphological features from matched transcriptomic types yielded similar and preserved morphologies from acute and culture preparations. The combination of these approaches provides a robust and accurate method to characterize the signature properties of genetically-defined human neuron types, including diverse neocortical GABAergic neuron types that have previously been difficult to reliably target.

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Poster

P918. Single-Cell Techniques III

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Program #/Poster #: P918.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH P51OD010425

NIH NS123959
Northwest Epilepsy Center of Excellence, Department of Veteran's Affairs

Title: Cross-areal differences in the multimodal properties of non-human primate pyramidal neurons

Authors: *N. DEMBROW[1,2,3], S. I. PERLMUTTER[2,1], S. F. OWEN[4], C. RADAELLI[4], M. KIM[4], N. JORSTAD[4], N. J. WEED[4], N. TASKIN[4], X. OPITZ-ARAYA[4], R. DALLEY[4], M. HUDSON[1], T. BAKKEN[4], S. A. SORENSEN[4], W. J. SPAIN[1,3], E. LEIN[4], J. T. TING[4], B. E. KALMBACH[4];
[1]Physiol. and Biophysics, [2]Washington Natl. Primate Res. Ctr., Univ. of Washington, Seattle, WA; [3]Northwest Epilepsy Ctr. of Excellence VA Puget Sound, DVA, Seattle, WA; [4]Cell Types Program, Allen Inst. for Brain Sci., Seattle, WA

Abstract: Neocortical pyramidal neurons display significant diversity within and between cortical areas and across species, and understanding this diversity is key to understanding species and areal specializations in neocortical function. Single cell/nucleus (sn)RNA sequencing now allows robust cross-species/areal comparisons by generating and aligning cellular taxonomies across areas and species, while Patch-seq methods allow morpho-electric characterization of transcriptomically-identified cells. In the current study we used Patch-seq to begin understanding cross-areal pyramidal neuron differences in non-human primate (NHP), by collecting morphological, electrophysiological, and transcriptomic data from many individual pyramidal neurons in temporal cortex (TC) and primary motor cortex (M1) brain slices from the macaque.Morpho-electric properties of NHP pyramidal neurons depended upon their laminar location, cortical region and long-range axonal projection. Similar to previous reports in human neocortex, but unlike rodent cortex, subsets of supragranular pyramidal neurons in both M1 and TC displayed prominent h-current related membrane properties. We found that Layer 5 (L5) pyramidal neurons broadly segregated into two groups with morpho-electric and transcriptomic properties aligned to rodent projection neurons: extratelencephalic (ET) neocortical pyramidal neurons with long range axonal projections outside the telencephalon and intratelencephalic neurons (IT) with axonal projections constrained to the telencephalon. To directly test whether these putative L5 ET neurons projected to subcerebral regions, we injected retrograde adeno-associated virus (rAAV) into the cervical spinal cord of three macaque monkeys to express the fluorescent protein tdTomato. Targeted recordings of labeled corticospinal neurons from ex vivo slices of M1 confirmed that these neurons exhibited ET-like morpho-electric and transcriptomic properties. Cross-areal analysis of snRNA sequencing data demonstrated substantial cross areal differences in L5 ET neuron gene expression. Similarly, L5 ET neurons in M1 possessed distinct sub/suprathreshold properties and dendritic morphology compared to those found in TC. Thus, while both TC and M1 contain neuron types homologous to those found in rodents, distinct cell-type specific ion channel gene expression, physiology and morphology emerge in the non-human primate depending upon brain region.

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Poster

P918. Single-Cell Techniques III

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Program #/Poster #: P918.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Cross species cell types mapping of cortical inhibitory neurons to populate mouse cortex with detailed neuron morpho-electrical models.

Authors: *Y. ROUSSEL, C. VERASZTÓ, D. RODARIE, T. P. L. DAMART, M. W. REIMANN, D. KELLER, H. MARKRAM;
EPFL, Blue Brain Project, Geneva, Switzerland

Abstract: The ability of the brain to produce complex computational behavior arises from its organization and properties at the cellular level. One way to probe these principles is to study the cell type composition in its different areas. We estimated the distribution of well characterized morphological and electrophysiological neuron types (me-types) in the whole mouse cortex by converting molecularly defined cell type densities from the Blue Brain mouse cell atlas into the desired me-types. We used models from the Blue Brain Project inhibitory neurons model database to populate the cortex, enabling detailed cell modelling. However the models still lacked molecular markers which were necessary for me-type densities estimates. The conversion thus required the development of a method able to assign probable molecular markers to the desired me-types. To extrapolate this missing information, we employed an additional dataset from Allen Institute for Brain Science containing molecular identity data for mouse cortical neurons. We focused on inhibitory neurons because of their established subclassifications using molecular markers (PV, SST, VIP and Lamp5). Since data came from different animal models and from different cortical areas, we first normalized the reconstructed morphologies from both datasets using cortical layers delineation before extracting morphological features (m-features). Electrophysiological features (e-features) were extracted from recordings obtained using comparable protocols such as current steps. We then built a subspace upon a number of m- and e-features common to both data sources. We optimized the weight given to m-features relative to e-features so that mouse neurons with identical molecular markers would cluster together in the resulting subspace. We identified 13 molecularly homogeneous clusters that still merged neurons from both datasets. Finally, we probabilistically assigned a molecular identity to a me-type based on the assigned latent space clusters. The resulting mapping was then used to derive inhibitory me-types densities in the cortex. Results showed relatively comparable me-type distributions across the cortical areas with only a few exceptions in layer 6 of the orbital ventrolateral area. Finally, we validated the approach using labels common to both datasets. We believe our method to be a solid approach to compile data from different sources (e.g. mouse and rat) and extrapolate additional information from sparse data (e.g. morpho-electrical description from molecular marker).

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Poster

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P918.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NINDS Grant R01NS109916

Title: Identifying Transcriptional Regulators of Ion Channel Gene Expression using CRISPRi

Authors: *R. KIRK, S. NELSON, R. XIAO;
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Abstract: Healthy neuronal function requires balanced regulation of the relative abundance and distribution of ion channels and ionotropic receptors in the cell. Despite their well-established significance, little is known about the transcriptional mechanisms that control the expression and abundance of mRNA encoding these critical proteins. Therefore, we sought to identify candidate transcriptional regulators of ion channel genes by leveraging bulk RNA-seq and ATAC-seq data collected in parallel from several neuronal cell types throughout the adult mouse brain. Motif enrichment analysis from our data implicates the Kruppel-like factor (KLF) and Regulatory Factor X (RFX) families of transcription factors as potential novel regulators of ion channel gene expression. To test our predictions, we have developed an *in vivo* CRISPR-interference (CRISPRi)-based knockdown strategy to knock down abundantly expressed (RFX3 and RFX7) or activity-regulated (KLF6 and KLF9) members of each transcription factor family individually or in combination. By injecting neonatal Emx1-Cre;LSL-dCas9-KRAB mice with AAV9 containing guide RNA's (gRNA) targeting our genes of interest, we are able to reliably produce 90-95% knock down of up to 3 genes of interest in specific cell types with a single virus. The inclusion of a Cre-dependent fluorescent reporter in our virus allows us to sort infected cells by their fluorescence and perform RNA-sequencing to understand the effects of individual or combinatorial transcription factor knockdown(s) on the neuronal transcriptome. Furthermore, the multiplexed application of CRISPRi allows us to interrogate gene expression networks in specific cell types while overcoming or unmasking the redundancy or synergy in transcription factor function. These experiments may reveal many previously unknown targets of RFX3, RFX7, KLF6, or KLF9 in the mammalian cortex, among which are expected to be ion channel genes.

Disclosures: R. Kirk: None. **S. Nelson:** None. **R. Xiao:** None.

Poster

P918. Single-Cell Techniques III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P918.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Comparative evaluation of dendritic spine imaging techniques- Golgi staining and microinjection

Authors: P. ROGU[1], ***I. MOLLICONE**[1], A. LIPSHUTZ[1], R. KHAN[1], G. B. ROSOKLIJA[1], A. J. DWORK[1], G. TURI[1], M. REIMERS[3], T. SALTZ[2,4], D. DUMITRIU[1];

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Abstract: Dendritic spines are submicron-sized protrusions of the dendrite that form connections between neurons. Implicated in development, age-related memory impairment, stress response, motivation, addiction, and behavior, spines are plastic, meaning that experience affects their morphology and density. Morphological changes of spines represent changes in postsynaptic receptor expression and electrochemical potentials. There are many ways to visualize spines, including the Golgi staining method and single cell microinjection of fluorescent dyes. Golgi staining is the first technique, dating back to 1873 and remaining popular today. It involves tissue-wide analysis via mercury impregnation. This staining process takes several months, after which, spines are visualized via brightfield microscopy and analysis is conducted via manual counting. Although widely used, Golgi staining lacks control and precision, and the mechanism behind the staining is not well understood. Microinjection of fluorescent dye is a newer technique that is validated and backed by its comparability to the "gold standard" of neuroimaging: serial section transmission electron microscopy. As compared to ssTEM, microinjection technique utilizes more easily acquired resources while also being faster. Although in contrast to Golgi, microinjection requires a higher degree of technical skill and expensive imaging equipment. After microinjection of individual cells, spines are visualized via a combination of confocal microscopy and 3D reconstruction software that allows for semi-automated analysis of the spines' physical properties. In this confirmatory study, we look to compare the results between the two methods (Golgi & microinjection) within the same animals and identify where the differences in results lie. Within 8 rat brains, 2 sections containing the hippocampus were Golgi stained (n=224 dendrites) and 2 sections were microinjected (n= 282 dendrites) in the CA1 region. Using 2D Golgi staining, average density in spines/10 μm was found to be 16.99 +/- 0.35 and 11.11 +/- 0.29, as rated by two different raters. In the same rat brains, using 3D microinjection, the average density value was 41.35 +/- 0.97. Three-fold magnitude differences in the spine densities recorded between the two methods were observed. The three main sources of variance come from dimensionality (2D vs. 3D imaging), microscopy type (brightfield vs. confocal), and interrater variability. Using inconsistent techniques leads to fundamentally erroneous results in the field. Here we sought to clarify the precise magnitude and sources of differences between two commonly employed techniques in spine analysis.

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Poster

P918. Single-Cell Techniques III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P918.08

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Graduate Research Fellowship
Caltech Rosen Bioengineering Center Fellowship

Title: Time-resolved and cell-type-specific analyses of protein expression during sleep and wake in the zebrafish brain

Authors: *S. E. MILLER[1], D. A. PROBER[2], E. M. SCHUMAN[3], D. A. TIRRELL[1];
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Abstract: Humans spend nearly a third of their lives in the immobile state of reduced responsiveness and altered consciousness that we call sleep. Nevertheless, much about the function of sleep remains an evolutionary and biological mystery. Lack of adequate sleep is associated with a plethora of immediate and lasting negative effects on human health, including reduced cognitive performance, mood regulation, and motor function, as well as compromised immune response, neurological disorders, and even death. The importance of sleep is also reflected in its ubiquity, having been observed in most multicellular animals. Zebrafish, as a result of their genetic tractability, rapid development, optical transparency, diurnal sleep cycle, and ability to be used in high-throughput behavioral analyses, have emerged as a valuable model organism for dissecting the conserved genes and neural circuitry involved in sleep. However, proteomic analyses of sleep, which can uncover the molecular and mechanistic links between genes and behavior, have been relatively scarce. In this work, we used bio-orthogonal non-canonical amino acid tagging (BONCAT) to label newly synthesized proteins in larval zebrafish during defined time windows with azidohomoalanine (AHA). Labeled proteins were affinity purified for subsequent proteomic analysis via liquid chromatography-tandem mass spectrometry (LC-MS/MS). We were able to compare protein expression between larvae deprived of sleep for 48 hours with control fish to examine the proteomic signature of sleep deprivation. We are also working towards optimizing and applying recently developed BONCAT methods for cell-type-specific labeling of newly synthesized proteins for use in proteomics experiments. This version of BONCAT uses zebrafish that express a mutant methionyl-tRNA synthetase, which is capable of charging the bulkier non-canonical amino acid azidonorleucine (ANL), under the control of the neuron-specific promoter HuC. This ensures that only proteins synthesized in neurons during the time period of interest are enriched for LC-MS/MS analysis. Finally, by improving the labeling efficiency by both AHA and ANL in zebrafish, we aim to facilitate more time-resolved analysis of protein expression. This would enable, for example, labeling during shorter time windows of night or day for analysis of proteins that are differentially expressed during periods dominated by sleep or wake, respectively. Our work opens the door to further mechanistic analyses, such as through the use of genetic knockouts or mutants, of the role that differentially expressed proteins play in regulating sleep and wake in zebrafish.

Disclosures: S.E. Miller: None. **D.A. Prober:** None. **E.M. Schuman:** None. **D.A. Tirrell:** None.

Poster

P921. Bioinformatics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.01

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant 1R24MH114788-01

Title: The Neuroscience Multi-Omic (NeMO) Archive: A repository for single-cell genomic data from the mammalian brain

Authors: *H. CREASY, S. ADKINS, S. AMENT, R. CARTER, J. CRABTREE, V. FELIX, P. GANDT, B. HERB, C. MCCRACKEN, D. OLLEY, M. GIGLIO, A. MAHURKAR, O. WHITE;
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Abstract: Scalable technologies to sequence the transcriptomes and epigenomes of single cells are transforming our understanding of cell types and cell states in the mammalian brain. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative Cell Census Network (BICCN) is applying single-cell multi-omic technologies at unprecedented scale to map the cell types in the mammalian brain. In an effort to increase data FAIRness (Findable, Accessible, Interoperable, Reusable), the NIH has established data repositories to make data generated by the BICCN and related BRAIN Initiative projects accessible to the broader research community. The Neuroscience Multi-Omic Archive (NeMO, nemoarchive.org) serves as the primary repository for genomic data generated by Brain Initiative researchers. NeMO currently provides access to raw and uniformly processed transcriptomic and epigenomic data from >12 million cells in all the major regions of the mouse, human, and non-human primate brains, totaling >280 TB. The goals of the NeMO Archive are to: 1) support researchers in deposition of raw and processed data to NeMO, 2) perform uniform data processing and quality control, 3) assign all data objects and datasets a persistent NeMO identifier, resolvable through identifiers.org, 4) provide a central repository for browsing, querying and accessing genomic data through the NeMO data portal, 5) enable linking of genomic data to data generated by other experimental modalities, such as neuronal morphology, connectivity, and electrophysiology, by federating with other archives through use of common data models with standardized controlled vocabularies and ontologies, and 6) engage in outreach to understand community needs and to develop resources to meet these needs. In summary, we aim to provide a comprehensive infrastructure to enable the scientific community to access, analyze and interpret neuro-omics data, in order to advance a comprehensive understanding of cell type diversity in the mammalian brain.

Disclosures: H. Creasy: None. **S. Adkins:** None. **S. Ament:** None. **R. Carter:** None. **J. Crabtree:** None. **V. Felix:** None. **P. Gandt:** None. **B. Herb:** None. **C. McCracken:** None. **D. Olley:** None. **M. Giglio:** None. **A. Mahurkar:** None. **O. White:** None.

Poster

P921. Bioinformatics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.02

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH/NIDA UM1 DA052244
NIH/NIMH R24 MH114788
NIH/NIMH R24 MH114815

Title: Nemo-scorch: data coordination for the single cell opioid responses in the context of hiv (scorch) program

Authors: *S. A. AMENT[1], M. BASU[1], R. R. CAMPBELL[1], R. CARTER[1], H. H. CREASY[1], K. DEGATANO[2], B. R. HERB[1], K. IFEONU[1], L. CHANG[1], M. GIGLIO[1], R. HERTZANO[1], M. LOBO[1], A. MAHURKAR[1], T. L. TICKLE[2], O. R. WHITE[1];
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Abstract: Substance use disorders (SUD) and HIV, independently and as comorbid conditions, are major public health concerns. Increasing evidence suggests that cell type-specific transcriptomic alterations underlie the development and persistence of SUD and HIV. However, there remain substantial gaps in our understanding of the precise mechanisms that drive neural dysfunctions and cognitive impairments that are prevalent in both disorders. In particular, there is a need for new studies to characterize the diversity of cell types within brain regions relevant to SUD and HIV, as well as to investigate how chronic or acute exposures to addictive substances influence the states and functions of these cells. The Single Cell Opioid Responses in the Context of HIV (SCORCH) program was established in 2020 by the National Institute on Drug Abuse (NIDA), with the mission of generating resources that will enable comprehensive characterization of SUD and HIV at the single-cell level. This will be accomplished primarily through single-nucleus RNA sequencing of *postmortem* brain tissues from human donors who died with HIV and/or SUD, as well as animal models. SCORCH is an interdisciplinary effort, currently involving teams of investigators at five institutions: Yale University, the J. Craig Venter Institute, the Icahn School of Medicine at Mt. Sinai, the Broad Institute of Harvard and MIT, and the University of Maryland School of Medicine. The SCORCH Data Center (scorch.igs.umaryland.edu) is responsible for coordinating and sharing the resources generated by this program, ensuring that the data is FAIR (Findable, Accessible, Interoperable, and Reusable). We will also integrate additional HIV/SUD genomic data sets and atlases of cell types in relevant brain regions that are being produced by other researchers and consortia, with the goal of creating a comprehensive resource for the HIV and SUD research communities. This will be accomplished by extending the Neuroscience Multi-Omic (NeMO) Archive (nemoarchive.org), the NeMO/Terra cloud-computing environment (terra.bio), and the NeMO Analytics single-cell genomics visualization and analysis tools (nemoanalytics.org). Here, we will describe the rationale, design, goals, and expected outcomes of the SCORCH program.

Disclosures: S.A. Ament: None. **M. Basu:** None. **R.R. Campbell:** None. **R. Carter:** None. **H.H. Creasy:** None. **K. Degatano:** None. **B.R. Herb:** None. **K. Ifeonu:** None. **L. Chang:** None. **M. Giglio:** None. **R. Hertzano:** None. **M. Lobo:** None. **A. Mahurkar:** None. **T.L. Tickle:** None. **O.R. White:** None.

Poster

P921. Bioinformatics II

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Program #/Poster #: P921.03

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant 1R24MH114815-01A1

NIH Grant 1R24MH114788-01

Title: Nemo analytics: a visualization and analysis environment for genomic and single-cell data

Authors: *B. HERB[1], J. ORVIS[2], H. HUOT CREASY[3], V. FELIX[3], R. S. ADKINS[3], Y. SONG[3], A. CASELLA[3], K. ROSE[4], B. GOTTFRIED[3], A. CHATTERJEE[3], C. MCCRACKEN[3], R. CARTER[3], J. CRABTREE[3], J. KANCHERLA[7], A. MAHURKAR[3], H. BRAVO[7], M. GIGLIO[3], C. COLANTUONI[8], S. A. AMENT[5], O. WHITE[3], R. HERTZANO[6];
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Abstract: NeMO Analytics (nemoanalytics.org) is a web-based suite of data visualization and analysis tools, focusing on single-cell data analysis. The portal allows users to visualize multi-omic data across experiments and species side-by-side. The portal is pre-populated with thematically organized datasets. Users can also upload their own data for private or public use, utilize curated datasets from other users, or select a dataset from the vast NeMO Archive. Tools include cluster visualization based on expression/cell type, cluster comparison, identification of marker genes, comparison of marker genes across datasets and note taking. Additional tools include a workbench to perform *de novo* analysis of scRNA-seq data, visualization and analysis of spatial transcriptomics data, and visualization of epigenomic data. The platform supports visualization of datasets across species and modalities side-by-side keyed on by gene symbol. *Future* functionality will include multi-gene visualization and gene regulatory analysis and tools that allow the user to explore gene set enrichment analysis of their data. NeMO Analytics is built on the gEAR portal, an open source platform for viewing and analyzing genomics data available at github.com/IGS/gEAR and described in Nature Methods: https://rdcu.be/cndgK.NeMO Analytics aims to foster a knowledge ecosystem by supporting publications and creating “living figures” that can be explored, and the underlying data further analyzed. Our goal is to be a natural continuation of the results presented in publications and allow users to pick up the analysis where the paper left off. Further, we strive to facilitate access to data held on disparate archives and allow users to analyze this data in a common workspace. A user can then better understand their own data when added to this workspace and seen in the context of countless other studies, currently spanning more that 10 million cells.

Disclosures: B. Herb: None. **J. Orvis:** None. **H. Huot Creasy:** None. **V. Felix:** None. **R.S. Adkins:** None. **Y. Song:** None. **A. Casella:** None. **K. Rose:** None. **B. Gottfried:** None. **A. Chatterjee:** None. **C. McCracken:** None. **R. Carter:** None. **J. Crabtree:** None. **J. Kancherla:** None. **A. Mahurkar:** None. **H. Bravo:** None. **M. Giglio:** None. **C. Colantuoni:** None. **S.A. Ament:** None. **O. White:** None. **R. Hertzano:** None.

Poster

P921. Bioinformatics II

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Program #/Poster #: P921.04

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH grant 5R21HG009274
NIH grant 5R21MH112161
NIH grant 5U19MH114831

Title: Cell type cross validation using single nucleus multi-omics of human cortical cells

Authors: *F. XIE[1], C. LUO[6], H. LIU[6], E. J. ARMAND[2], J.-F. CHIEN[1], R. FANG[3], W. I. DOYLE[2], T. STUART[9], R. D. HODGE[10], B.-A. WANG[6], Z. ZHANG[6], S. PREISSL[4], D.-S. LEE[7], J. ZHOU[6], S.-Y. NIU[6], R. CASTANON[6], A. BARTLETT[6], A. C. RIVKIN[6], X. WANG[4], J. LUCERO[8], J. R. NERY[6], D. A. DAVIS[11], D. MASH[12], R. SATIJA[9], J. R. DIXON[7], M. BEHRENS[8], B. REN[5], J. R. ECKER[6], E. A. MUKAMEL[2];
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Abstract: Single-cell transcriptome and epigenome profiling technologies have transformed our understanding of brain cell type diversity, with hundreds of cell types identified in the mouse brain by recent studies (Armand et al., 2021). However, it is challenging to comprehensively validate the statistical reproducibility and biological function of the vast number of cell types identified. Moreover, we lack objective and operable criteria to define cell type distinctions that balance between over- and under-splitting of cells to establish a consensus taxonomy of brain cell types.

Here, we develop computational methods that use multi-omic data to cross-validate cell types, and evaluate their level of over- or under-splitting. The methods build on the assumption that the cell type identity of a cell is consistently represented in its transcriptome and epigenome. Therefore, we can compare a cell's multi-modal profiles with those of its neighbors to objectively assess the validity of cell types, based on similarities and differences that are supported by both transcriptomic and epigenomic features.

We applied our methods to a multi-omic dataset from the human frontal cortex, containing 3,898 neuronal cells profiled by single-nucleus methyl-cytosine, chromatin accessibility and transcriptome sequencing (snmCAT-seq). This dataset provides high-resolution information about three modalities for each cell: DNA methylation, regions of open chromatin, and gene expression. Cluster cross-validation analysis identifies a range of 20 to 50 reliable cell types that are supported by both transcriptomes and DNA methylomes. Under- vs. over-splitting analysis reveals that splitting neuronal population into 17 major cell types under-estimated cell type diversity, with 16 types containing substantial within-cell type heterogeneity. Further splitting the 17 major types into 52 subtypes greatly reduces within-cell type heterogeneity, at a slight cost of reduced uniqueness. In addition, we benchmarked the effectiveness of several computational integration methods, using the matched transcriptomes and DNA methylomes as ground truth. All five methods we tested can reliably assign matched transcriptomes and DNA methylomes to the same major cell types (n=17; accuracy 31.0%~87.3%), while the performance decreases at the subtype level (n=52; maximum accuracy 62.6%).

As the amount of human brain multi-omics data grows, we expect our methods to be useful for objectively validating the appropriate resolution of cell types. Moreover, cross-validation will be important for identifying reliable inter-individual variability among human brain cell types.

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Poster

P921. Bioinformatics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.05

Topic: I.02. Systems Biology and Bioinformatics

Title: Computational analysis of functional coding/non coding single nucleotide polymorphisms (SNPs/ Indels) in human NEUROG1 gene.

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Abstract: Background: Human *NEUROG1* gene encodes neurogenin1protein. It has an essential role as a transcription factor in neurogenesis and neuron repair. Mutations in this gene linked to many congenital and brain diseases. Method: This study used bioinformatics tools to evaluate the effects of mutations along the sequence of the gene. Genomic data has been retrieved from NCBI, GenBank, and Ensembl databases. Result: From 617 SNPs and INDels reported in the dbSNP, only four in coding has been predicted as deleterious by all software. Modeling of three-dimensional structure of NEUROG1 was generated by I-TASSER and validated by different software. Analysis of 3' UTR region showed that 8 SNPs were found to affect microRNA binding sites either by creating or disturbing them. Computational analysis has been used for the possible effects of reported SNPs on the functionality of the gene and its protein. Conclusion: This gene has been suggested as a candidate for gene therapy at genetics and epigenetics levels and\or drug design of neurodegenerative and other neurological diseases.

Disclosures: S. Mahalah: None. **Z. Hamid:** None. **S. Ibrahim:** None. **S. Babiker:** None.

Poster

P921. Bioinformatics II

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Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.06

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant 5R01NS111220

Title: Soft Clustering by Consensus (SoCCo) enables robust and scalable characterization and interpretation of diverse brain cell population structures

Authors: *S. GOGGIN[1], E. ZUNDER[2];
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Abstract: Single cell molecular profiling technologies have enabled major advances in our ability to identify and characterize functionally important subsets of cells and their complex roles in the brain. These studies have increasingly revealed that in any given snapshot of the brain there may exist a range of cell population structures - from defined, discrete populations that align well with the canonical concept of a “cell type" to those which can be better described as complex landscapes of continuous phenotypes. Identification of meaningful population structure within a single cell dataset generally relies on some form of clustering, but these approaches are not able to robustly capture and describe this broad range of population structures. Most clustering techniques force a discrete and categorical perspective on defining cell populations, do not generalize well across datasets, and have low reproducibility in response to small changes to input data or algorithm parameters. To address the need for a method that can provide robust, generalizable, and actionable descriptions of observed heterogeneity of molecularly-defined cell population structures, we have developed a new method called Soft Clustering by Consensus (SoCCo). Our method utilizes an ensemble of clusterings to explore a wide range of data subspaces at many different resolutions, and then applies a consensus function across these ensemble members to obtain a final soft cluster membership matrix. The process of integrating information from the diverse ensemble members enables our method to capture the complex cell population structures that exist in a given single cell dataset, and the soft clustering output is able to quantitatively describe the resulting cellular landscape without forcing cells into a single discrete grouping. This approach has two further advantages - the use of data subsampling allows our method to be scalable to very large datasets, and the internal hyperparameter search and optimization removes the need for extensive manual hyperparameter tuning which contributes to the usability of SoCCo. Finally, we have also developed a fuzzy differential expression approach that enables direct interpretation of the biological complexity captured by our soft clustering outputs. We have validated our method through simulation studies and with real mass cytometry and scRNA-seq datasets. Our results demonstrate that SoCCo is more generalizable to diverse datasets, scalable to large datasets, and yields more reproducible results than current state of the art methods. SoCCo will enable effective use of powerful single cell analysis approaches by a broader community of neuroscientists.

Disclosures: S. Goggin: None. **E. Zunder:** None.

Poster

P921. Bioinformatics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.07

Topic: I.02. Systems Biology and Bioinformatics

Support: R01MH118239

Title: Assessing and Improving on PrediXcan's Ability to Impute Gene Expression

Authors: *J. DRAKE[1], N. TAYLOR[1], J. MARTEL[1], N. GILLESPIE[2], J. POWELL[3], N. MARTIN[4], V. VLADIMIROV[1];
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Abstract: Gene expression is the consequence of environmental and genetic factors, which include epigenetic regulators and interactions between non-coding and protein coding RNAs. Gene expression (GE) imputation is becoming a powerful tool to derive and test for an association between GE patterns and phenotype of interest in a much larger than previously thought sample sizes. The correlation's strength between the genetic and expression profile of a given sample can be used to calculate the genetic contribution to GE (in the form of weights), which are then used to impute GE from unrelated genotypic data. PrediXcan, among others, is a recent software for GE imputation that utilizes this relationship by using the genetic and GE data in the Genotype-Tissue Expression Project (GTEx) database. PrediXcan has gained popularity in psychiatric genetics due to its ability to circumvent the necessity of post-mortem brain tissues. However, an important question is estimating the reliability and accuracy of the imputed GE. To address this question, here, we tested the correlation between imputed and measured GE derived from nucleus accumbens of 63 subjects. Among the number of matched genes (n=975), i.e., between the GTEx database and our sample, we identified only 1.3% with Pearson correlation ≥ 0.5. To address this seemingly low number of genes with an agreement between imputed and measured GE, and to improve on PrediXcan's imputation quality, we have expanded on their work by including much larger samples (i.e., N=630) from the Brisbane Longitudinal Twin Study and utilized heritability estimates to screen for poorly performing models.

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Poster

P921. Bioinformatics II

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Program #/Poster #: P921.08

Topic: I.02. Systems Biology and Bioinformatics

Title: Machine learning identifies metabolic clusters of IDH-wild type glioblastoma and predicts prolonged survival within the neuronal subtype

Authors: *M. ALEXANDER[1,2], J. GOODMAN[3];
[1]Yale Univ., New Haven, CT; [2]Frank H. Netter MD Sch. of Med., New Haven, CT; [3]Frank H. Netter MD Sch. of Med., North Haven, CT

Abstract: In our previous work we identified that differential metabolic pathway activation in low-grade glioma predicts prolonged patient survival. Here we test the hypothesis that differences in metabolic pathway activation would be associated with differences in survival of patients with glioblastoma

multiforme (GBM), the high-grade form brain tumors that remain associated with 100% mortality and poor survival time after diagnosis. Using expression data from all TCGA GBM studies, we estimate reaction activity scores for the cell's metabolic pathways, and cluster GBM tumors into three distinct metabolic clusters. We show that, unlike in LGG, in GBM, the metabolic clusters by themselves to not predict any differences in patient survival. However, our cluster 1 metabolic cluster is associated with higher survival within the neuronal subtype of GBM, which itself is has the shortest patient survival. We then apply a LASSO regularization survival model that allows us to include all reaction activity scores in our estimation. Using this variable selection approach, we identify expression of three catalytic units of G6P, GLUD1, GLUD2, and CSP-S to be predictive of differences in survival of GBM patients. These results are consistent with recent findings in the literature on the role of glutamate in glioma. Our results point towards development of metabolic markers of patient survival in GBM using gene expression, as well as leading to hypotheses about potential targets for treatment designed to disrupt GBM metabolism.

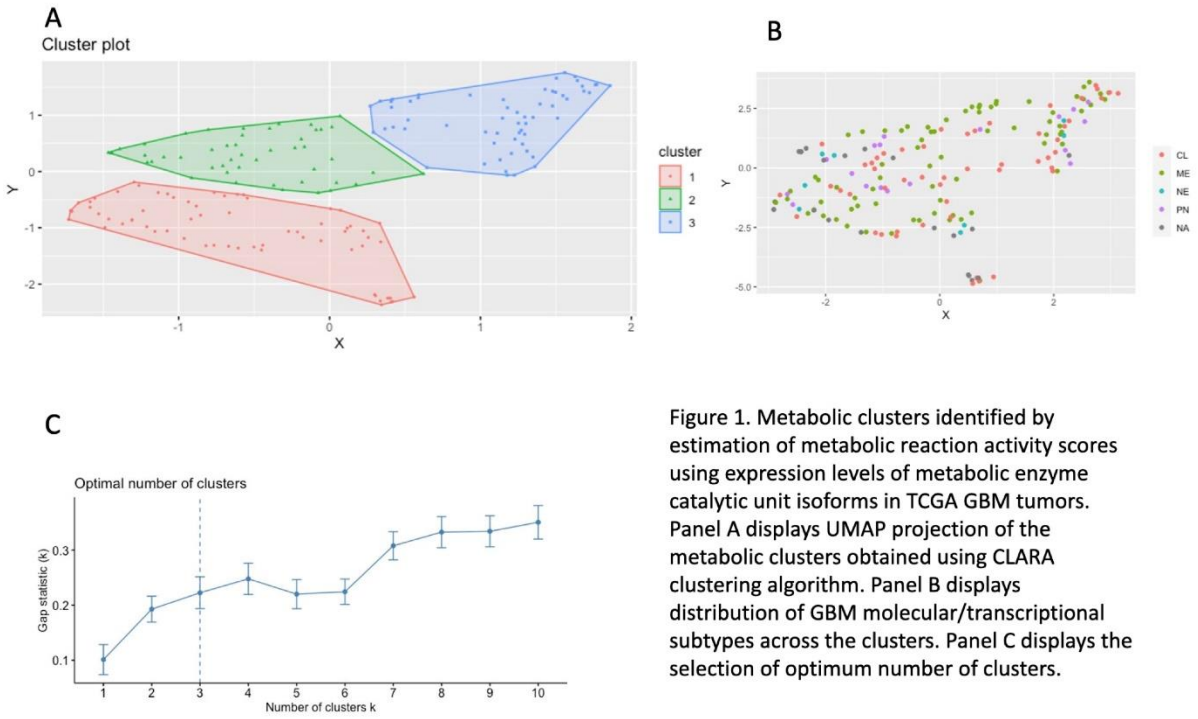


Figure 1. Metabolic clusters identified by estimation of metabolic reaction activity scores using expression levels of metabolic enzyme catalytic unit isoforms in TCGA GBM tumors. Panel A displays UMAP projection of the metabolic clusters obtained using CLARA clustering algorithm. Panel B displays distribution of GBM molecular/transcriptional subtypes across the clusters. Panel C displays the selection of optimum number of clusters.

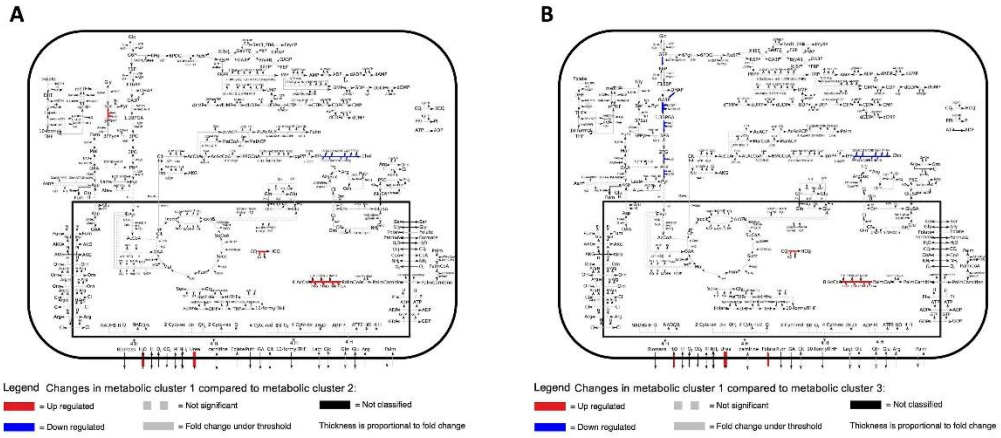


Figure 2: Differentially expressed metabolic reaction pathways estimated from RNA-Seq expression data for all GBM studies in TCGA. Panel A displays differentially upregulated and downregulated metabolic reactions in metabolic cluster 1 compared to metabolic cluster 2. Panel B displays differentially upregulated and downregulated metabolic reactions in metabolic cluster 1 compared to metabolic cluster 3.

Disclosures: M. Alexander: None. **J. Goodman:** None.

Poster

P921. Bioinformatics II

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P921.09

Topic: I.02. Systems Biology and Bioinformatics

Support: Healthy Brains for Healthy Lives
FRQS

Title: Relationship between heritability and latent dimensions of behaviour in the striatum, thalamus and globus pallidus

Authors: *N. BLOSTEIN[1], S. PATEL[3], R. PATEL[2], G. A. DEVENYI[4], S. TULLO[5], E. PLITMAN[2], M. COSTANTINO[2], R. MARKELLO[7], S. BEDFORD[8], M. CHAKRAVARTY[6];
[1]McGill Univ., Town of Mount-Royal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada;

[3]Neurogenetics, Ctr. For Addiction and Mental Hlth., Toronto, ON, Canada; [4]Cerebral Imaging Ctr., Douglas Univ. Mental Hlth. Institute, McGill, Montreal, QC, Canada; [5]CIC pavilion, [6]Cerebral Imaging Ctr., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada; [7]Dept. of Human Develop., Cornell Univ., Ithaca, NY; [8]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Introduction. Although the basal ganglia are traditionally associated with habit formation and motor control, non-motor basal ganglia loops have been found to modulate cognitive and limbic brain functions. The following study seeks to examine how latent dimensions of cognitive and emotional behaviour relate to heritability in shape measures of the striatum, thalamus and globus pallidus as a means of examining how cognition may be related to genetics.
Methods. Heritability measures were computed via a twin and non-twin sibling design, using MRI data of healthy adult twin and non-twin siblings from the Human Connectome Project (HCP; n=1086 participants; 3T; T1w; 0.7 mm isotropic voxels). Images were preprocessed using the minc-bpipe-library, and subcortical structure segmentations and vertex-wise shape measures obtained using MAGeTbrain and the CoBrA Lab subcortical atlases. OpenMx (version 2.12.2) was used to compute heritability estimates using structural equation modeling. Pyls 0.01 was used to run a partial least squares correlation (PLSC) analysis in Python 3.6.8. We obtained latent variables (LV) relating vertex-wise surface area and displacement to 30 behavioural variables related to cognition and emotion. For each significant latent variable, we adapted the Alexander-Bloch 2018 surface-based spin test to assess the significance of the correlation between vertex-wise heritability measures and LV-specific brain loadings.
Results. We found 4 significant LVs for both vertex-wise surface area and displacement. The bootstrap resampling ratios of the brain loadings had significant correlations with vertex-wise heritability measures for all 3 structures and across most LVs (Figure 1). Negative affect, emotion recognition, language processing and executive function loaded heavily onto our significant LVs.
Conclusion. The following study honed in on the understudied subcortex in order to further uncover gene-brain-behaviour interactions. We identified latent variables of behaviour whose brain patterns were significantly correlated with heritability.

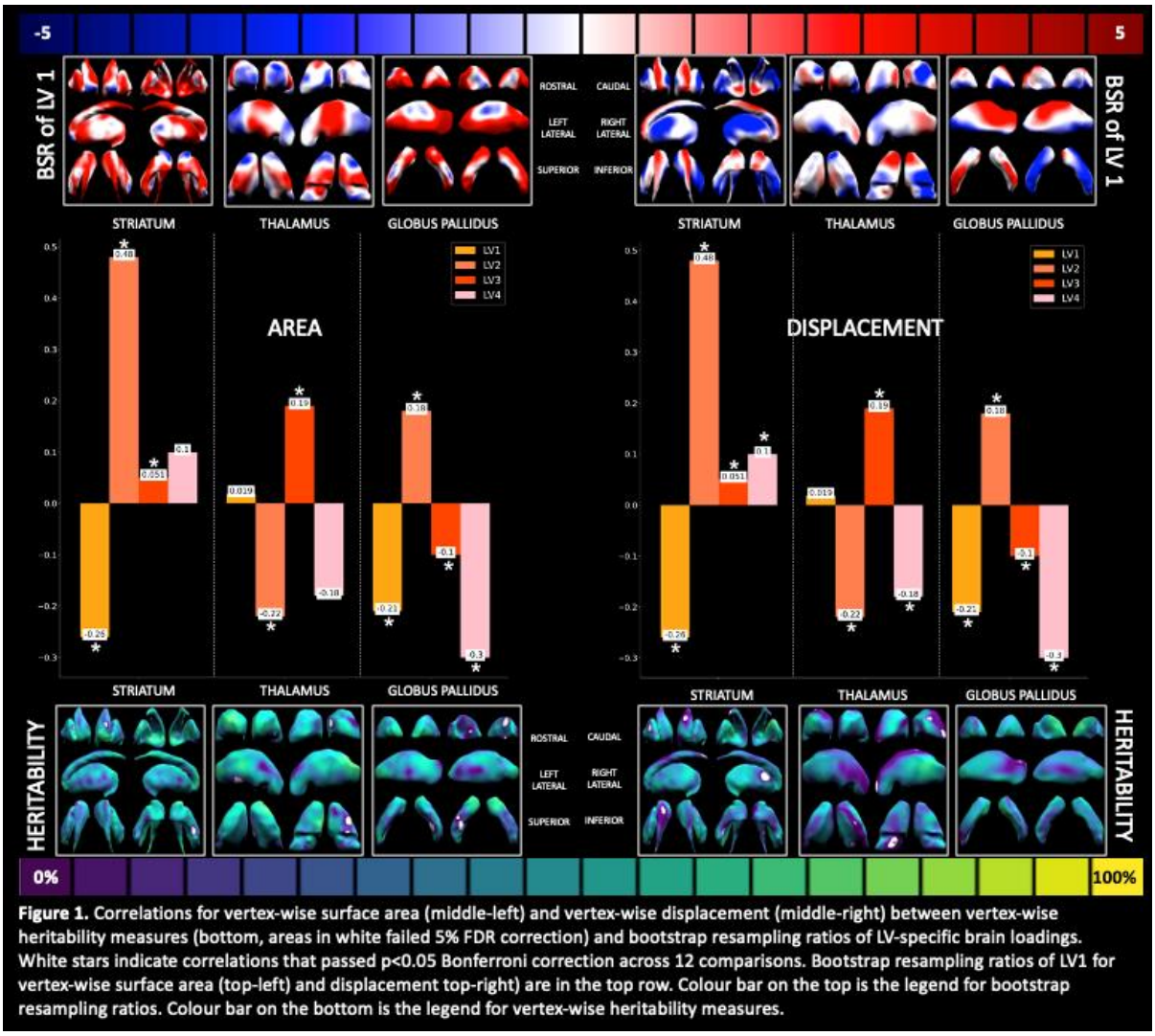


Figure 1. Correlations for vertex-wise surface area (middle-left) and vertex-wise displacement (middle-right) between vertex-wise heritability measures (bottom, areas in white failed 5% FDR correction) and bootstrap resampling ratios of LV-specific brain loadings. White stars indicate correlations that passed p<0.05 Bonferroni correction across 12 comparisons. Bootstrap resampling ratios of LV1 for vertex-wise surface area (top-left) and displacement top-right) are in the top row. Colour bar on the top is the legend for bootstrap resampling ratios. Colour bar on the bottom is the legend for vertex-wise heritability measures.

Disclosures: N. Blostein: None. **S. Patel:** None. **R. Patel:** None. **G.A. Devenyi:** None. **S. Tullo:** None. **E. Plitman:** None. **M. Costantino:** None. **R. Markello:** None. **S. Bedford:** None. **M. Chakravarty:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.01

Topic: I.06. Computation, Modeling, and Simulation

Support: Helmholtz Association Initiative and Networking Fund (ZT-I-0003)
Human Brain Project HBP Grant No. 785907 (SGA2 and SGA3)
RTG2416 MultiSenses-MultiScales (DFG)

Title: Surrogate methods for robust significance evaluation of spike patterns in non-Poisson data

Authors: *P. BOUSS[1,2], A. STELLA[1,2], G. PALM[3], S. GRÜN[1,2];
[1]Inst. of Neurosci. and Med. (INM-6/ INM-10), Inst. for Advanced Simulation (IAS-6), Forschungszentrum Jülich, Jülich, Germany; [2]Theoretical Systems Neurobio., RWTH Aachen Univ., Aachen, Germany; [3]Neuroinformatics, Univ. of Ulm, Ulm, Germany

Abstract: Spatio-temporal spike patterns were suggested as indications of active cell assemblies. We developed the SPADE method [1-3] to detect significant spatio-temporal patterns (STPs) with millisecond accuracy. STPs are defined as repeating spike patterns across neurons with potential temporal delays between the spikes. The significance of STPs is derived by comparison to the null hypothesis of independence implemented by surrogate data. SPADE first discretizes the spike trains into bins of a few ms and clips bins with more than 1 spike to 1. The binarized spike trains are examined for STPs by counting repeated patterns using frequent itemset mining. The significance of STPs is evaluated by comparison to pattern counts derived from surrogate data, i.e., modifications of the original data intended to destroy potential spike correlation but under conservation of the firing rate profiles. To avoid false results, surrogate data are required to retain the statistical properties of the original data as close as possible. A classically chosen surrogate technique is Uniform Dithering (UD), which displaces each spike independently according to a uniform distribution. We find that UD surrogates applied to our data (motor cortex) contain fewer spikes than the original data. As a consequence, fewer patterns are expected and, thus, false positives may be generated. We identified as the reason for this spike reduction a change of the ISI distribution: UD surrogates are more Poisson-like than the original data which are in tendency more regular. Thus UD destroys a potential dead time and, therefore, spikes are clipped away.To overcome this problem, we studied several surrogate techniques, in particular methods that consider the ISI distribution, i.e., a modification of UD preserving the dead time, (UDD), (joint-)ISI dithering, trial shifting [4]. Another ansatz is a surrogate that shuffles bins of already discretized spike trains within a small window. We examined the surrogates for spike loss, ISI distribution, auto-correlation, and false positives when applied to different ground truth data sets. These are stationary point process models but also non-stationary point processes mimicking the statistical features of the experimental data. It turned out that trial-shuffling [4] best preserves the features of the original data and generates few false positives; we used it then for application to real data.
References: [1] Torre et al (2016) DOI:10.1523/JNEUROSCI.4375-15.2016. [2] Quaglio et al. (2017). DOI:10.3389/fncom.2017.00041. [3] Stella et al. (2019). DOI:10.1016/j.biosystems.2019.104022. [4] Pipa et al. (2008) DOI: 10.1007/s10827-007-0065-3.

Disclosures: P. Bouss: None. **A. Stella:** None. **G. Palm:** None. **S. Grün:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.02

Topic: I.06. Computation, Modeling, and Simulation

Support: Emory Neuromodulation and Technology Innovation Center (ENTICe)

NSF NCS 1835364
DARPA PA-18-02-04-INI-FP-021
NIH Eunice Kennedy Shriver NICHD K12HD073945
Alfred P. Sloan Foundation
Simons Foundation

Title: Representation learning for neural population activity with Neural Data Transformers

Authors: *J. YE[1], C. PANDARINATH[2];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Biomed. Engin., Emory Univ. / Georgia Tech., Atlanta, GA

Abstract: Neural population activity is theorized to reflect an underlying dynamical structure. This structure can be accurately captured using state space models with explicit dynamics, such as those based on recurrent neural networks (RNNs). However, using recurrence to explicitly model dynamics necessitates sequential processing of data, slowing real-time applications such as brain-computer interfaces. Here we introduce the Neural Data Transformer (NDT), a non-recurrent alternative. We test the NDT's ability to capture autonomous dynamical systems by applying it to synthetic datasets with known dynamics and data from monkey motor cortex during a reaching task well-modeled by RNNs. The NDT models these datasets as well as state-of-the-art recurrent models. Further, its non-recurrence enables 3.9ms inference, well within the loop time of real-time applications and more than 6 times faster than recurrent baselines on the monkey reaching dataset. These results suggest that an explicit dynamics model is not necessary to model autonomous neural population dynamics. Code github.com/snel-repo/neural-data-transformers.

Disclosures: J. Ye: None. **C. Pandarinath:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.03

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01NS110806-01A1
NSF 1901338
NIH R01NS097764

Title: Stochasticity of Brain Rhythms

Authors: *C. HOFFMAN[1], J. CHENG[2], D. JI[2], Y. A. DABAGHIAN[3];
[1]Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX; [2]Baylor Col. of Med., Houston, TX; [3]Neurol., Univ. of Texas At Houston, McGovern Med. S, Houston, TX

Abstract: The discovery of EEGs in 1930's revolutionized the field of neuroscience by providing a non-invasive tool for understanding and diagnosing physiological functions, neurological pathologies, etc. Currently, most analysis methods are based on using either instantaneous or time-averaged characteristics

of the brain waves. We propose an alternative approach that focuses on temporal patterns of brain waves over finite timescales. Specifically, we use two independent methods for quantifying structural regularity and irregularity of the recorded signals and correlate the resulting "stochasticity scores" with behavior. The first method, discovered by A. Kolmogorov in 1933, produces a λ-score that quantifies the pattern's consistency with the underlying mean behavior. The second method, introduced by V. Arnold in the 2000's, yields a β-score that measures how "structured" (e.g., periodic-like or time-clustered) the pattern is. We then analyzed subcortical EEGs recorded in the hippocampal CA1 area of mice running a U-shaped track and studied series of short sequences of their θ-peaks, γ-peaks, and Sharp Wave Ripple (SWR) events. We found that θ-stochasticity in all mice is typically low, indicating almost-periodicity of the θ-rhythm, with occasional bursts. In contrast, γ-waves and SWRs are on average stochastically unbiased, displaying a full range of patterns. Importantly, the dynamics of both λ- and β-scores for all waves are overtly coupled to the animal's behavior; particular patterns of the animal's brain waves correlate with its location, speed, and acceleration. For example, we observe γ-bursts during slow motion, and orderly, nearly periodic sequences of SWRs around food wells which we make explicit using the Dynamic Time Warping method. Overall, these results offer a novel perspective on studying the structure, the dynamics, and the functionality of the brain waves.

Disclosures: C. Hoffman: None. **J. Cheng:** None. **D. Ji:** None. **Y.A. Dabaghian:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.04

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant DC014701

Title: Annolid - an instance segmentation-based multiple animal tracking and behavior analysis package

Authors: *C. YANG, M. EINHORN, T. A. CLELAND;
Psychology, Cornell Univ., Ithaca, NY

Abstract: Animal behavior is hugely complex, and the goals of behavioral analysis are correspondingly diverse. Methods of behavior quantification range from the tracking of single or multiple animals, or specific body parts of animals, to the identification of freezing, other behavioral states, interactions with objects, or the scoring of urine deposition. Such behaviors often are quantified based on video recordings, and the annotation and scoring of such recordings often are rate-limiting steps for research progression. A variety of software packages have been produced to facilitate video annotation, including a recent generation of deep learning-based pose estimation packages in which only a subset of the video frames must be explicitly scored. However, using these packages off-label for other behavior analyses has yielded mixed results; the tracking of multiple identified animals, particularly within complex or cluttered environments, has proven particularly challenging.
We present Annolid, a deep learning-based package for behavior analysis that is optimized for a range of common animal behavior assessments and requires substantially less manual frame annotation than

related packages. Uniquely, Annolid is based on instance segmentation models, and leverages overfitting to achieve robust tracking of multiple identified animals even in environments where animals may be partially or entirely obscured by environmental features or by one another. Using relatively few scored frames (tens to hundreds), we demonstrate robust behavior classification results for a wide variety of tasks, including animal tracking, body part tracking, and specialized measurements such as freezing or urine deposition. We further demonstrate successful multiple animal tracking under challenging conditions such as the partial or complete obscuring of tracked animals within visually cluttered environments. Arbitrary behaviors also can be directly recognized by the Annolid network, sometimes requiring higher numbers of scored frames; alternatively, such behaviors can be identified in post-processing analysis by the conjunction of simpler factors (such as nose location or body mask overlap). Model fitting can be performed locally or using online resources such as Google Colab. Results can be edited using our manual video scoring package Glitter2. Annolid and Glitter2 are both freely available from Github: https://github.com/healthonrails/annolid, https://github.com/matham/glitter2.

Disclosures: C. Yang: None. **M. Einhorn:** None. **T.A. Cleland:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.05

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R43GM134789
Oregon State SBIR Matching grant
WSU Gap Fund grant
WSU Postdoctoral Alcohol and Drug Abuse Research Program grant
NIH DA 033404
NIH DA 040965

Title: How to turn a microscope into a Tesla: Leveraging artificial intelligence transfer learning for identification and quantification of novel biomarkers in microscopy images.

Authors: J. J. THEIS[1], W. M. O'KEEFFE[2], G. W. WADE[2], C. V. KING[2], K. J. LAWTON[3,2], *J. H. HARKNESS[3,2];
[1]Univ. of St. Thomas, St. Paul, MN; [2]Rewire Neuro, Portland, OR; [3]Neurosci., Washington State Univ., Vancouver, WA

Abstract: Many fields of neuroscience utilize microscopy imaging to evaluate a broad range of cell types and subcellular structures. Imaging data is crucial for evaluating experimental outcomes and inferring relationships between relevant biomarkers. With progress in imaging technology, researchers can view much greater detail from larger datasets. Unfortunately, identification and quantification of these biomarkers remains a bottleneck, often requiring significant hand annotation that is both time consuming and introduces intra- and inter-rater errors. While some automated solutions exist, these often require a great deal of user involvement to correct inaccuracies. In recent years, machine learning (ML) emerged as

an excellent solution to accurately recognize regions of interest in microscopy images. The ML training process generally requires 1000's to 100,000's+ of user annotated images. Although hand-annotation is still a large upfront time investment, it produces a highly accurate model that is useful long-term for much faster and more consistent analysis of frequently studied cell types and biomarkers. Regrettably, this method is less useful for studying novel cell types or biomarkers, with few training images available. To combat these limitations, we used a ML technique known as transfer learning, which starts with a pre-trained model of a roughly similar biomarker as a base to create a new model. With transfer learning, we are able to reduce the number of required annotated images from several 100 to a few dozen, depending on cell density. We tested this method for several novel biomarkers from our *Pipsqueak AI* machine learning database, including models that are trained to detect staining for Parvalbumin, 8-oxo-dG, c-Fos, WFA, and DAPI. Our preliminary experiments trained new deep ML models with unique user annotated datasets based on similar existing biomarkers in our database. For one such dataset containing just 28 annotated images, we achieved a 5.5% increase in accuracy (86.9% vs. 82.4%) and a 11.1% increase in precision (84.3% v.s. 75.9%) compared to the original model. Further, when comparing this new model against a model which used only the user's annotated images for training, we achieved an accuracy increase of 24.8% (86.9% vs. 69.6%). Our results indicate that this computational method will greatly reduce the time and resources needed to train accurate detection algorithms, thus broadening the reach of machine learning to novel biomarkers and smaller image sets. Overall, this technology will allow the analysis bottleneck to catch up to the current hardware advances in the field, and rapidly advance research findings across disciplines.

Disclosures: J.J. Theis: A. Employment/Salary (full or part-time):; Rewire Neuro. **W.M. O'Keeffe:** A. Employment/Salary (full or part-time):; Rewire Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuro. **G.W. Wade:** A. Employment/Salary (full or part-time):; Rewire Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuro. **C.V. King:** A. Employment/Salary (full or part-time):; Rewire Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuro. **K.J. Lawton:** A. Employment/Salary (full or part-time):; Rewire Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuro. **J.H. Harkness:** A. Employment/Salary (full or part-time):; Rewire Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuro.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.06

Topic: I.06. Computation, Modeling, and Simulation

Title: Dendritic Spine Counter plugin for ImageJ

Authors: *M. VOLOSHIN[1], P. C. ROMERO[1], J. PARATO[2];
[1]Mighty Data, Inc., Weaverville, NC; [2]SUNY Empire State, Brooklyn, NY

Abstract: In the central nervous system, most excitatory synapses are represented as small protrusions called dendritic spines. The number of excitatory synapses on a neuron impacts overall excitability, and, on a larger scale, network activity. In diseases such as Alzheimer's Disease, Autism Spectrum Disorder, and schizophrenia, spine density is abnormal, resulting in improper brain function. Therefore, computing spine density is an important data-gathering step for many avenues of research into these disorders. Here, we have created a free ImageJ plugin, Dendritic Spine Counter, that will allow researchers and students to count spines in 2D. This plugin allows a user to submit a 2D image of stained neuronal tissue, mark a dendrite on that image for analysis, and receive an automated visually interactive list of structural features along that dendrite that are likely to be spines. The plugin operates “semi-automatically”, requiring minimal input from the user outside of specifying the dendrite to analyze. It also offers manual override options, permitting the user to directly add or remove spines. The machine vision algorithms underlying Dendritic Spine Counter were implemented using a heuristic-driven “expert system” approach, primarily employing basic image transformation functions and statistical analyses of pixel areas.

Disclosures: M. Voloshin: None. **P.C. Romero:** None. **J. Parato:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.07

Topic: I.06. Computation, Modeling, and Simulation

Support: BMBF, grant 01ZX1904A

Title: Developing multivariate methods for structural brain-based BMI estimation for healthy individuals and patients with psychiatric disorders

Authors: *A. KHUNTIA[1,2], R. PAUL[3], J. KAMBEITZ[4], R. SALOKANGAS[5], J. HIETALA[5], A. BERTOLINO[6], P. BRAMBILLA[7,8], R. UPTHEGROVE[9], S. WOOD[10,11], R. LENCER[12,13], S. BORGWARDT[14,13], N. KOUTSOULERIS[1,2,15];
[1]Dept. of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany; [2]Max-Planck Inst. of Psychiatry, Munich, Germany; [3]Dept. of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany; [4]Dept. of Psychiatry and Psychotherapy, Fac. of Med. and Univ. Hospital, Univ. of Cologne, Collogne, Germany; [5]Dept. of Psychiatry, Univ. of Turku, Turku, Finland; [6]Dept. of Basic Med. Science, Neurosci. and Sense Organs, Univ. of Bari Aldo Moro, Bari, Italy; [7]Dept. of Neurosciences and Mental Health, Fondazione Inst. di Ricovero e Cura a Carattere Scientifico Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]Dept. of Pathophysiology and Transplantation, Milan, Italy; [9]Inst. for Mental Health, Univ. of Birmingham, Birmingham, United Kingdom; [10]Ctr. for Youth Mental Health, Univ. of Melbourne, Melbourne, Australia; [11]Orygen, the Natl. Ctr. of Excellence for Youth Mental Hlth., Melbourne, Australia; [12]Dept. of Psychiatry and Psychotherapy, Univ. of Muenster WWU, Muenster, Germany; [13]Dept. of Psychiatry and Psychotherapy, Univ. of Lübeck,

Lübeck, Germany; [14]Dept. of Psychiatry, Psychiatric Univ. Hospital, Univ. of Basel, Basel, Switzerland; [15]Inst. of Psychiatry, Psychology and Neuroscience, King's Col. London, London, United Kingdom

Abstract: Research has established the association between psychiatric disorders with somatic comorbidities like cardiovascular risks and type II diabetes. In this study we are interested to understand the relation of obesity (measured by BMI) in individuals with mental disorders. We investigated the relationship between Grey Matter Volume (GMV) and Body Mass Index (BMI) by the use of multivariate analyses in two large, multi-site cohorts: IXI (https://brain-development.org/ixi-dataset/) and PRONIA (https://www.pronia.eu/). We extracted age-matched mentally healthy samples from both cohorts and further selected a balanced population covering people across all BMI ranges as a discovery group. The remaining healthy individuals were retained as replication samples. Another replication sample included the PRONIA clinical patient participants (Clinical High Risk, Recent Onset Psychosis and Recent Onset Depression). We developed multivariate regression and classification models to estimate BMI labels/classes using whole-brain grey matter volume data. For the regression model, we measured the difference between neuroanatomically predicted and observed BMI (BMIgap). For the classification model, we distinguished between normal and obese individuals (Overweight (BMI ≥ 25), Obese Class I (BMI ≥ 30), Obese Class II (BMI ≥ 35) and Obese Class III (BMI ≥ 35)). We removed the effects of age, sex and site by performing a partial correlation analysis. Repeated nested cross-validation as implemented in NeuroMiner (https://github.com/neurominer-git) was used to derive and test models. Models were also externally validated using the structural GMV images of healthy controls (replication sample) and the clinical PRONIA participants. The regression model performed with an MAE of 3.3 BMI points (r=0.37; P<.001) during model discovery. The classification model identified the obese group with a balanced accuracy of 64% during model discovery. During model application, the balanced accuracy was reported to be 59% with the structural images of the patients. The study will be essential in finding out underlying important signatures of somatic comorbidities associated with psychiatric disorders.

Disclosures: A. Khuntia: None. **R. Paul:** None. **J. Kambeitz:** None. **R. Salokangas:** None. **J. Hietala:** None. **A. Bertolino:** None. **P. Brambilla:** None. **R. Upthegrove:** None. **S. Wood:** None. **R. Lencer:** None. **S. Borgwardt:** None. **N. Koutsouleris:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.08

Topic: I.06. Computation, Modeling, and Simulation

Support: NIDILRR 90REGE0005-01

Title: Structural design optimization of a network of springs for supplementing muscle torque during gait

Authors: *B. MALIZIA[1], M. JACOBSON[1], P. RYALI[1], M. KIM[1], C. FRIGO[2], J. PATTON[1]; [1]Univ. of Illinois Chicago, Chicago, IL; [2]Politecnico di Milano, Milan, Italy

Abstract: Commercially available exoskeletons for gait assistance and rehabilitation, implementing strategies such as gravity compensation and metabolic cost reduction, often require the use of motors and

controllers. Our research shows that it is possible to use structural optimization to arrange a network of diagonal tension elements, which act mathematically as basis functions, to reproduce the muscular torques generated during physiological walking. This network of muscle-like elastic elements, called ExoNET, is a multidimensional spring system that shifts control intelligence from software to physical hardware. The resulting device has the potential to be simple, inexpensive, customizable, and wearable. Importantly, it can deliver any desired torques to multiple joints at many operating points. Moreover, the ExoNET overcomes the need for a rigid skeleton, using the very anatomy of the human body as a rigid link. It is quick and easy to use, and hence is valuable for therapy. Here, we present Dynamic Simulations through Musculoskeletal Models that validate the results of the structural optimization. Desired kinematics and a hip-knee ExoNET model determined the necessary muscle torques, and simulations demonstrated successful walking with significantly reduced muscle torques. This study demonstrates that the active energy input from muscles can be decreased by intelligently storing and returning energy during the gait cycle. Further developments involve Human-in-the-loop optimization (HITLO), while the patient walks on a treadmill, for the design of ExoNETs. Such bio-inspired passive systems may hold promise for neurorehabilitation and human augmentation. Supported by NIDILRR 90REGE0005-01

Disclosures: B. Malizia: None. **M. Jacobson:** None. **P. Ryali:** None. **M. Kim:** None. **C. Frigo:** None. **J. Patton:** None.

Poster

P964. Computational and Analysis Tools III

Location: Virtual Only

Time: Thursday, November 11, 2021, 11:00 AM - 12:00 PM

Program #/Poster #: P964.09

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF NCS 1835364
Alfred P. Sloan Foundation

Title: Advancing the investigation of neural population structure with the Neural Latents Benchmark

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Abstract: Advances in neural recording are presenting increasing opportunities to study neural activity in unprecedented detail, across a wide variety of neural systems and diverse behaviors. In parallel, progress in machine learning is yielding powerful computational approaches for analyzing neural population activity. In particular, latent variable models (LVMs) facilitate visualization and interpretation of complex population activity by uncovering time-varying patterns that capture the internal state of the population. Because LVMs do not strictly depend on external variables, they can be applied to diverse brain areas and behaviors. However, modeling progress is currently impeded by a lack of standardized comparisons, resulting in methods being developed and compared in an ad hoc manner. We introduce the Neural Latents Benchmark, a planned series of benchmark suites aimed at providing standardized quantitative evaluation of LVMs. We discuss challenges in comparing approaches as well as key principles and metrics that can overcome these challenges. We select co-smoothing - i.e., prediction of activity of held-out neurons - as a metric that is practical to implement and quantifies quality of inferred latent variables, yet makes only weak assumptions about the experimental task and brain area. We identify other commonly-used metrics, such as behavioral decoding and prediction of future timesteps, to serve as secondary evaluations of model quality.
Our first benchmark suite tests the broad applicability of LVMs to neural population spiking activity and consists of benchmarks that measure performance using four datasets: motor cortex during stereotyped and free-paced reaching, somatosensory cortex during reaching with perturbations, and frontal cortex during cognitive timing tasks. Each dataset poses unique modeling challenges, e.g., the need to account for a large number of behavioral conditions, unstructured trials, external perturbations, and limited behavioral correlates. For stereotyped reaching, we also include datasets of varying trial counts to evaluate LVMs on limited amounts of data. For evaluation, models must infer firing rates of both seen and unseen neurons in testing data. To ensure accessibility and standardization, we provide datasets in the Neurodata Without Borders format, host the benchmarks on the growing EvalAI platform, and offer a code package that demonstrates data preprocessing and submission. We anticipate that this benchmark suite will provide valuable points of comparison for LVM developers and users, enabling the community to identify and build upon promising approaches. http://neurallatents.github.io

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Poster

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Title: Direct inference of signal and noise correlations from two-photon calcium imaging data without intermediate spike deconvolution

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Abstract: Two-photon calcium imaging has created a unique opportunity to simultaneously record the activity of large populations of neurons and thereby probe the mechanisms through which neurons collectively encode information. Accurate extraction of neuronal activity correlations from two-photon data is crucial for this purpose, yet it is largely hindered by several key limitations faced by existing methods. First, since the two-photon observations of calcium activity are temporally blurred and noisy surrogates of spiking events, estimation methods tailored for spike train analyses are not directly applicable. Secondly, although there exist well-developed techniques for spike deconvolution, they are generally biased towards obtaining accurate first-order statistics (i.e., spike timings) via spatiotemporal priors, which may be detrimental to recovering second-order statistics (i.e., correlations). Finally, even if spikes were perfectly recovered, inferring network-level features from spiking data is a challenging task due to the non-linear relation of neuronal spiking to endogenous and exogenous variables.
We address these challenges by developing a multi-tier Bayesian model to directly estimate signal and noise correlations from two-photon fluorescence observations, without requiring intermediate spike deconvolution. Signal correlations quantify the similarity of neural responses that are time-locked to repeated stimuli, while noise correlations account for the stimulus-independent trial-to-trial variability shared by neural responses, both of which are jointly estimated by our proposed method.
We demonstrate the utility of our proposed approach through theoretical analysis and applications to simulated and experimentally recorded two-photon imaging data from the mouse primary auditory cortex. Our method reliably extracts noise correlation structures that are invariant across spontaneous vs. stimulus-driven neural activity. In addition, our joint estimation of signal and noise correlations corroborates existing hypotheses regarding the distinction of their structures. While application of our proposed method to spatial analysis of signal and noise correlations in the mouse auditory cortex is consistent with existing work, it reveals novel and distinct spatial trends in the correlation structures of primary cortical layers 2/3 vs. 4. Our proposed method provides a robust and scalable alternative to existing approaches for inferring neuronal activity correlations from two-photon imaging data.

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